TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

DIPLOMARBEIT

N-HETEROCYCLIC CARBENE CONTROLLED DEHOMOLOGATION OF ALDOSES – STRUCTURE-REACTIVITY RELATIONS OF SUBSTRATE AND CATALYST

ausgeführt zum Zwecke der Erlangung des akademischen Grades eines Diplomingenieurs der technischen Wissenschaften unter der Leitung von

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durch

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Wien, 13.09.2018

"Maktub" (It is written.)

Paulo Coelho, The Alchemist

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Acknowledgements

This thesis marks the end of an important step in my life. Therefore, I would like to take the opportunity and thank the many people, who have guided, supported and accompanied me along this journey.

First and foremost, I want to thank Prof. Marko D. Mihovilovic for giving me the opportunity to conduct my master's thesis in his research group and under his supervision. It was always reassuring to know, that despite his busy schedule he was quick and enthusiastic to act, when some sort of problem arose, he could help with. I learned a lot during this thesis and look forward to expanding my knowledge and skills even further during my PhD studies within his group.

Next, Christian, who came up with the idea for the project and helped me in the execution of this thesis, deserves my deepest gratitude for the invaluable advices he has given me and the many things I learned from him, even beyond chemistry.

Special thanks go to Prof. Florian Rudroff and Prof. Michael Schnürch, whose qualified input in and outside of the regular seminars I really grew to appreciate.

Moreover, Dipl.-Ing. Markus Draskovits, who started working on the project of this thesis half a year before me, was a great help, especially in the beginning, but basically throughout the whole thesis. Without his work this thesis would have never turned out to be what it became.

I would also like to thank the operators of GC, GC-MS, and NMR, especially Markus, Sebastian and David, for their contribution, who not only made hundreds of measurements, but also offered a helping hand whenever a question came up.

Furthermore, I would like to thank my colleagues Alex, Anna, Blanca, Charlie, Clemens, Daniela, David S., David Sch., Dominik, Erna, Hamid, Laszlo, Leticia, Markus, Martin, Philipp, Rafaela, Resi, Sarah, Thomas, Wiesi and Yago who extensively contributed to the great working environment and many unforgettable moments in- and outside of the lab.

Finally, I would like to thank my family, my friends and especially my girlfriend, who gave me all the support in my private life I needed to be able to focus on this thesis and my studies in general. Without this support I would not have been able to become the person I am.

Abstract

Despite being regularly referred to as Nature's largest chiral pool, actually, only a small number of carbohydrates are readily available at reasonable scale and cost. Within this project we aim to develop new synthetic methodology for the interconversion of carbohydrate derivatives focusing on the aldehyde moiety as uniting chemical feature.

In this light, carbohydrates have recently been reported as sacrificial feedstock for the *N*-heterocyclic carbene (NHC) catalyzed formylation of activated double bonds (Stetter reaction). Based on this report we set out to investigate and establish an NHC-controlled dehomologation of sugar derivatives by interception of the putative mechanism.

Initial experiments with 3-*O*-benzyl-D-glucose delivered the aspired proof of concept, however, a critical follow-up elimination towards 2-deoxy-lactone was also identified. The selectivity between these two main reactions is currently in the focus of our attention. Addressing the presumed relevance of the relative stereochemistry, we prepared several epimers of 3-*O*-benzyl-D-glucose and the expected products of NHC-catalysis. Furthermore, a small library of *N*-aryl-thiazolium based pre-catalysts with varying electronic and steric properties was both prepared and its compounds were evaluated as mediators for the dehomologation of the above sugar probes.

Detailed analysis of the reactions in a time-resolved fashion based on quantifiable GC-analysis (upon derivatization) revealed important features of substrates and catalysts for the targeted selectivity and resulted in the first finding of a perfect match between substrate and catalyst structure. Striking selectivity for the intercepted dehomologation and a strong suppression of undesired lactone formation could be accomplished. The results of this study will further fuel mechanistic considerations and the development of the NHC-controlled dehomologation of aldoses towards a general and practical synthetic solution.

Deutsche Kurzfassung

Obwohl regelmäßig als der größte chirale Pool in der Natur bezeichnet, steht tatsächlich nur eine kleine Anzahl von Zuckerderivaten in vertretbarem Ausmaß und zu vernünftigen Kosten zur Verfügung. In diesem Projekt verfolgen wir das Ziel, neue Synthesemethoden für die Umwandlung von Kohlenhydratderivaten zu entwickeln, die sich auf die Aldehydfunktionalität konzentrieren.

Vor diesem Hintergrund wurden kürzlich Kohlenhydrate als Einsatzmaterial für die *N*-heterocyclische Carben (NHC) katalysierte Formylierung aktivierter Doppelbindungen (Stetter-Reaktion) beschrieben. Auf der Grundlage dieser Publikation wird von uns versucht, die Möglichkeit einer NHC-kontrollierten Dehomologisierung von Zuckerderivaten zu untersuchenund weiterzuentwickeln. Dazu wird der mutmaßliche Reaktionsmechanismus an einer bestimmten Stelle gezielt unterbrochen.

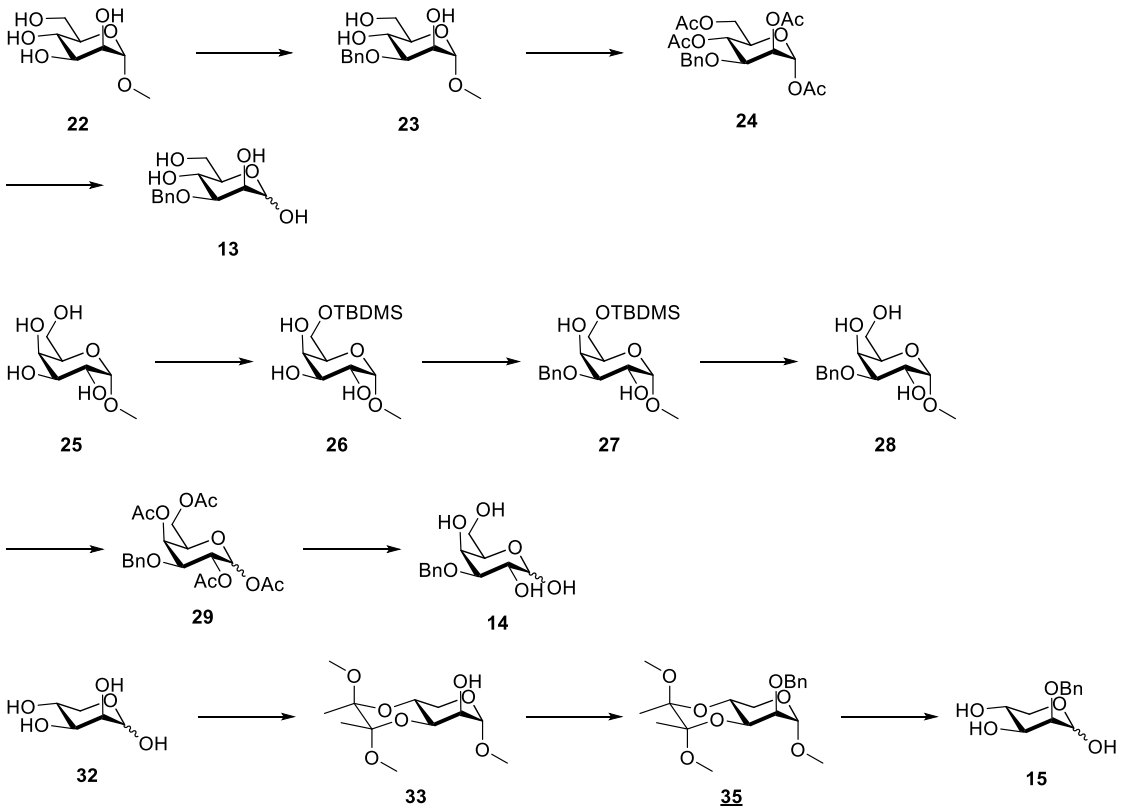
Erste Versuche mit 3-*O*-Benzyl-D-glucose in einer Machbarkeitsstudie verliefen erfolgreich, jedoch wurde auch eine Eliminierung zum entsprechenden 2-Desoxylacton als kritische Nachfolgereaktion identifiziert. Die Selektivität zwischen diesen beiden Reaktionen steht im Mittelpunkt unserer Untersuchungen. Unter Berücksichtigung der vermuteten Relevanz der relativen Stereochemie wurden mehrere Epimere von 3-*O*-Benzyl-D-glucose sowie der erwarteten Reaktionsprodukte hergestellt. Des Weiteren wurde eine kleine Bibliothek von *N*-Arylthiazoliumsalzen mit unterschiedlichen elektronischen und sterischen Eigenschaften synthetisiert und als Katalysatoren für die Dehomologisierung getestet.

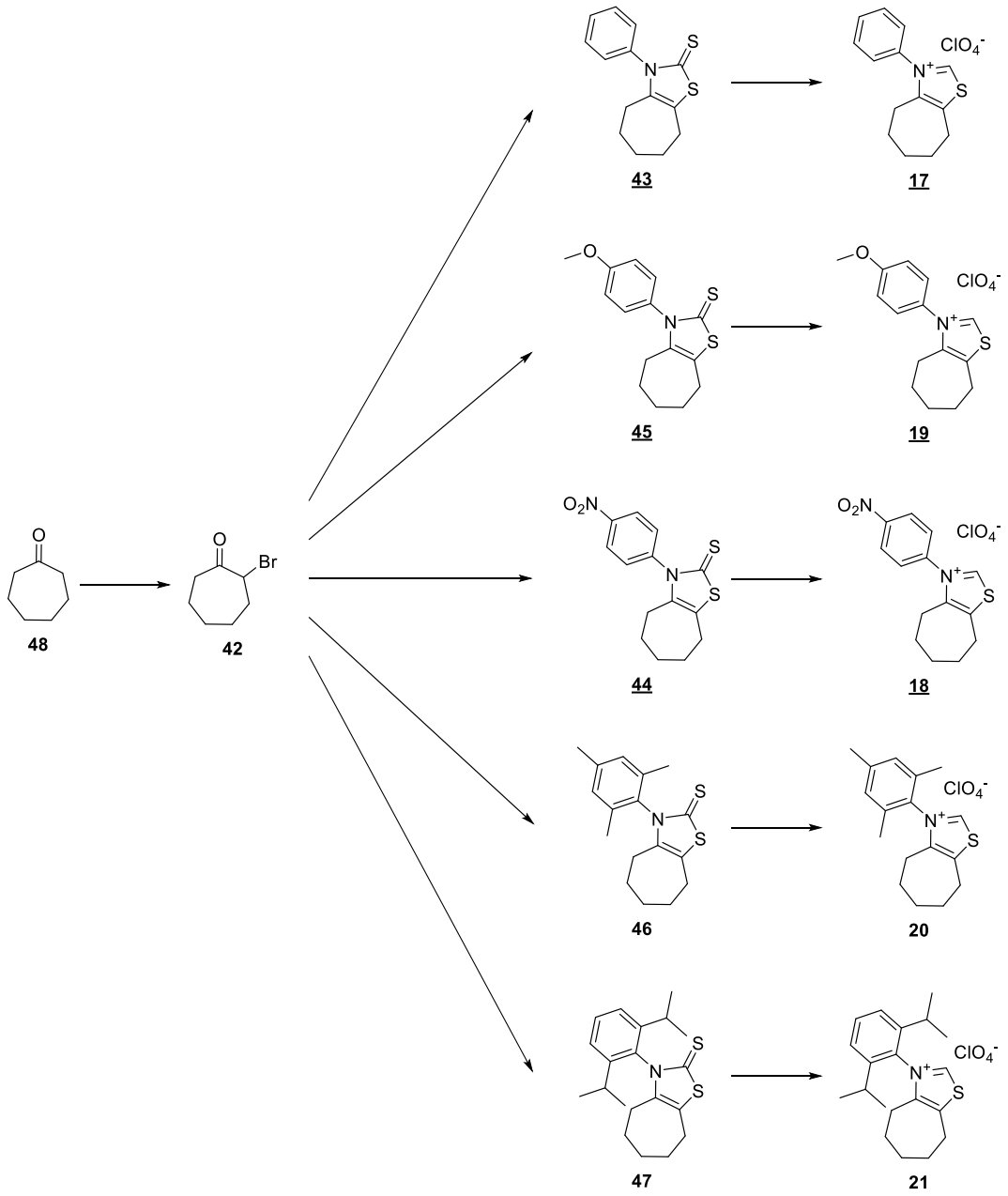
Die detaillierte Analyse der Reaktionen in zeitaufgelöster Form basierend auf quantifizierbarer GC-Analyse (nach Derivatisierung) zeigte wichtige Einflüsse von Substrat- und Katalysatorstruktur auf die angestrebte Selektivität und führte zum ersten Durchbruch in Form einer synergistischen Interaktion zwischen Substrat und Katalysator.

Eine bemerkenswerte Selektivität für die kontrollierte Dehomologisierung und eine starke Unterdrückung der unerwünschten Lactonbildung konnten erreicht werden. Die Ergebnisse dieser Studie werden unsere mechanistischen Überlegungen und die Entwicklung der NHC-kontrollierten Dehomologisierung von Aldosen in Richtung einer allgemeinen und praktischen Synthesemethodik weiter vorantreiben.

1 General schemes

All compounds prepared or used as starting materials as well as unisolated intermediates in this thesis are numbered in bold Arabic numerals. Compounds unknown to the literature are additionally underscored. Literature citations are indicated by superscript Arabic numbers.





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2 Abbreviations

anh.	anhydrous
app.	apparent
BDA	butanediacetal
BSTFA	*N*,*O*-bistrifluoracetamid
COSY	correlation spectroscopy
c	concentration
CSA	10- camphorsulfonic acid
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBTO	dibutyltinoxide
dipp	2,6-diisopropylphenyl
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
E	electrophile
equiv	equivalent
ESI^+	Electrospray ionization
EWG	electron-withdrawing group
FID	Flame ionization detector
GC	gas chromatography
GC-MS	gas chromatography-mass spectroscopy
Gal	galactose
Glu	glucose
HMBC	Flame ionization detector
HOMO	highest occupied molecular orbital

HPLC	high-performance liquid chromatography
HPTLC	high-performance thin-layer chromatography
HR-MS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
LP	light petroleum
LUMO	lowest unoccupied molecular orbital
lit	literature
m	multiplet
M	molecular weight
m.p.	melting point
Man	mannose
Mes	mesityl
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nuc	nucleophile
p-TSA	*p*-toluenesulfonic acid
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
pent	pentet
PG	protecting group
ppm	parts per million
q	quartet
R_f	retention factor
rt	room temperature
s	singlet

satd.	saturated
sept	septet
sm	starting material
SPE	solid phase extraction
t	triplet
t0	initial time
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
t_R	retention time
UV	ultra-violet
µW	microwave
δ	chemical shift

3 Introduction

3.1 *N*-Heterocyclic carbenes (NHCs)

3.1.1 Background and structure of NHCs

N-Heterocyclic carbenes (NHCs), are heterocyclic structures that contain both a carbene carbon and at least one neighboring nitrogen atom, with some typical examples being given in Figure 1. Generally, carbenes are inherently unstable, as the carbene carbon atom constitutes a 6-valence-electron-system, violating the octet rule, thus a counteracting force needs to stabilize it. This stabilization is achieved by the heteroatom substituents; mesomeric π-donating and inductive σ-withdrawing properties (that are especially pronounced with nitrogen) result in an electronic push-pull system and in addition lower the energy level of the HOMO and increase the energy level of the LUMO. The carbene therefore adopts a singlet state with a structure similar to an sp^2-configuration, where the two non-bonding electrons occupy the HOMO and the LUMO corresponds to an unoccupied p-orbital. As a result, the carbene has no unpaired electrons and, therefore, it is referred to as a singlet carbene, as opposed by the linear triplet carbenes, where one of the electrons occupies the former empty molecular orbital (Figure 2).[1] This configuration results in their chemical behavior to be good nucleophiles and strong ligands. However, their high reactivity and therefore their instability is presumably also the reason why it took until the early 1990s when the first stable *N*-heterocyclic carbene (Figure 2, left) was isolated and identified by the group of Arduengo. The two bulky *N*-substituents in the so-called Arduengo-carbene lead to further stabilization by preventing, for example, otherwise occurring dimerization to olefines.[2] This achievement was the kick-off for NHCs to transcend the status of “lab curiosities” and to become widely considered useful tools in synthetic chemistry. Nevertheless, some ground-breaking work predates this discovery: Ukai’s first use of NHC catalysts (generated *in situ*) for homo-dimerisation of aldehydes date back to 1943[3], Breslow proposed the commonly accepted intermediate that is now named after him as early as 1958[4] and Stetter employed NHCs for the 1,4-condensation of aldehydes and α,β-unsaturated compounds in 1976[5] – all of which will be met again in the following.[6]

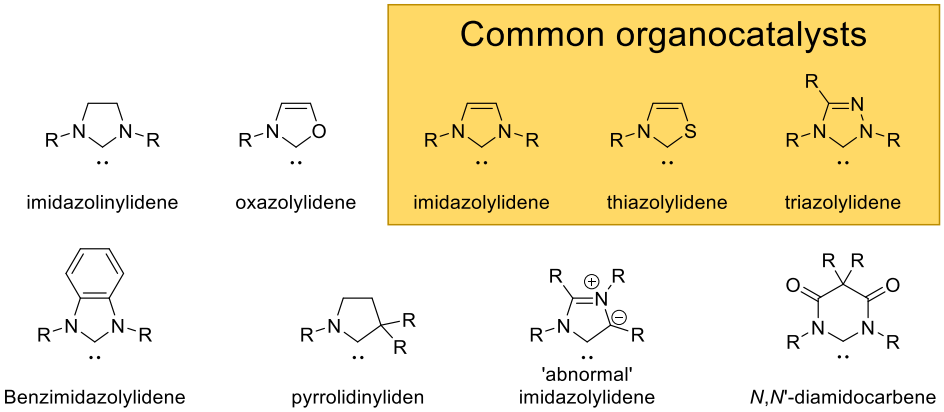


Figure 1: Examples of NHCs

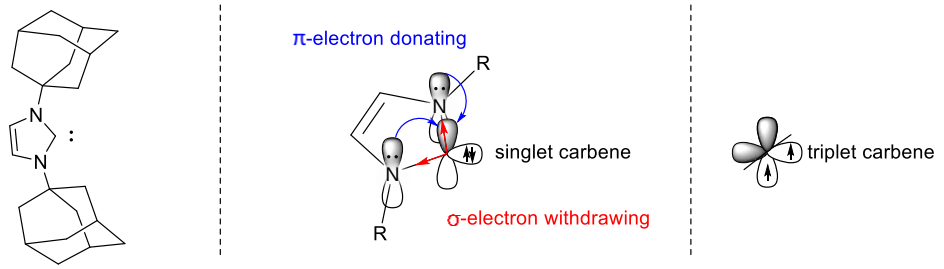


Figure 2: Arduengo carbene, stabilization of the NHC structure, singlet and triplet carbenes

The ultimate precedence of the utilization of NHC reactivity is, of course, found in nature within vitamin B1, also referred to as thiamine (as it was identified early on as a sulfur containing vitamin). Thiamine plays an important role as a coenzyme for a number of enzymes activating pyruvate (pyruvatdehydrogenase[7], pyruvatdecarboxylase[8]), or other α-ketoesters (α-ketoglutarate dehydrogenase complex[9]), as well as for transketolases[10] and acetolactate synthases[8]. It is therefore of little surprise, that chemists mimicked its scaffold when designing early NHC catalysts (see Figure 3).[3]

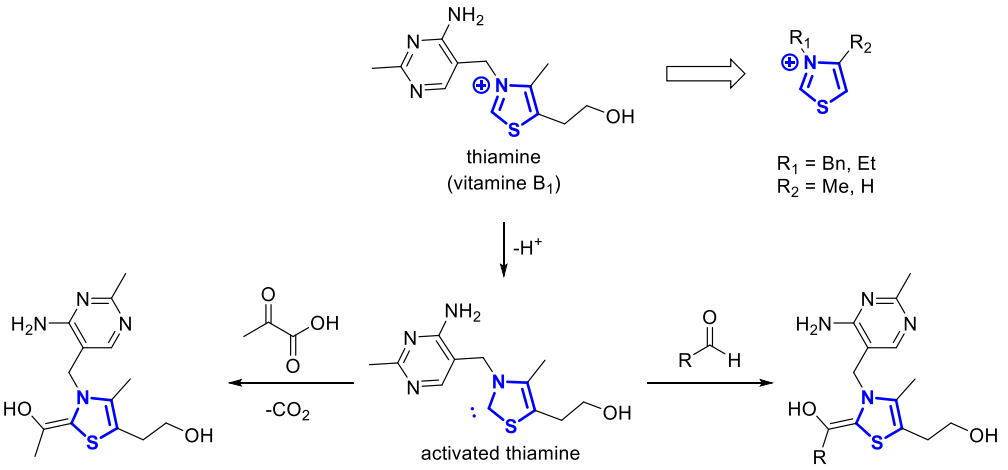


Figure 3: Vitamine B_1, a naturally occurring NHC catalyst, its reactivity and early derived structures thereof[5]

3.1.2 Areas of application of NHCs

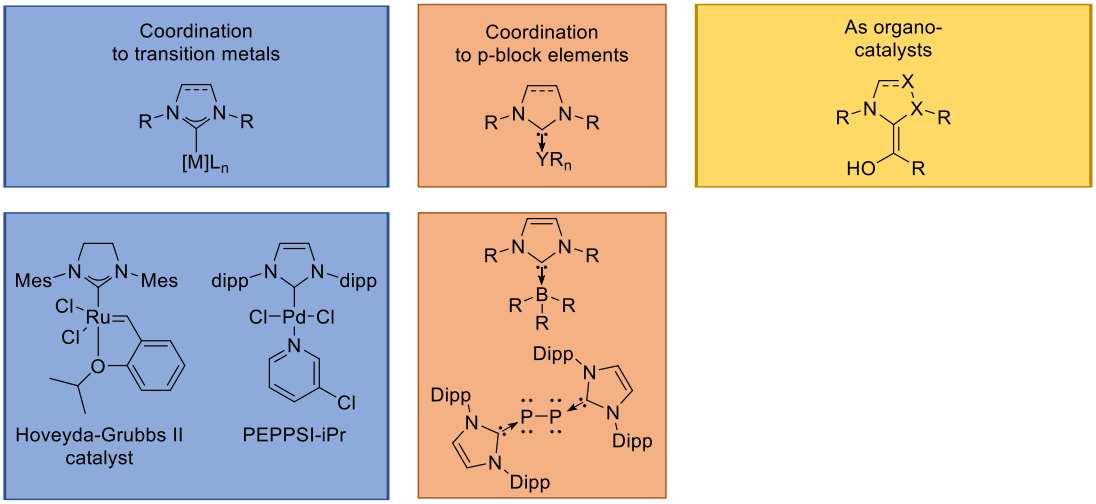
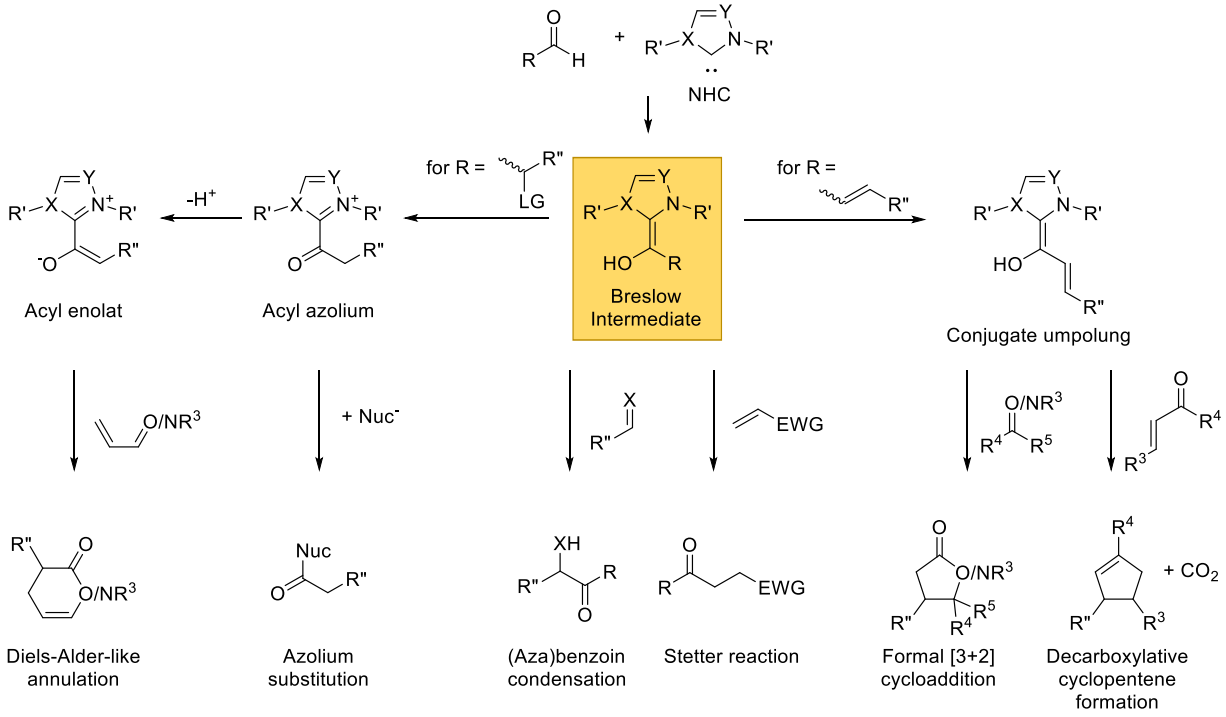


Figure 4: Areas of application of NHCs

Their unique properties have led to the development of some interesting applications. Their free electron pair enables coordination to transition metals, the most famous example being probably the Hoveyda-Grubbs II catalyst[11]. Another remarkable example is the PEPPSI-iPr catalyst, where the coordination of an NHC significantly increases stability towards air and moisture compared to other, more common Pd catalysts like tetrakis(triphenylphosphine) palladium(0) (Figure 4, bottom left)[12]. NHCs have also been reported to strongly bind to p-block elements, stabilizing for example different exotic boron species[13], or even phosphorous[14] or silicon dimers[15] by coordination (Figure 4, bottom center).[6]

The third major area of application of NHCs is their use as organocatalysts, which is also the context NHCs are used in within this thesis. The majority of NHC catalyzed reactions involve

carbonyl (like) compounds. Thereof, aldehydes comprise the most relevant group, as when converted to the Breslow intermediate they display a significantly different reactivity compared to the original aldehydes. These Breslow intermediates are formed after nucleophilic attack of the NHC onto the aldehyde, followed by a proton shift (Scheme 1, top). Thereby, regular aldehydes are capable of undergoing the benzoin and the Stetter reaction, which will be discussed in more detail in the next section. Starting from α,β-unsaturated aldehydes, cyclization reactions become available, as both the original carbonyl position and the β-position become electrophilic when the Breslow intermediate is formed.[16] Alternatively, a leaving group in α-position, or an oxidant can result in the formation of an acyl azolium species which is trapped by a nucleophile resulting in the formation of an acid derivative[17], or after deprotonation even enable Diels-Alder like annulations.[18] Additionally, several reactions with NHCs taking the role of a Lewis base[19] are known as well (e.g. transesterification).[6]



Scheme 1: NHC catalyzed reactions of aldehydes (based on Hopkinson 2014)[6]

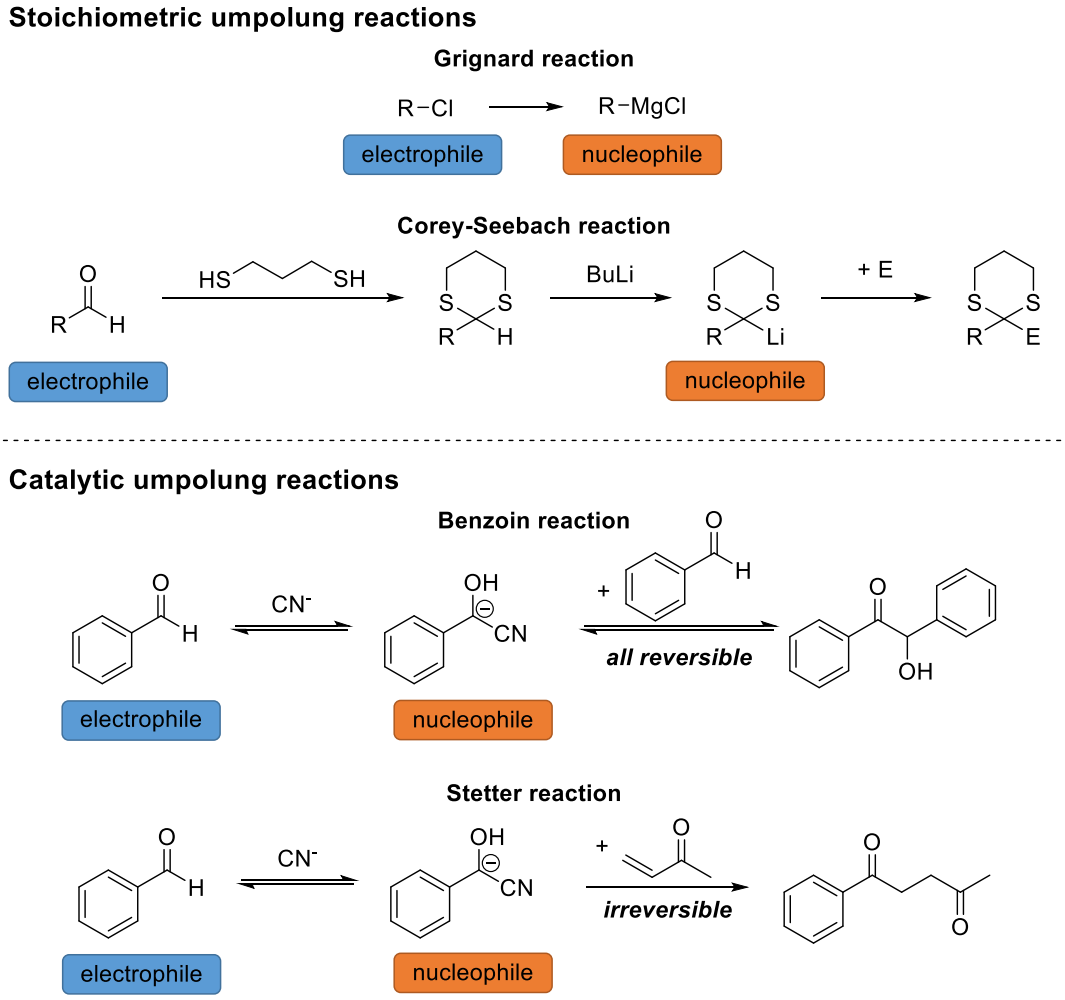
Throughout all areas of applications, the major strength of NHCs is that the principle structure can be widely tuned for the specific purpose, in particular with respect to two major influences: On one hand, the heterocyclic core scaffold is of great importance[20], with some common examples of those structures already being given in Figure 1. On the other hand, the *N*-

substituents in vicinity of the carbene moiety were shown to also play a significant role for the catalyst's reactivity, both in terms of electronic as in steric influence.[21-22]

3.2 Catalytic umpolung reactions

3.2.1 Overview

The originally German word umpolung was introduced by Wittig[23] and describes the inversion of polarity on an atom, turning nucleophiles into electrophiles and *vice versa*. There are several famous umpolung reactions involving stoichiometric reagents (e.g. Seebach umpolung[24], Grignard reaction[25]), but also reactions, where the umpolung of an intermediate is achieved catalytically, examples being the benzoin[26] and the Stetter reaction[27] (Scheme 2) in which course aldehydes are converted to nucleophilic species reacting with aldehydes or Michael type acceptors. Both of the latter reactions were originally reported using cyanide as catalyst, however have later been discovered to be also possible under NHC catalysis.[5] This is due to the similar electronic properties of both catalysts, caused by the free lone pair, that is common to them and is exposed to a similar electronic envirmonment. . Both entities are good nucleophiles, good leaving groups and exert electron-witdrawing properties.[1] With both these reactions being essential for the understanding of the proposed mechanisms of the NHC catalyzed dehomologation of aldoses discussed in this thesis, they will be discussed in more detail.



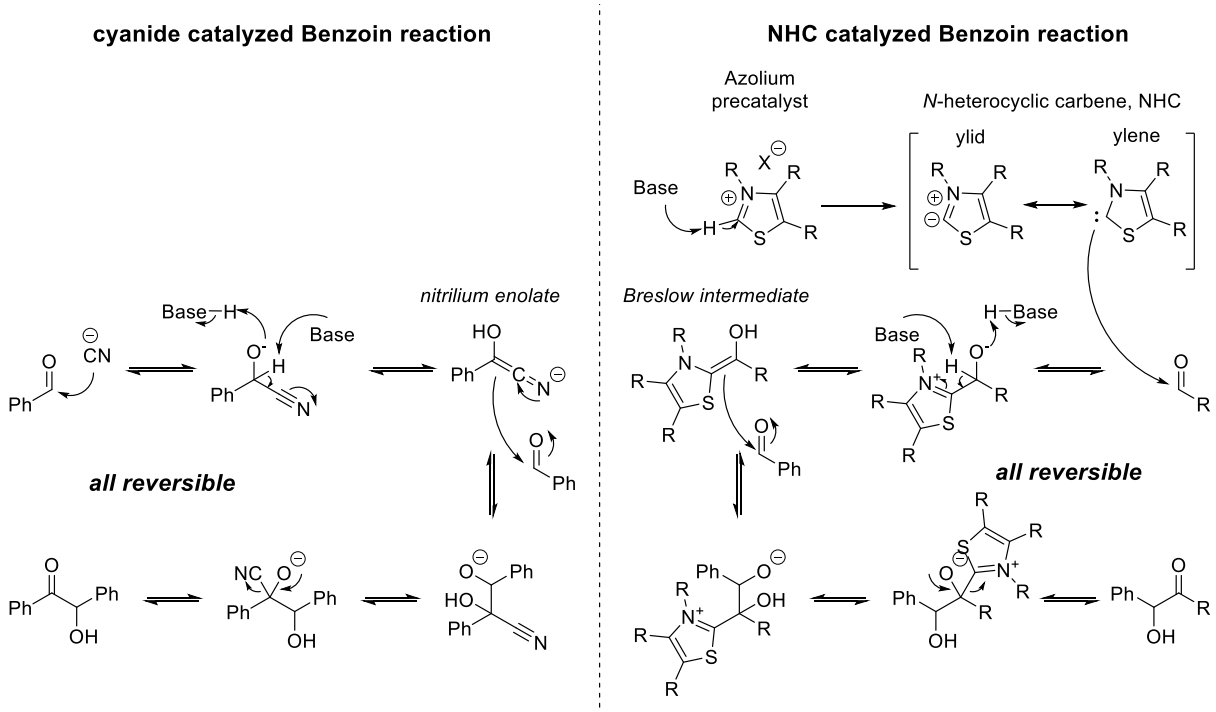
Scheme 2: Examples for umpolung reactions with stoichiometric (top) and catalytic activation (bottom)

3.2.2 The benzoin reaction

The benzoin reaction dates back as far as 1832, when Wöhler and Liebig first reported the cyanide catalyzed condensation of two equivalents of benzaldehydes.[26] However, the scope of the selective activation remained limited to certain aromatic aldehydes. Furthermore, the application of cross-benzoin reactions was rather limited. Usually, only one out of the four possible products, two homo-benzoin and two hetero-benzoin, is desired and shifting the reaction to a product that is not already favored was futile due to the products being in equilibrium with the starting materials.[28] With the introduction of NHCs as catalysts instead of cyanide the reaction profile was significantly expanded towards the activation of aliphatic aldehydes along with so far unreactive aromatic aldehydes.[29] Furthermore, the coupling partner could be successfully varied to include ketones[30] and imines[31]. Even selective cross-benzoin reactions could be achieved through the right choice of catalyst.[29, 32] For example, thiazolium based catalysts selectively activated aliphatic aldehydes, whereas triazolium based

ones attacked aromatic ones, preferentially.[33] In turn, enantioselective versions of the benzoin reaction have also been accomplished through the installation of chiral *N*-substituents.[34]

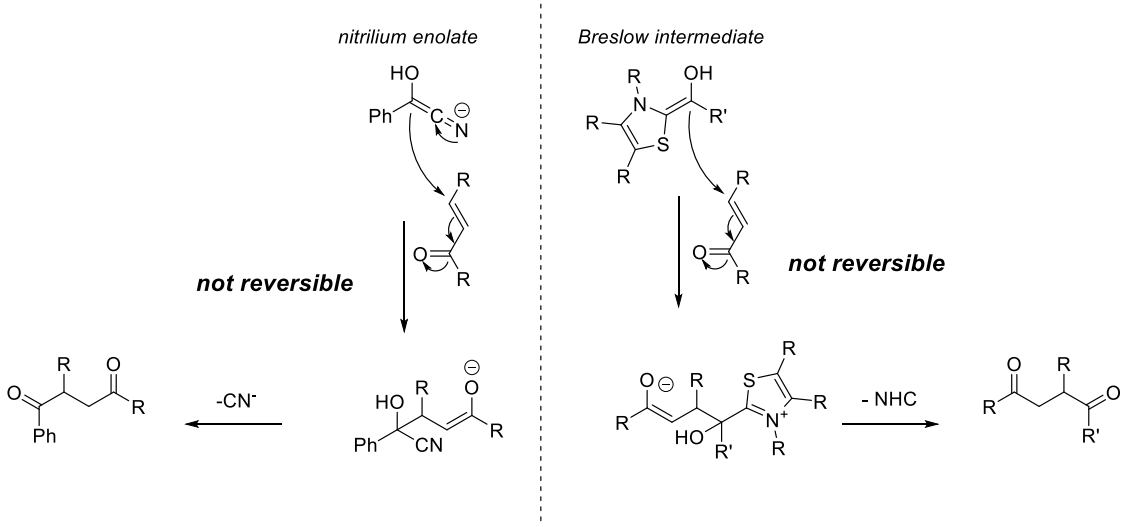
The mechanism for the NHC catalyzed benzoin reaction resembles the one catalyzed by cyanide. Usually, from a corresponding azolium salt the NHC catalyst is liberated by deprotonation *in situ*. Then, in both mechanisms the cyanide or the NHC attacks the aldehydes. After a proton shift, where the umpolung takes place, the active species is formed, the nitrilium enolate or the Breslow intermediate, respectively. These can then add to another aldehyde and after another proton migration the catalyst is cleaved, releasing the benzoin product. All steps in this reaction are in principle reversible, which allows to tune conditions towards the retro-benzoin reaction (Scheme 3).



Scheme 3: Mechanism of benzoin reaction catalyzed by cyanide and by NHC

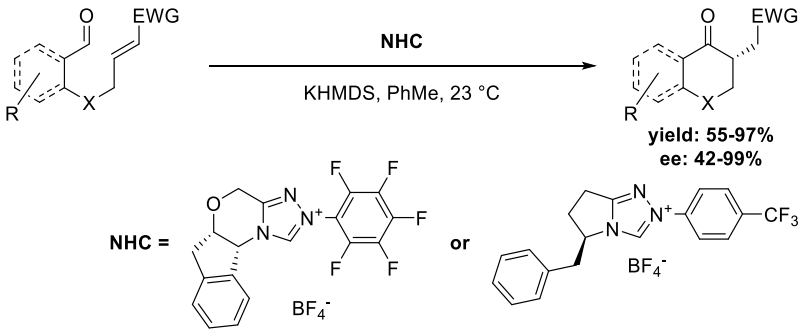
3.2.3 Stetter reaction

In the seminal work by Stetter in the early to middle 1970s he could show that benzaldehyde and activated α,β-unsaturated carbonyl species could be reacted to form 1,4-substitued keto derivatives, first, under cyanide catalysis[27] and, subsequently, also under NHC catalysis.[5] Mechanistically, the initial steps of the Stetter reaction are identical to the ones in the benzoin reaction, however, the nitrilium enolate or the Breslow intermediate is subsequently attacking the β-position of the α,β-unsaturated carbonyl species in a non-reversible manner. In turn, the catalyst is cleaved, yielding the substituted 1,4- diketo derivatives. [35]



Scheme 4: Mechanism of Stetter reaction

The scope and applications of this reaction have been significantly expanded since the days of Stetter, with e.g. de Alaniz having reported an asymmetric intramolecular variant of the Stetter reaction (Scheme 5).[36] Quite typical for NHC organocatalysis, fine tuning with respect to sterics and electronics was required to achieve the reported high yields and high enantioselectivity.

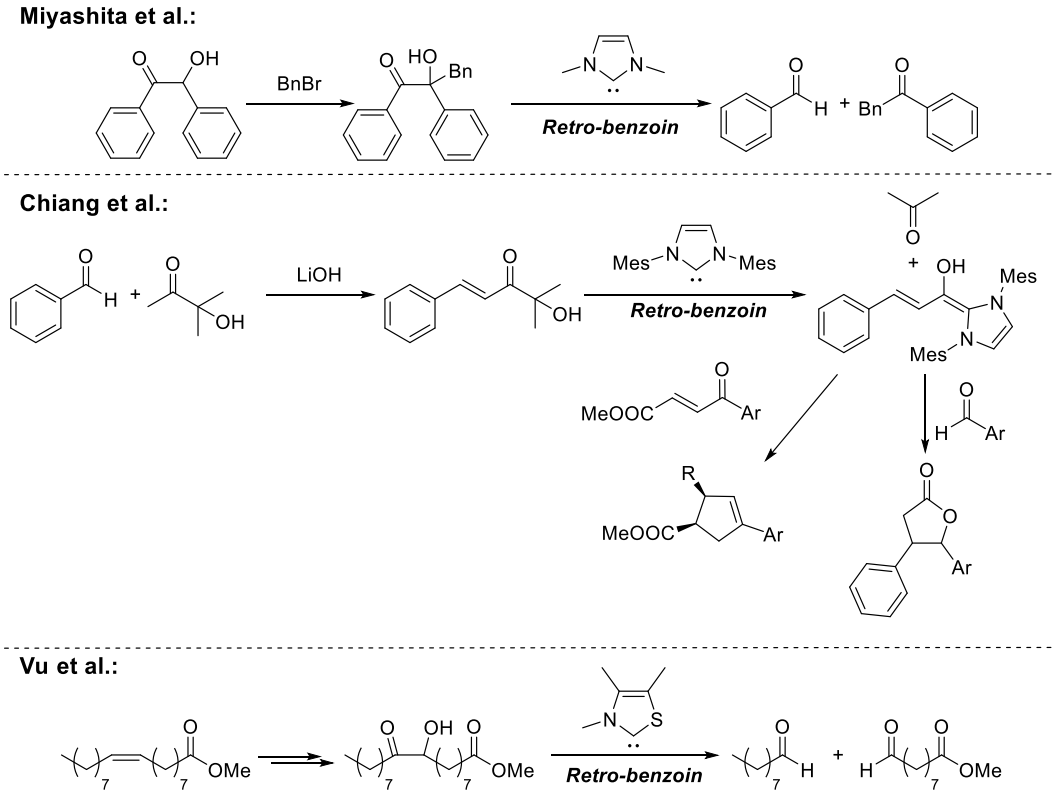


Scheme 5: Enantioselective intramolecular Stetter reaction, as employed by de Alaniz[36]

3.2.4 Retro-benzoin reaction

On the other hand, in the retro-benzoin reaction this reversibility to cleave α-hydroxyketones is exploited, forming two separate carbonyl species. For example, Miyashita showed that benzoins could be cleaved after α-alkylation to the respective aromatic ketones and benzaldehyde.[28] Chiang cross-coupled benzaldehydes with 3-hydroxy-3-methylbutanone to form masked and storage-stable cinnamaldehyde surrogates, that could be cleaved *in situ* to liberate acetone (*via* retro-benzoin) and form the respective Breslow intermediate of the corresponding cinnamaldehyde.[37] Recently, Vu *et al.* have demonstrated the cleavage of

unsaturated fatty acid *via* the corresponding α-hydroxyketones, yielding valuable aldehyde intermediates from renewable resources (Scheme 8).[38]



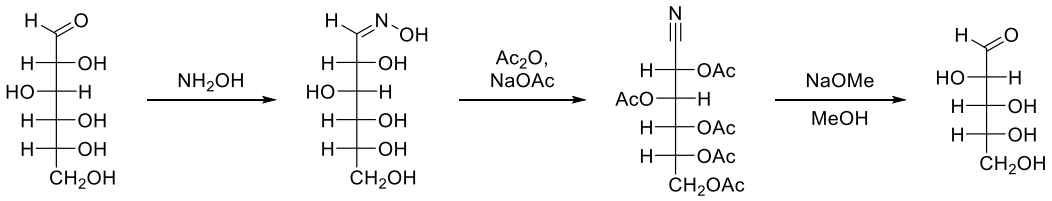
Scheme 6: Applications for the retro-benzoin reaction

3.3 Dehomologation reactions of Aldoses

A number of dehomologation reactions for sugars are known and date back as far as the late 19th century, addressing either the anomeric carbonyl function (Wohl degradation, MacDonald-Fischer degradation), C1-oxidized acid derivatives (Ruff degradation, Weerman reaction, Hunsdiecker reaction) or vicinal diols (Malaprade reaction, Criegee reaction). However, despite the numerous reactions known and some of them being known for over a century, most of them have their limitations when it comes to yield, number of steps or functional/protecting group tolerance as will be outlined below. Of course, some of these problems for now also apply to the dehomologation reactions reported in this thesis. In part, this is due to the interest in specific sugar substrates, that have a less straight-forward synthesis, but are necessary for their correct comparison. But most importantly, we are still in the learning phase, when it comes to the interesting interaction between NHCs and sugars and there are still several aspects we have to fully understand.

3.3.1 Wohl degradation

In a reversion of the Kilani-Fischer synthesis[39] Wohl in 1893 has first found a way to dehomologate carbohydrates via the corresponding hexose nitriles (Scheme 7).[40-41] First the oxime was formed with hydroxylamine that upon peracetylation can dehydrate (at least in the case of the syn oxime) to give the peracetylated aldose nitrile. While Wohl used an ammonia solution of Ag_2O for the elimination of hydrogen cyanide, followed by acidic deacetylation, Zemplén improved upon that procedure by using a sodium methoxide / methanol solution to achieve both steps at once.[42] Yields are reported in the range of up to 34% overall in the case of D-arabinose formation from D-glucose.[43-44]

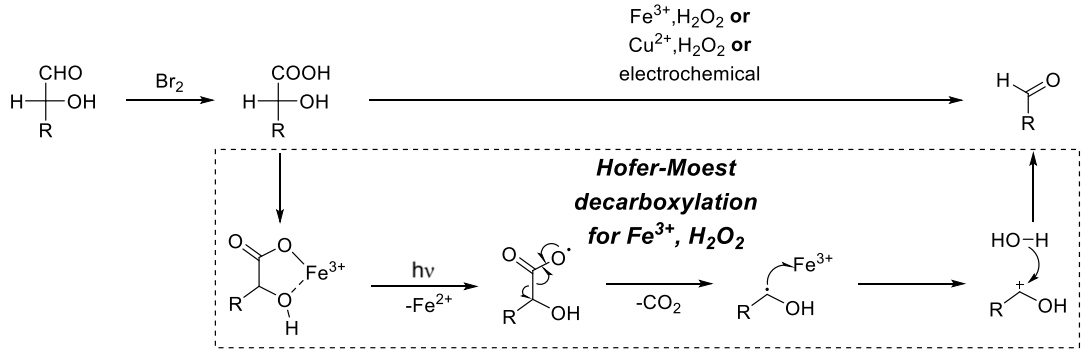


Scheme 7: Wohl dehomologation (Zemplén modification) shown for D-glucose

3.3.2 Ruff degradation

In the Ruff dehomologation aldonic acids (usually formed from the respective aldose with aqueous bromine) are oxidatively cleaved.[45-46] In the original report Fe^{3+} and H_2O_2 (Fenton's reagent) were used, variants replacing Fe^{3+} with Cu^{2+} [47] or switching to an electrochemical

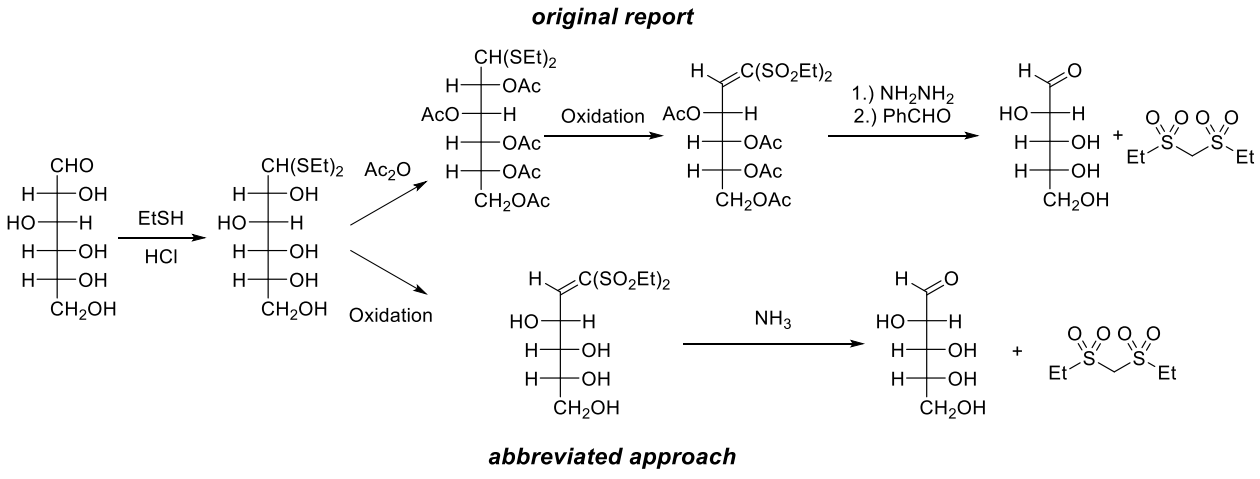
process are also known.[48] The latter has the benefit that it can also cleave uronic acids upon which a dialdose is formed.[48] The mechanism of this reaction is still being debated, with the most recent publications arguing in favor of a progress similar to a Hofer-Moest decarboxylation (Scheme 8).[49] Yields usually do not exceed 50% under classical conditions[49] and reach 60-65% with copper catalysis.[47]



Scheme 8: Ruff degradation with mechanism assuming Hofer-Moest decarboxylation

3.3.3 MacDonald-Fischer degradation

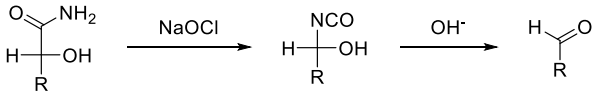
In the original report of the MacDonald-Fischer dehomologation the respective carbohydrate is first converted to its dithioacetal, followed by per-acetylation, oxidation of the dithioacetal to a disulfone and finally deacetylation and cleavage of bis(ethylsulfonyl)methane with hydrazine (Scheme 9). Yields are usually okay with 55-60% starting from the diethylmercaptale per-acetate sugar (and previous steps being reported in high to nearly quantitative yield[50-51]).[52-53] However, they could show in a later publication that at least for specific sugars the acetylation step could be by-passed resulting in an increase in overall yield to 80-83%.[54]



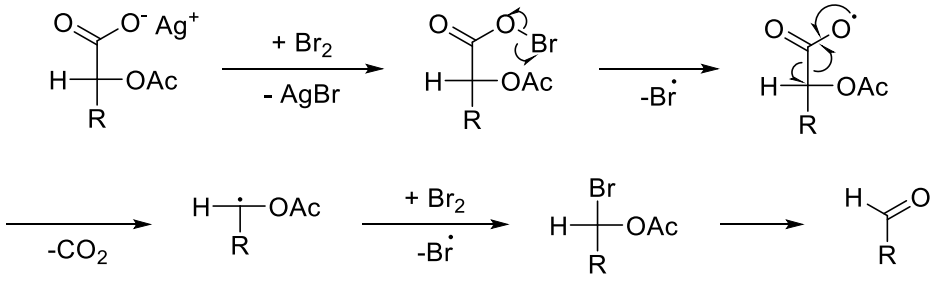
Scheme 9: MacDonald-Fischer degradation

3.3.4 Weerman and Hunsdiecker reaction

Two lesser mentioned dehomologation reactions are the Weerman reaction, cleaving the amide of aldonic acides[55] (Scheme 10), and the Hunsdiecker reaction, cleaving the carboxylate moiety of the silver salts of aldonic acids [56-57] (Scheme 11).



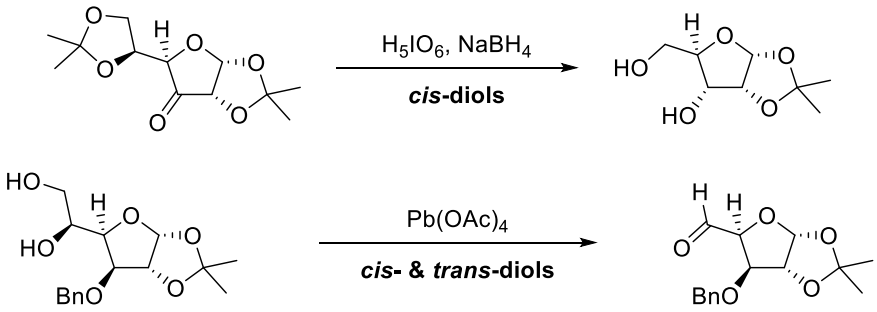
Scheme 10: Weerman reaction



Scheme 11: Hunsdiecker reaction

3.3.5 Malaprade and Criegee reaction

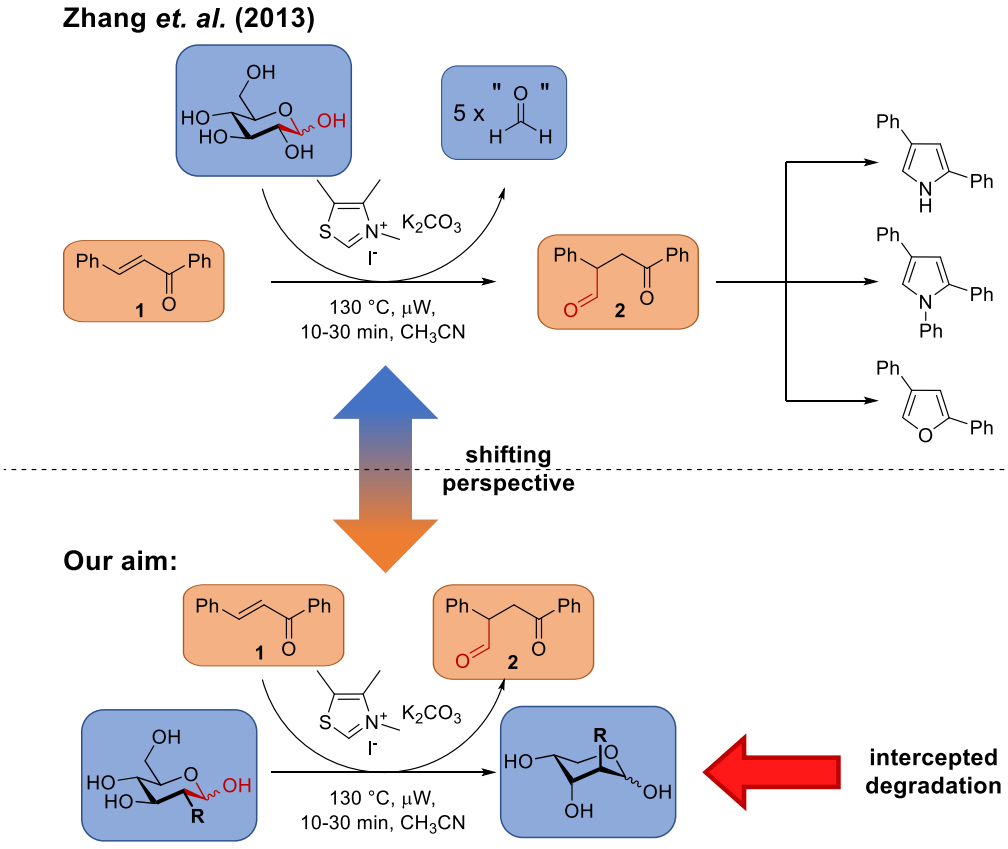
Both the Malaprade and the Criegee reaction are oxidative cleavage reactions of vicinal diols. While in the former case periodic acid or periodate species are used to selectively cleave *cis*-diols, the use of lead(IV) acetate enables also the oxidation of *trans*-diols (Scheme 21). This differentiates these reactions from aforementioned dehomologation reactions, as they are not limited to C1-dehomologation. With the abundance of diols in sugar species the selectivity for cis-diols of the Malaprade reaction makes it the standard approach and even allows good selectivity in certain unprotected sugars with only one cis-diol in the dominant ring-form.[58-59] In other cases an adequate protecting group pattern has to be installed first.



Scheme 12: Representative Malaprade[58] and Criegee reactions[60]

3.4 The NHC controlled aldose dehomologation

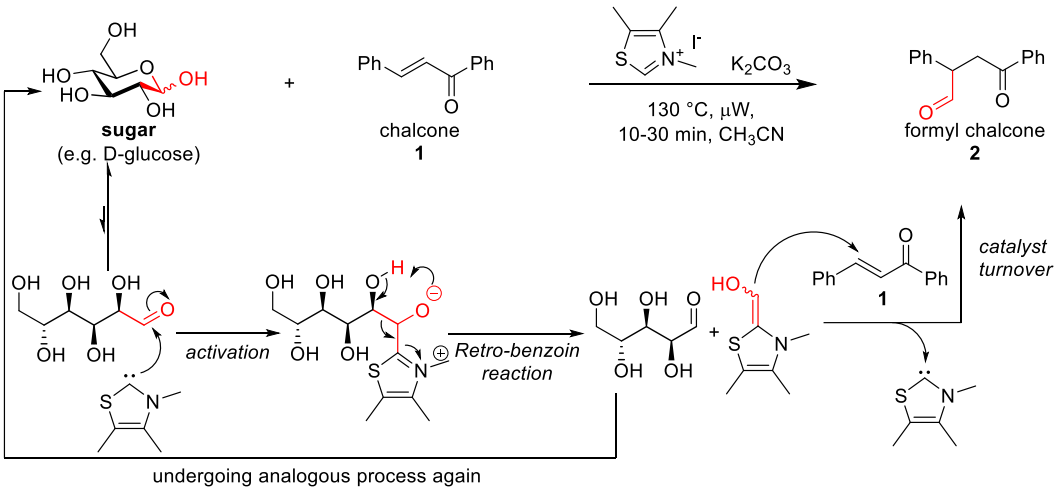
The idea for the overall project this thesis is part of was inspired by a recent publication by Zhang et.al.[61] Therein, they described an NHC catalyzed formylation of chalcones, α,β-unsaturated ketones, in a Stetter reaction. However, the necessary formyl equivalents cannot be obtained from formaldehyde directly, as formaldehyde would oligomerize (Formose reaction) rather than react with the chalcone under the reaction conditions.[62] Instead, common pentoses and hexoses were shown to be viable substitutes for formaldehyde, forming formaldehyde Breslow intermediates upon NHC attack and retro-benzoin reaction, without significant amounts of free formaldehyde being present at any time. Experiments confirmed that the shortened sugars are attacked again, as using as little as 0.20 equiv. of glucose still gave high yields of the formylated chalcone. In turn, these formylated chalcones were converted to furan and azole derivatives (Scheme 13, top).[61]



Scheme 13: NHC catalyzed degradation of sugars (top) and intercepted dehomologation (bottom)

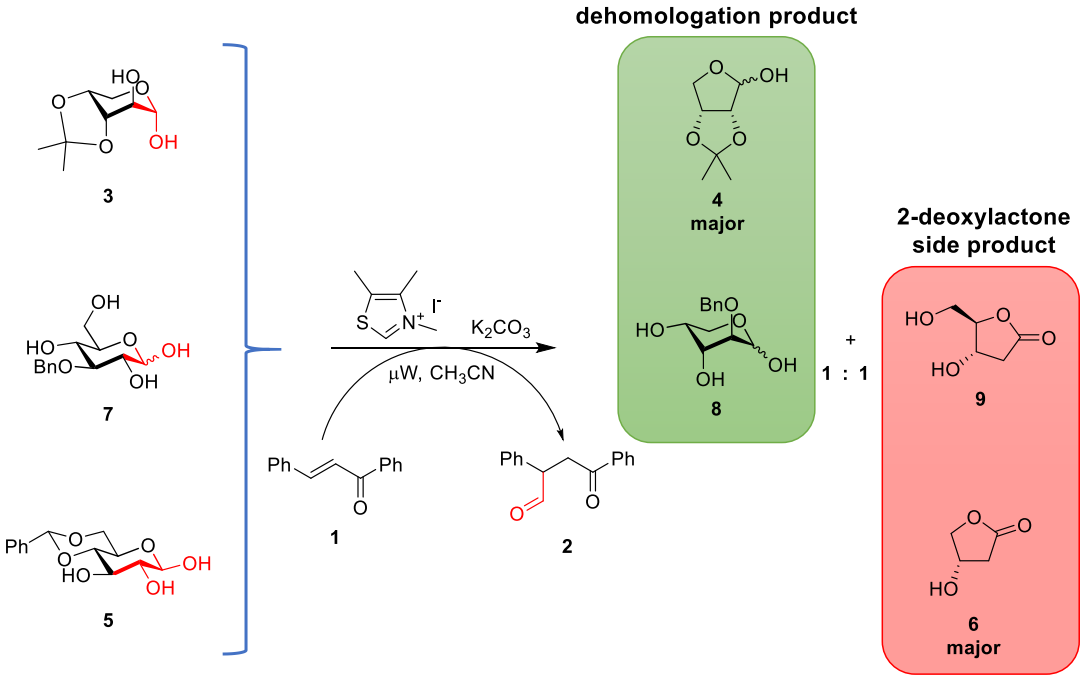
To us, this reaction had the intrinsic potential to yield rare or unnatural shorter carbohydrate derivatives, if the reaction can be intercepted at a specific position, by e.g. a suitable protecting group on the next position (Scheme 13, bottom) along the chain. This would also be in line

with the mechanism proposed in the original paper (Scheme 14). Successful implementation of such methodology could give convenient access to semi-protected derivatives of e.g. expensive tetroses and pentoses, for which applications are currently limited due to expensive starting materials or unavailable protecting group protocols. It can be employed as a single step selective 1,2-diol cleavage reaction, that - unlike $Pb(OAc)_4$ or $NaIO_4$ - leaves non-terminal *trans*-diols intact. The reaction also enables easy access to reducing pentosides, a class barely reported, then becoming directly available from abundant reducing hexosides.



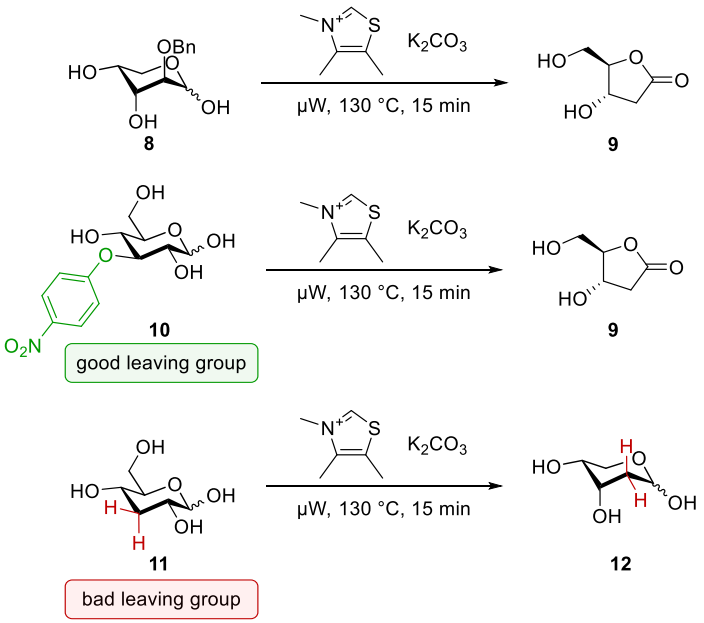
Scheme 14: Putative mechanism of NHC catalyzed degradation of carbohydrates[61]

Initial test reactions delivered the aspired proof of concept but also showed in some cases the formation of the corresponding 2-deoxylactone as a detrimental side-reaction under the reaction conditions. While with 3,4-*O*-isopropylidene-D-arabinose **3** the dehomologated sugar **4** was the primary product, 4,6-*O*-benzylidene-D-glucose **5** yielded predominantly deoxylactone **6** and 3-*O*-benzyl-D-glucose **7** gave a nearly equimolar mixture (Scheme 15) of targeted and side product **8** and **9**. Without a doubt further studies investigating the substrate dependence are required and 3-*O*-derivatives of D-glucose were chosen as initial starting point, as several derivatives (both with respect to substituent and sugar backbone) are accessible with relative ease. Any sort of structure-selectivity relationships reflected in a change in product ratio would more easily be detectable starting from the eventually formed 1:1 mixture than from cases of one dominant product. In the latter cases, a decrease in quantity of the minor species would be harder to detect.



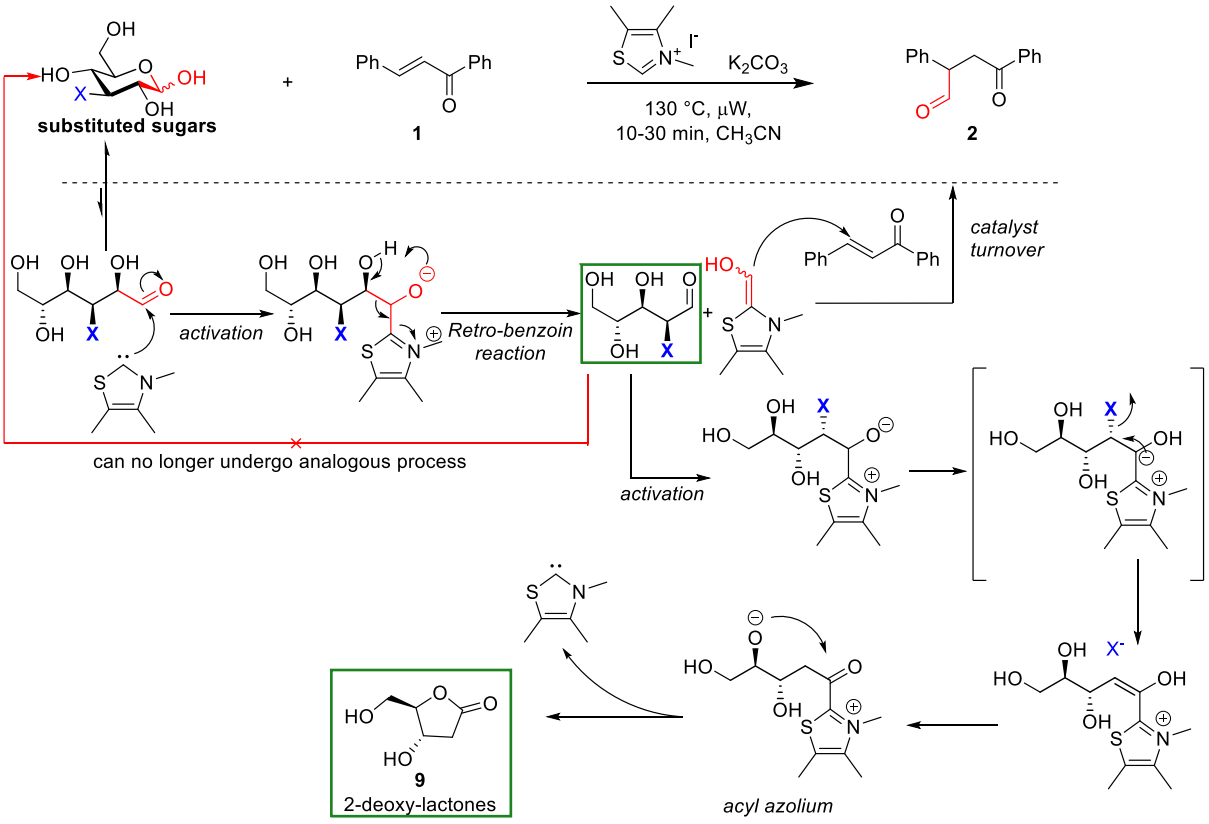
Scheme 15: Different ratios of dehomologation and side product discovered in initial test reactions

In a further experiment, it was shown that 2-*O*-benzyl-D-arabinose **8**, the dehomologation product of 3-*O*-benzyl-D-glucose **7**, reacts under the dehomologation conditions to the deoxylactone **9**. This observation confirms that the deoxylactone is a follow-up product after successful dehomologation. In turn, the substituent on C3 of D-glucose was altered to investigate the influence of leaving group capabilities.



Scheme 16: Experiments confirming the deoxylactone formation to be a follow-up reaction and investigating the influence of leaving group capabilities on the observed product

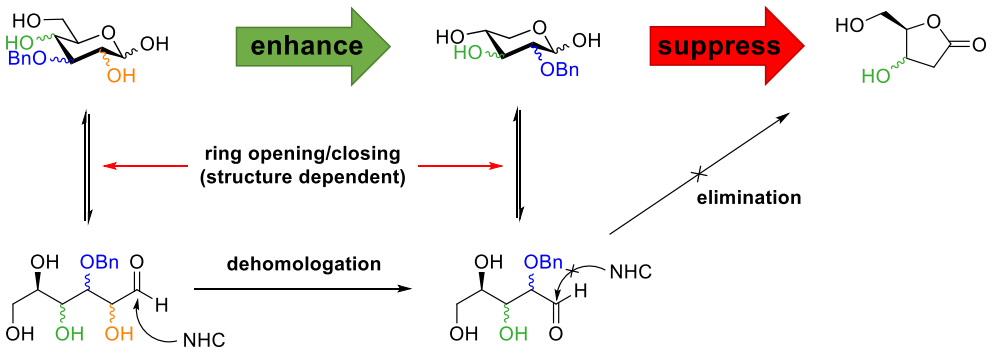
The installation of the 3-*O*-(4-nitrophenyl) group (**10**), a good leaving group, gave predominantly the deoxylactone **9**, while a very poor leaving group like hydride, present in 3-deoxy-D-glucose **11**, gave no deoxylactone but dominantly 2-deoxy ribose **12** (Scheme 16). These observations lead to the current working hypothesis of the mechanism indicating that after the intended dehomologation the catalyst activates the intermediate's carbonyl function. Incapable of further dehomologation a proton-shift induced elimination can occur, resulting in the formation of an acyl azolium species, that forms the 2-deoxylactone **9** after intramolecular attack (Scheme 17).



Scheme 17: General mechanism for dehomologation and follow-up elimination

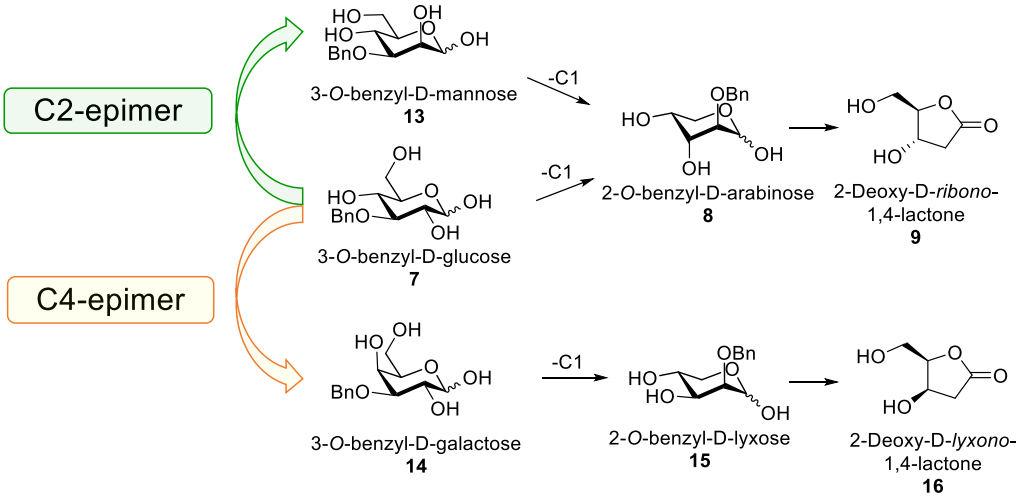
3.5 Aim of this thesis

The goal of the overall project was to develop a robust synthetic method for the controlled dehomologation of aldoses catalyzed by NHCs. Within this thesis, first insight into the interdependent influence of structure and reactivity was to be obtained, aiming at gaining further knowledge about and additional control over this challenging reaction. For sugars, this means primarily an alteration of stereochemistry in the target compound. For catalysts, a so far untested core structure was combined with different *N*-Aryl substituents.



Scheme 18: influence of stereochemistry on reactivity

With this intent, the focus of this thesis was threefold: (i) Initially, two isomers of the already studied 3-*O*-benzyl-D-glucose **7**, the C2-epimer 3-*O*-benzyl-D-mannose **13** and the C4-epimer 3-*O*-benzyl-D-galactose **14**, needed to be synthesized to evaluate the possible influence of relative stereochemistry in the substrate on the reaction (Scheme 19, left). In the case of the mannose derivative **13** this brings along the advantage, that the dehomologation and elimination product are identical with the ones of the glucose derivative **7** and had already been prepared by Dipl.-Ing. Markus Draskovits. In the case of the galactose derivative those reference materials either had to be prepared or, as was the case with the lactone, had to show a comparable behavior on GC analysis to act as a viable substitute.



Scheme 19: Dehomologation and elimination of the investigated hexose derivatives

(ii) Next, a series of catalysts with varying electronic and steric properties were targeted (Figure 5). The new class of thiazolium catalysts were to be examined for their ability to shift the product ratio in favor of the dehomologated sugar through variation of their *N*-substituent. The cycloheptane annulated thiazolium structure was chosen as a base scaffold, as several representatives have been shown in the literature to outperform other parent structures and their synthesis allowed for a straight forward variation of the respective substituents.[63]

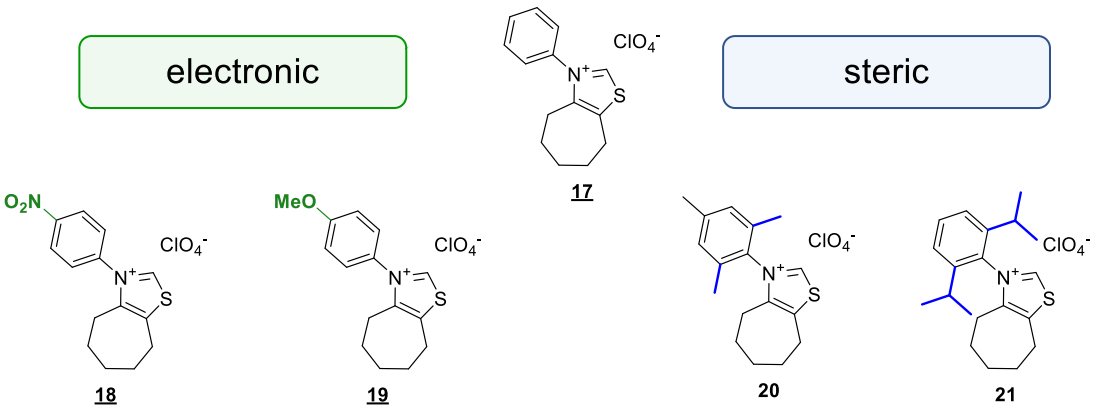


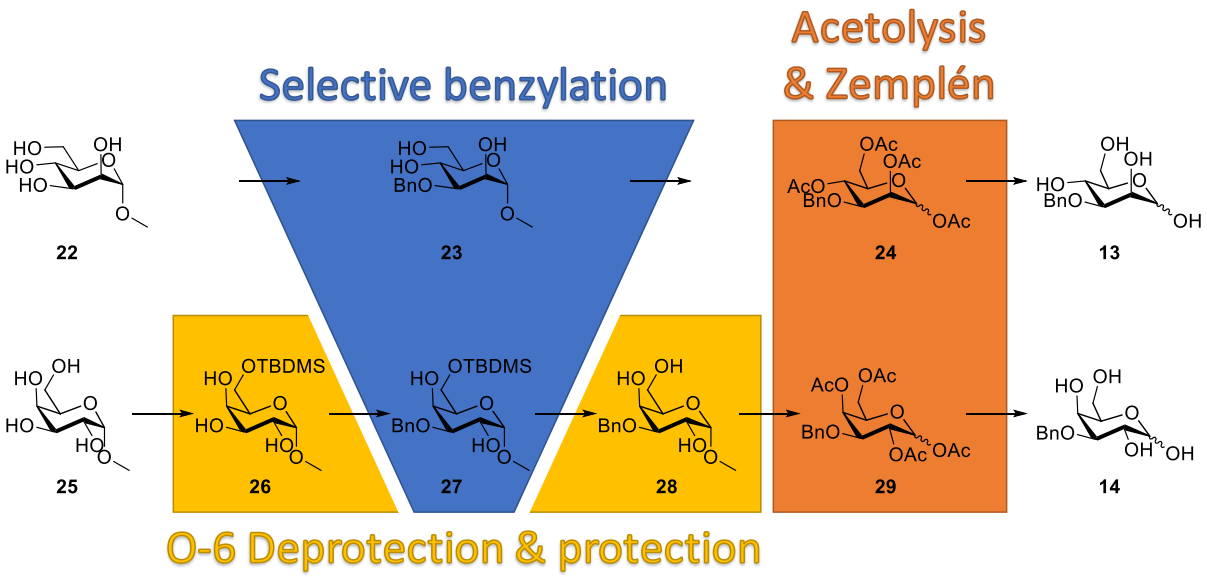
Figure 5: Target catalyst structures

(iii) Finally, the dehomologation reaction was meant to be tested with the three epimeric carbohydrate derivatives and the five prepared catalysts. To gain additional information about the kinetics of this reaction a time-resolved analysis was aimed for.

4 Results and discussion

4.1 Synthesis of 3-*O*-benzyl-D-mannose 13 and 3-*O*-benzyl-D-galactose 14

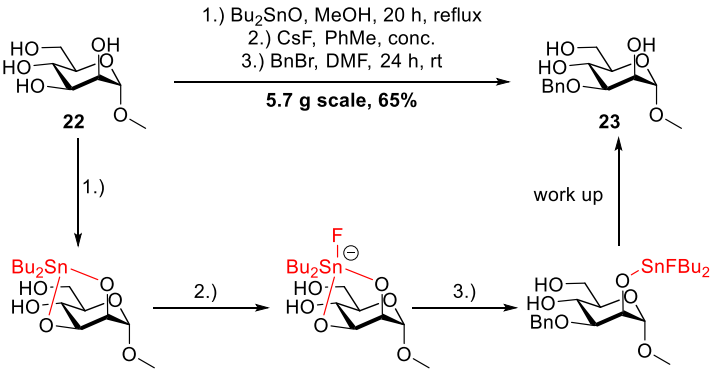
4.1.1 Alternative synthetic strategies towards selective 3-*O*-benzylation



Scheme 20: Synthetic strategy for the preparation of the two 3-*O*-benzyl hexoses

Both benzyl hexoses were prepared following a similar strategy, although employing two different procedures. Both synthetic routes start from the respective methyl α-pyranoside and feature a selective benzylation of the 3-O position as key step. In the mannose case **13** this is accomplished using stannylene acetal activation, while for the galactose derivative **14** more modern borinate catalysis was used. However, the latter requires prior installation of a temporary protecting group on 6-O position with TBDMS being selected. Finally, the methyl glycosidic bond is cleaved by acetolysis, which yields the peracetylated sugar derivative, and finally cleaving the ester bonds *via* Zemplén reaction (catalytic transesterification) (Scheme 20).

4.1.2 Stannylene acetale mediated benzylation of methyl α-D-mannopyranoside 22



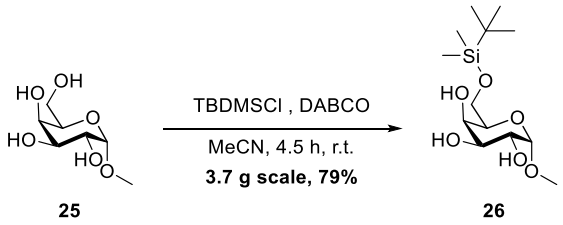
Scheme 21: Mechanism of DBTO activated selective benzylation.

For both the mannose and the galactose derivative, in contrast to glucose, no straightforward protecting group strategy is available, that would lead to a derivative without protecting group only in the 3*O*-position. Fortunately, for both alternative strategies are known *via* selective activation of the equatorial position of a *cis*-diol and concomitant blocking of the axial hydroxyl that allow introduction of the benzyl group in the 3*O*-position. The classical approach utilizing dialkylstannylene acetal activation was applied for the preparation of 3-O-benzyl-D-mannose **13**.

In the reaction with methyl α-D-mannopyranoside **22** dibutyltin oxide forms preferentially the 2,3-dialkylstannylene acetale as vicinale *cis*-diols are attacked predominantly. This intermediate yields the intended methyl 3-*O*-benzyl-α-D-mannopyranoside **23** after workup, as electrophilic substitution happens more prominently at the equatorial position. Nonetheless, selectivity can be further increased by adding caesium fluoride (alternatives are TBAF or *N*-methylimidazole), as the nucleophilic fluoride attacks the tin atom, further activating the intermediate towards benzylation.[64-65]

While the described reaction is definitely superior to any alternative lengthy protection and deprotection strategy, the method has unfortunately a number of drawbacks. Regioselectivity was still an issue; while the targeted species still formed predominantly, several incompletely separable regioisomers formed (in total <10%). Luckily, they could be completely removed after acetolysis in the subsequent step. The toxicity of the employed chemicals is noteworthy, as dibutyltin oxide, along with many other tin organyls, is known to be toxic and cause genetic defects.[66] Caesium fluoride is also toxic[67] and with both chemicals being used in stoichiometric amounts special care has to be taken, especially during work up and scale-up.

4.1.3 Catalytic borinate activated benzylation of the galactoside 26



Scheme 22: TBDMS protection

The protection of the primary 6-OH group required for the next step can easily be achieved by TBDMS etherification, having several advantages as protecting groups. First and foremost, an exquisite selectivity is observed for primary alcohol groups over secondary or tertiary. But also facile and selective cleavage conditions, easy analytics (giving e.g. only two singlets in the high field in ^{1}H-NMR not overlapping with other relevant proton signals) and higher stability to protic hydrolysis, a significant problem with TMS as protecting groups, is particularly noteworthy.[68-69] While at first pyridine was used as base following the literature procedure[70] yields significantly improved when switching to an in-house protocol[71] using DABCO instead. The use of 2.15 equiv. of TBDMS was required, as. methyl-α-D-galactopyranoside **25** is usually present as a hydrate, which resulted in consumption of 1.00 additional equiv. of silylation agent.[72] To confirm the position of the TBDMS group an NMR measurement in d6-DMSO was performed, preventing the OH hydrogen atoms from exchanging, as would be the case in solvents like CD_3OD or D2O. Thereby, the missing coupling between the hydroxyl group's protons and two hydrogen atoms on C6 could be shown, that exist for H2, H3 and H4 (H1 and H5 have no hydroxylgroup).

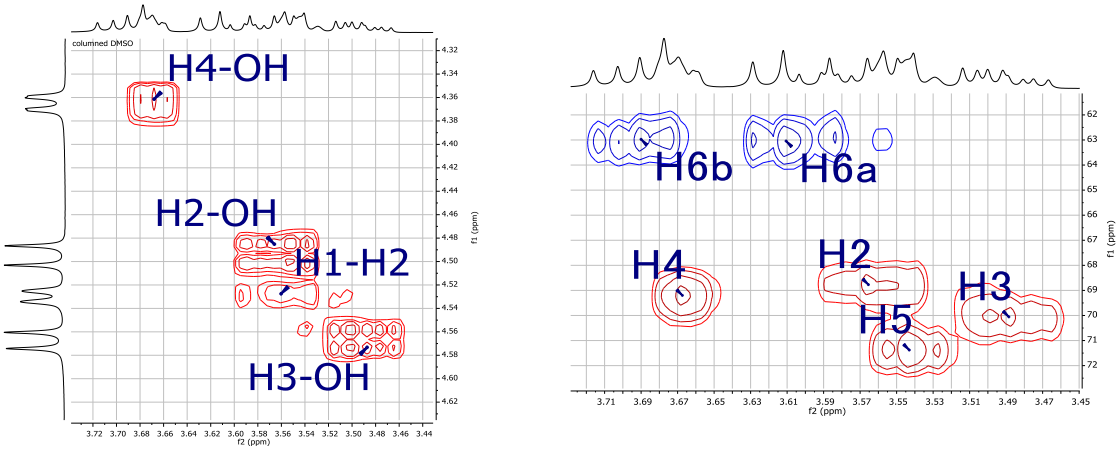
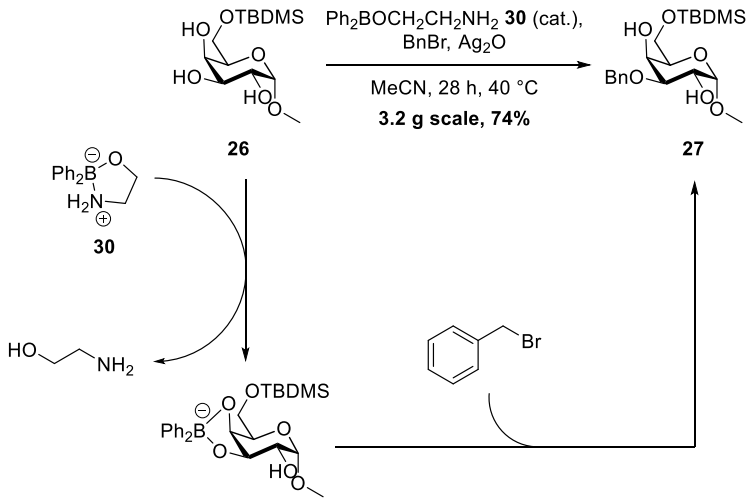


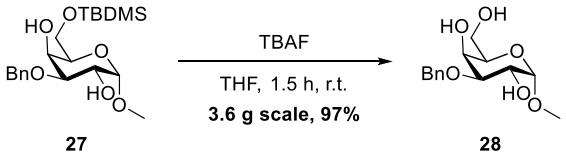
Figure 6: Details from COSY (left) and HSQC (right) spectra of Methyl 6-O-(tert-butyldimethylsilyloxy)-α-D-galactopyranoside 26



Scheme 23: Catalytic borinate mediated benzylation

Recently, however, an alternative approach to the stannylene acetale activation has been developed for the selective activation of diols by the group of Taylor. They could show that 2-aminoethyl diphenylborinate **30** (among similar reagents) can catalyze the substitution at the equatorial hydroxyl group of a *cis*-diols in a similar way compared to tin organyls.[70]

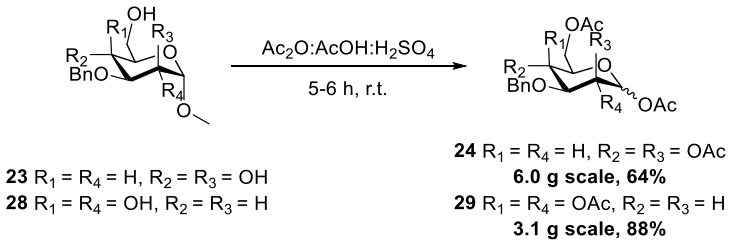
The higher selectivity and better overall yield of the borinate catalyzed reaction by far outweigh the increased cost of reagents, the required installation and cleavage of a protecting group and the inherent increase in the number of steps. In fact, the borinate method was successfully applied for the synthesis of the mannose derivative **13** outside of this thesis.[73]



Scheme 24: Desilylation of 27

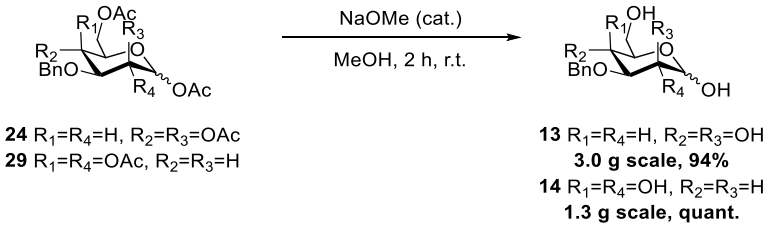
The silyl group in **27** was readily cleaved using TBAF affording the product **28** in near quantitative yield.

4.1.4 Methyl glycoside cleavage and final deprotection.



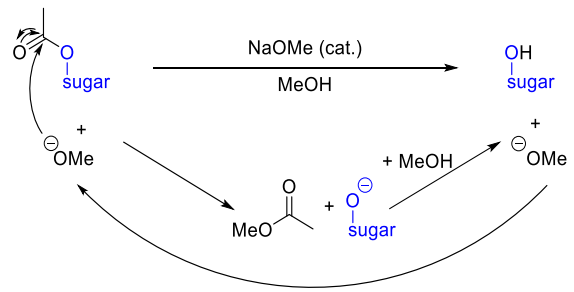
Scheme 25: Acetolysis of the two methyl pyranosides

The cleavage of the methyl glycoside in **23** and **28** was achieved by the concomitant acetylation/acetolysis Thereby, all free alcohol groups were acetylated, followed by the cleavage of the glycosidic bond by acetylation. This also enabled the separation of the various regioisomers of **23** (*vide infra*).



Scheme 26: Zemplén reaction

Another common method employed in carbohydrate synthesis is the Zemplén reaction, where catalytic amounts of sodium methoxide in MeOH (usually formed by adding small amounts of sodium to dry MeOH) are generally used to achieve complete deacylation. (Scheme 27).



Scheme 27: Deacetylation mechanism under Zemplén conditions

A high purity (> 95%) and a quantitative or close to quantitative yield was achieved. However, minor amounts of sodium acetate and sodium formate were still present in the isolated product. The base content was already known to have a significant impact on the following

dehomologation, which is why further purification using column chromatography was performed, nonetheless.

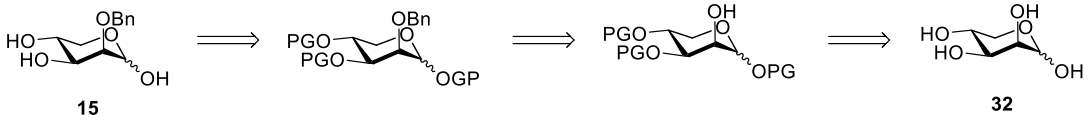
As a single step alternative to the acetolysis and Zemplén protocol, direct acidic hydrolysis of the methyl glycoside **28** was attempted. However, this led to a significant degree of additional cleavage of the benzyl group, resulting in the formation of D-galactose **31** as byproduct. For **23** the purification at the peracetate stage of acetolysis was necessary and, therefore, direct hydrolysis was no option to begin with.

While the stannylene acetale mediated approach contained less steps, the borinate catalyzed strategy gave at the cost of two simple and high-yielding additional steps a significantly less complicated side-reaction profile, establishing this approach to be significantly easier applicable. During writing of this thesis, the borinate strategy was also successfully applied to the synthesis of the other sugar, 3-*O*-benzyl-D-mannose **13,** by a student working at the group.

4.2 Synthesis of 2-*O*-benzyl-D-lyxose 15

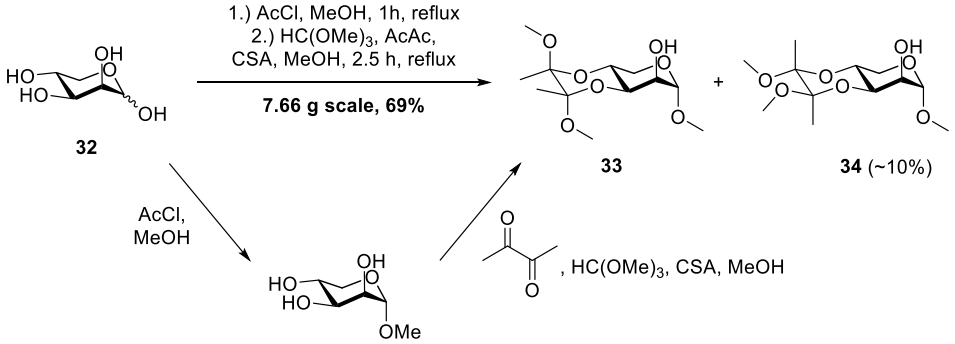
4.2.1 Synthetic strategy

The synthesis of 2-*O*-benzyl-D-lyxose **15** had to be conducted starting from free D-lyxose **32**, as no other inexpensive or viable protected lyxose derivative was commercially available. Both stannylene acetale and borinate catalyzed activation require a *cis*-diol, but lead to the alkylation of the equatorial hydroxyl group, which would be the wrong one in this case. Therefore, an alternative strategy had to be found. In the end, it was decided to employ a strategy that selectively protects all hydroxyl groups except for the one in position 2 that can in turn be selectively benzylated. The other protecting groups were to be cleaved again, yielding the target compound **15** (Scheme 28). As for the protecting groups, a wide array of methods exists to protect the anomeric position, but regular Fisher glycosylation is already sufficient in this case. The other two hydroxyl groups on position 3 and 4 can be addressed using the BDA (butanediacetal) protecting group that is selective for diequatorial vicinal diols.



Scheme 28: Synthesis strategy for 2-*O*-benzyl-D-lyxose 15

4.2.2 Fisher glycosylation and BDA protection of the diequatorial diol of D-lyxose

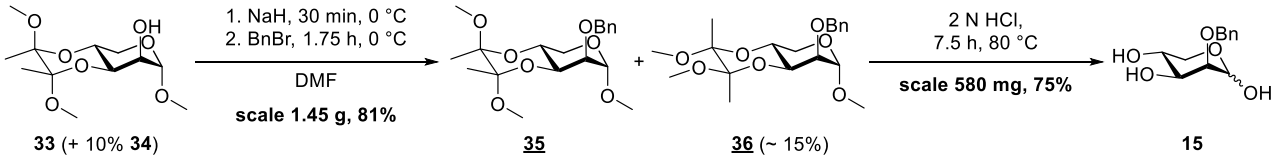


Scheme 29: Protection of positions 1, 3 and 4 of lyxose

In a first step, acetyl chloride in dry methanol formed defined amounts of hydrochloride *in situ* catalyzing the Fisher glycosylation of free D-lyxose **32** to the respective methyl glycoside which was used in crude form. The protection of positions 3-O and 4-O was achieved by *trans*-ketalization with 2,3-butanedione. Only vicinal diequatorial diols are capable of forming a six-membered dioxane ring, that is further stabilized by the anomeric effect of the two neighboring

methoxy groups.[74] This product **33** was isolated together with the inseparable isomer **34** in a content < 10%, which, however, yields the same target compound in the end. Therefore, the reaction sequence was continued with the product mixture. Recently, a similar by-product was observed in the BDA protection of methyl α-D-galactopyranoside **25**, which could be - upon derivatization – isolated and characterized as the galactopyranoside isomer similar to **34** (equatorial methoxygroups).[75]

4.2.3 Benzylation of 1,3,4-protected D-lyxose 33 and global deprotection



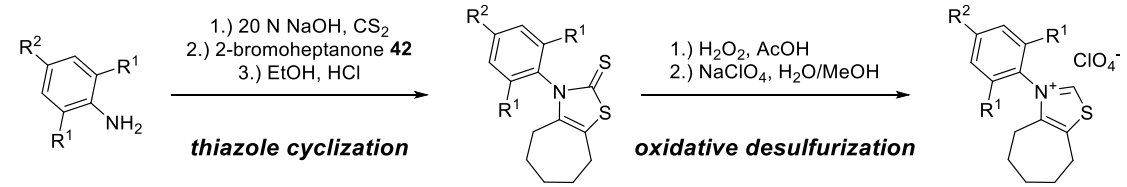
Scheme 30: Benzylation of the protected lyxose derivative

The previous protecting group procedure left the hydroxyl group on 2-position solely unprotected. As a result, a standard benzylation procedure with BnBr and NaH in DMF could be employed to obtain product **35** in good yield (accompanied by isomer **36**; Scheme 30).

In the final step, acidic conditions cleave both protecting groups yielding **15**. However, the reaction parameters had to be carefully optimized, as extended reaction time or elevated temperature led to additional cleavage of the benzyl group as side-reaction, while incomplete conversion was observed under milder conditions. It therefore seems, that 2-*O*-Bn-lyxose **15** is more stable to acidic conditions than 3-*O*-Bn-galactose **14**, when recalling the unsuccessful acidic cleavage of methyl galactoside **28**.

4.3 Synthesis of NHC precatalysts

Commercial trimethylthiazole catalyst was successfully used by Zhang and co-workers to conduct their unselective experiments (see section 3.4). *N*-Alkylthiazoles, however, face the drawback, that stereoelectronic and even steric tuning is only possible to a limited extend. In contrast, *N*-aryl thiazoles allow straightforward variation and were selected for this survey. Therefore, substituents with varying electronic and steric properties were chosen to be investigated in the following screening. In total five NHC precatalysts were prepared with each having a different *N*-substituent: phenyl **17**, 4-nitrophenyl **18**, 4-methoxyphenyl **19**, mesityl **20** and 2,6-diisopropylphenyl (dipp) **21**. Thereby, a closer understanding of the influence of the *N*-aryl substituent on the reaction outcome was aimed at.



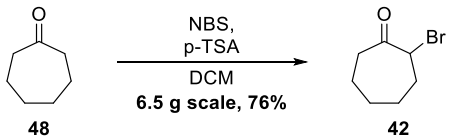
37 R^1=R^2=H,
38 R^1=H, R^2=NO_2,
39 R^1=H, R^2=OMe,
40 R^1=R^2=Me,
41 R^1=*i*-Pr, R^2=H

43 R^1=R^2=H,
44 R^1=H, R^2=NO_2,
45 R^1=H, R^2=OMe,
46 R^1=R^2=Me,
47 R^1=*i*-Pr, R^2=H

17 R^1=R^2=H,
18 R^1=H, R^2=NO_2,
19 R^1=H, R^2=OMe,
20 R^1=R^2=Me,
21 R^1=*i*-Pr, R^2=H

Scheme 31: General reaction scheme for NHC precatalyst preparation

Two of them, mesityl (**20**) and dipp (**21**) substituted structures were already described in the literature.[63] The general synthesis described was adopted for the other three derivatives successfully, however have not been optimized.



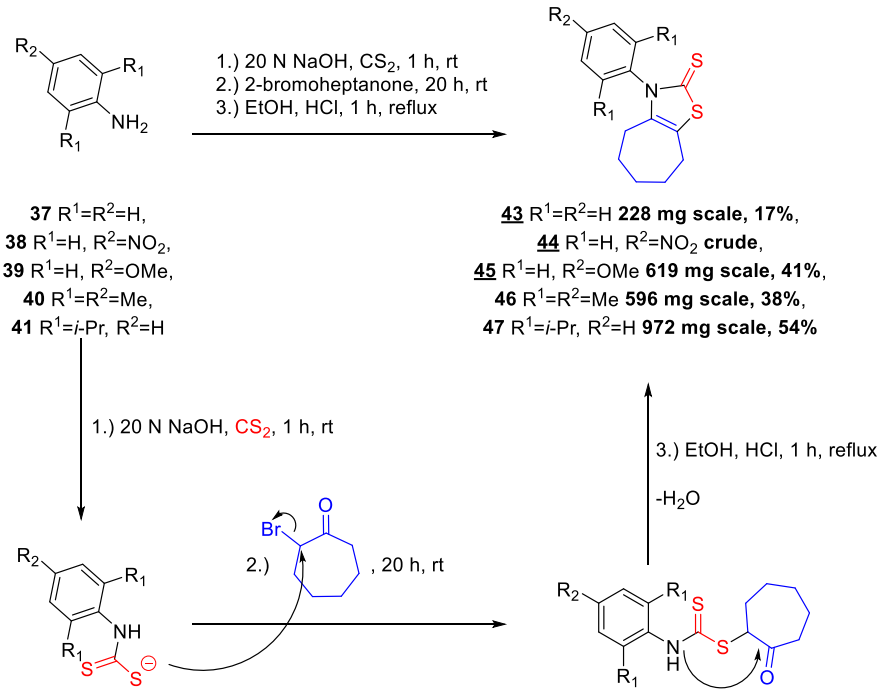
48 **42**

Scheme 32: α-bromination of cycloheptanone

The required 2-bromocycloheptanone **42** was prepared *via* α-bromination from cycloheptanone **48** using NBS as a brominating agent and p-TSA as acid (Scheme 32).[76] Minor amounts of 2,7-dibrominated ketone were also formed, but could be separated *via* distillation.

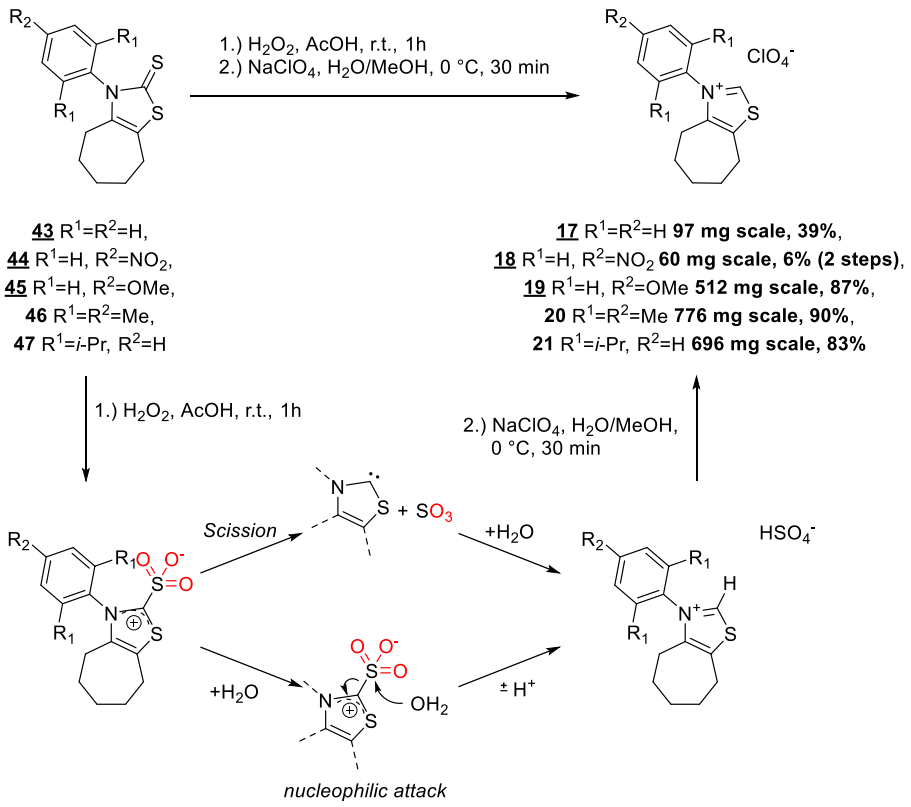
In the next step thiazole-2-thiones were formed from the variety of corresponding anilines. Therefore, the aniline of the *N*-aryl substituent was converted to its dithiocarbamate with 20 N

NaOH in DMSO and CS_2. This intermediate was reacted with 2-bromoheptanone **42**, enabling nucleophilic substitution of the bromine and subsequent cyclization by condensation upon change of pH to acidic conditions (Scheme 33).



Scheme 33: Mechanism of thiazole-2-thione cyclization

The obtained thiones (**43, 45, 46** and **47**) were isolated and in a separate step, the thione group was oxidized to the sulfonate, which under these conditions leads to elimination of SO_3. Two mechanisms are described in the literature, which might as well happen in a concurrent fashion: either the reaction is initiated by a C-S bond breaking, resulting in the formation of the carbene. This, in turn, gets protonated under the strong acidic conditions, yielding the target compound. Alternatively, nucleophilic substitution on sulfur releases the NHC moiety as a carbanion, that, in turn, also gets protonated, forming the precatalyst species.[77] Finally, anion exchange with $NaClO_4$ yields the respective perchlorate salt (Scheme 34).



Scheme 34: Mechanism of oxidative thione cleavage and anion exchange

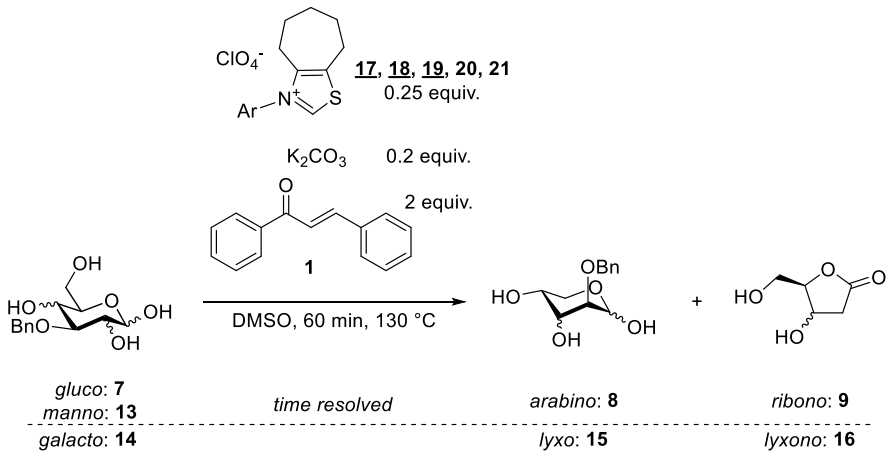
As both reaction steps are hard to monitor and were not reoptimized, yields are in part low to mediocre due to the fact that purification of intermediates relies on their physical properties, as isolation is based crystallization. The yields and scales for the two steps of each catalyst are compiled in Table 1.

Table 1: Scale and yields of both steps in NHC precatalyst synthesis

substituents		*thiazole cyclization*			*oxidative desulfurization*		
R^1	*R^2*	number	scale (g)	yield (%)	number	scale (mg)	yield (%)
H	*H*	**43**	0.23	17	**17**	97	39
H	*NO_2*	**44**	0.36	crude	**18**	60	6 (2 steps)
H	*OMe*	**45**	0.62	41	**19**	510	87
Me	*Me*	**46**	0.60	38	**20**	780	90
i-Pr	*H*	**47**	0.97	54	**21**	700	83

4.4 Time-resolved screening

4.4.1 Challenges and realization of the screening



Scheme 35: Standard reaction conditions for the dehomologation assay

To evaluate the various catalyst and sugar combinations a precise set of conditions has to be chosen to allow for comparability of the results. While they might not reflect the optimal performance of each catalyst or the best result obtainable from each sugar, they are likely to indicate general drivers for reactivity, selectivity and recovery of material.

Origin of the standard conditions for the screening

A previous optimization of conditions led to the set of parameters used for this screening (Scheme 35). An excess (second equiv.) of chalcone 1 was used to avoid side-reactions of the Breslow intermediate. An excess of base over the precatalyst had been shown to accelerate undefined degradation, however, the base was also shown to be clearly required for the deprotonation of the precatalyst. DMSO was chosen as a solvent, as it enabled the use of stock solutions for all components (except K_2CO_3), thereby significantly facilitating and improving reproducibility of the screening process at the small scale. The high temperature of 130 °C was required, as lower temperatures with several other catalysts did not show conversion or inferior selectivity and recovery. However, recovery also dropped upon extended reaction time. Therefore, samples were taken before heating (t0) and after 1, 3, 5, 10, 20, 30 and 60 min. The initial sample (t0) helped to more accurately determine the actual substrate concentration and the increasing time intervals were chosen to more closely observe changes at the beginning of the reaction, while still monitoring the recovery loss at the end.

Challenges in the analysis of crude mixtures

In order to evaluate changes in reactivity, selectivity and recovery, it is necessary to be able to determine reliably and efficiently the content of each sugar derived species in the samples for an increasing number of substrates. However, both starting material and dehomologation product are present in multiple anomeric forms and are very challenging to quantify or even distinguish *via* NMR or HPLC, as the respective signals tend to overlap heavily. Therefore, great effort was put into the identification and establishment of a robust, fast and quantifiable protocol for the analysis of the relevant components, starting material, targeted compound and sideproduct (deoxylactone). The method of choice is based on a solid phase extraction – derivatization and GC protocol which was established by Markus Draskovits, who is a PhD student on the project.

Analytical procedure

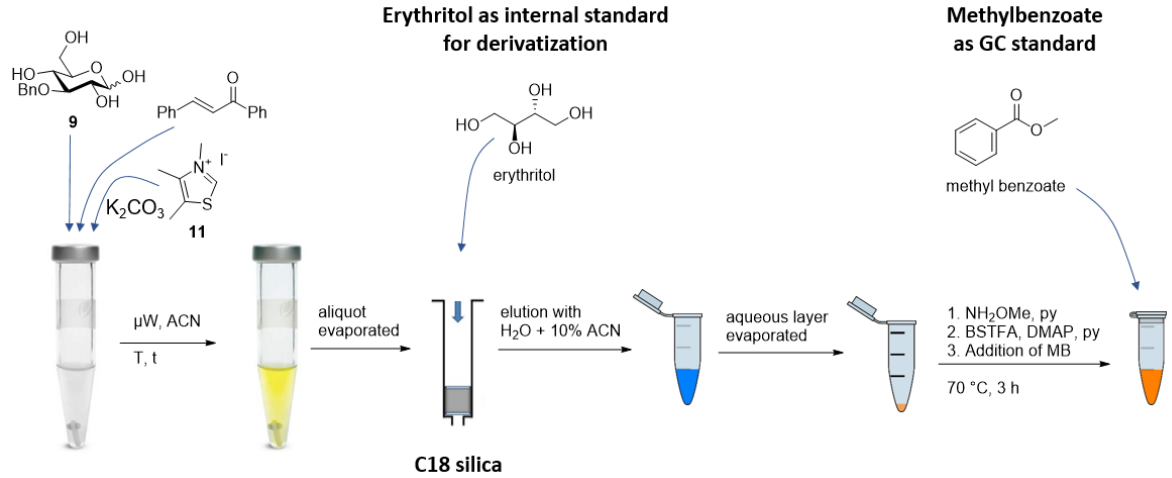


Figure 7: Workflow for sampling – processing derivatization and GC-analysis

For processing a large number of individual samples, a straight-forward routine protocol, like the one employed and described in the following, can greatly simplify the workflow. First, an aliquot was taken, a defined amount of erythritol-stock was added as a silylation standard and the solution was concentrated under reduced pressure. Therefore, any losses during the manipulation of the sample would be reflected in the change from the defined standard concentration. Next, the crude mixture was taken up in MeCN:H_2O (1:4) and flushed over a short SPE-C18 column, retaining the chalcone species which had been shown to give overlapping peaks with the analytes in the GC. Next, a derivatization protocol was used that first transforms the reducing sugars into their *O*-methyloximes, reducing the number of species to two diastereoisomers per compound, which were converted to per-TMS ethers. An aliquot of the so obtained solution was then diluted with a stock solution of methyl benzoate in EtOAc,

as GC standard to accurately monitor the sample volume injected. Finally, the analysis was conducted using a calibrated GC method (Figure 7). The exact procedure for the dehomologation and derivatization is described in the experimental part (see 5.4 General procedure for NHC-catalyzed dehomologation). The contents of the three analytes were calculated from the corresponding peaks' integrals and the respective calibration curves. For each catalyst-sugar combination a bar graph was generated, that had the content of each analyte and their sum blocked for each time point and color-coded as depicted in Figure 8. An example is shown in Figure 9, all bar graphs are displayed in section 5.4.

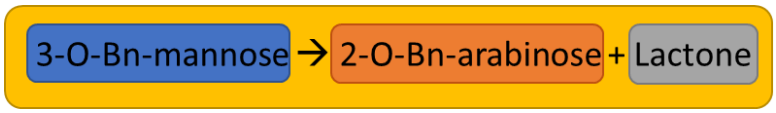
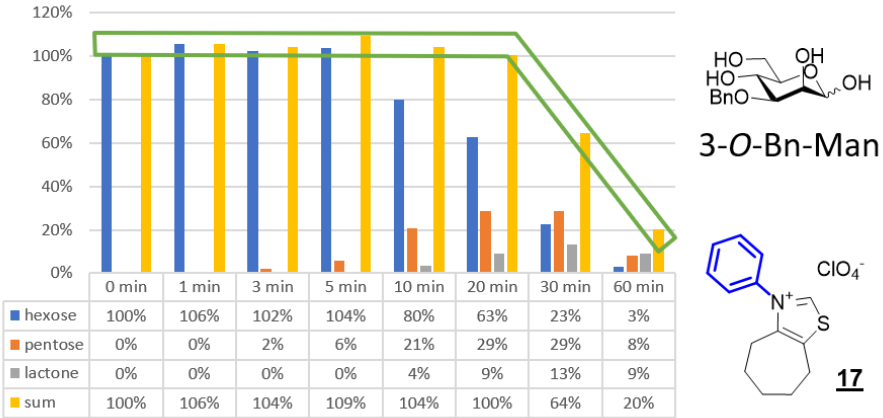


Figure 8: Color-code for the depiction of the analytical data

4.4.2 Degradation upon extended reaction time

A loss in recovery was already a known problem from previous experiments and was still an issue here. In all cases, where dehomologation occurred, total recovery of the three identified species, 3-O-benzyl hexose, 2-O-benzyl pentose and 2-deoxylactone, stayed rather constant, before it started dropping significantly after a period of 10 to 20 min at the investigated temperature of 130 °C. After 60 min at that temperature, generally 20% or less total recovery was observed (Figure 9 for the reaction of 3-*O*-Bn-mannose **13** with phenyl catalyst **17** as an example).



	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	106%	102%	104%	80%	63%	23%	3%
pentose	0%	0%	2%	6%	21%	29%	29%	8%
lactone	0%	0%	0%	0%	4%	9%	13%	9%
sum	100%	106%	104%	109%	104%	100%	64%	20%

Figure 9: Problem of unidentified degradation over time, exemplified on the data from the phenyl catalyst 17 and 3-O-benzyl-d-mannose 13

We attributed this effect initially to thermal degradation, as sugar derivatives are able to oxidize or decompose at elevated temperatures and the reaction solution visibly turned dark. However, no other peaks appeared in the GC analysis, even after 60 min. Therefore, the side-reaction occurring must significantly affect the properties of the analytes, either causing them to be already retarded on the C18 column, or even after derivatization preventing them to be detectable on GC.

Due to the combination of the dehomologation product being formed and the degradation taking place an optimal time frame exists, where the highest benzyl pentose concentration was detected. This time point was selected for comparison and, in all cases, it was at the 20 min time point (Table 2).

Table 2: Pentose content of the investigated sugar-catalyst combinations after 20 min

	3-O-*Bn-Glu* **7**	*3*-O-*Bn-Gal* **14**	*3*-O-*Bn-Man* **13**
Phenyl catalyst ***17***	12%	10%	29%
4-Nitrophenyl catalyst ***18***	0%	0%	2%
4-Methoxyphenyl catalyst ***19***	13%	13%	30%
Mesityl catalyst **20**	18%	15%	39%
Dipp catalyst **21**	23%	29%	78%

4.4.3 Comparison of the performance of the epimeric carbohydrates

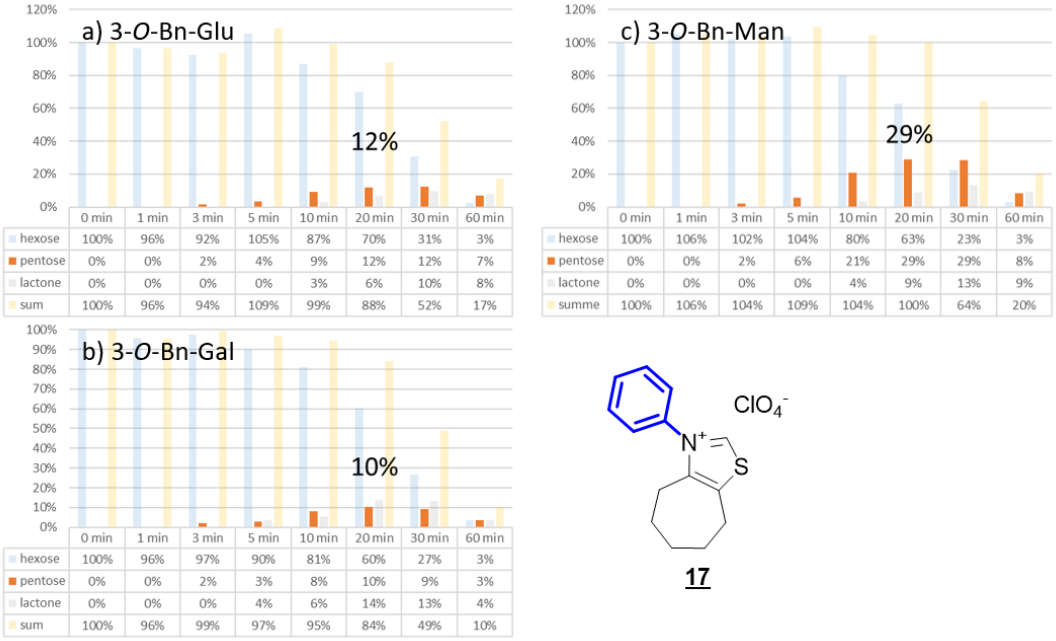


Figure 10: Comparison between carbohydrate derivatives as shown for the phenyl catalyst

For the three investigated sugars a general pattern could be identified. With all catalysts tested (parent *N*-phenyl catalysts **17** shown in Figure 10) 3-*O*-benzyl-D-mannose **13** (Figure 10, c)) gave a significantly better conversion to the targeted 2-*O*-benzyl-pentose than 3-*O*-benzyl-D-glucose **7** and 3-*O*-benzyl-D-galactose **14**, which performed similarly (Figure 10 a) and b)).

4.4.4 Influence of the electronic properties of the aryl substituents on conversion

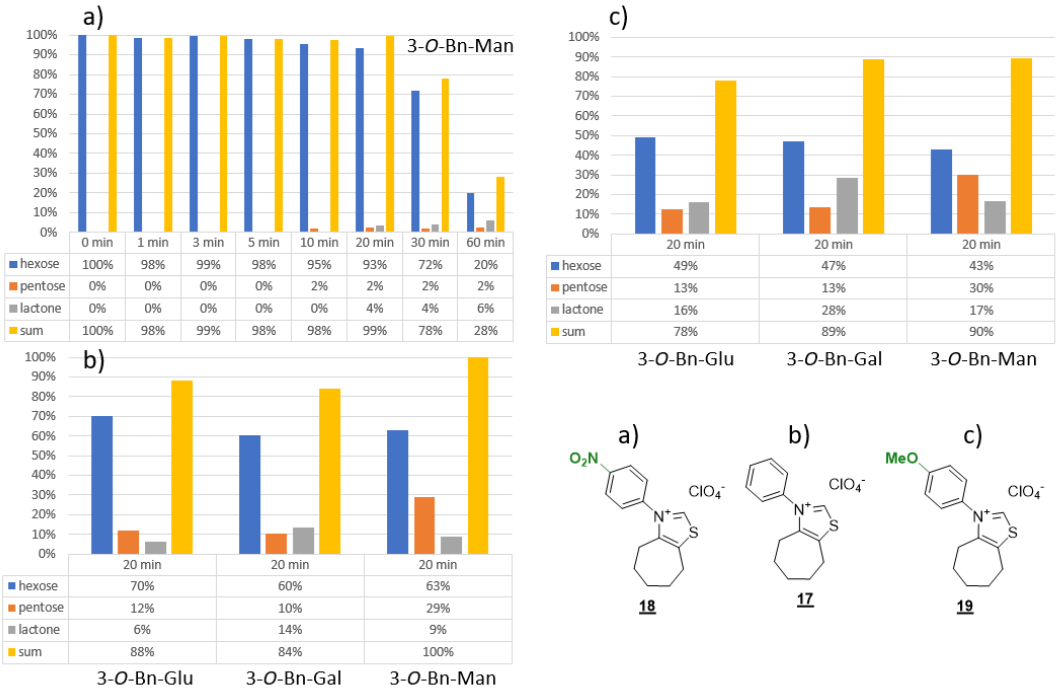


Figure 11: Influence of electronic properties of *N*-aryl substituents on reactivity; a) 4-nitrophenyl catalyst 18 (no reactivity), b) phenyl catalyst 17, c) 4-methoxyphenyl catalyst 19

Time-resolved screening of catalysts was performed with *N*-aryl substituents executing varying electronic properties: neutral (*N*-phenyl catalyst, **17**), electron-withdrawing (*N*-(4-nitrophenyl) catalyst, **18**) and electron-donating (*N*-(4-methoxyphenyl) catalyst, **19**). Apparently, the presence of the nitro group is sufficient to deactivate the catalyst to the point, where it is no longer able to participate in the reaction efficiently. Even with the generally best performing sugar 3-*O*-benzyl-D-mannose **13** only trace amounts of dehomologation and elimination product could be found (Figure 11, a)). In contrast, the introduction of the 4-methoxy group had only a slightly accelerating effect over the unsubstituted phenyl group. While the content of dehomologation product was roughly the same, a higher lactone content in the experiments with the methoxyphenyl catalyst **19** indicated that the catalyst is capable of accelerating both dehomologation and elimination reaction (Figure 11).

4.4.5 Influence of the steric properties of the aryl substituents on reactivity

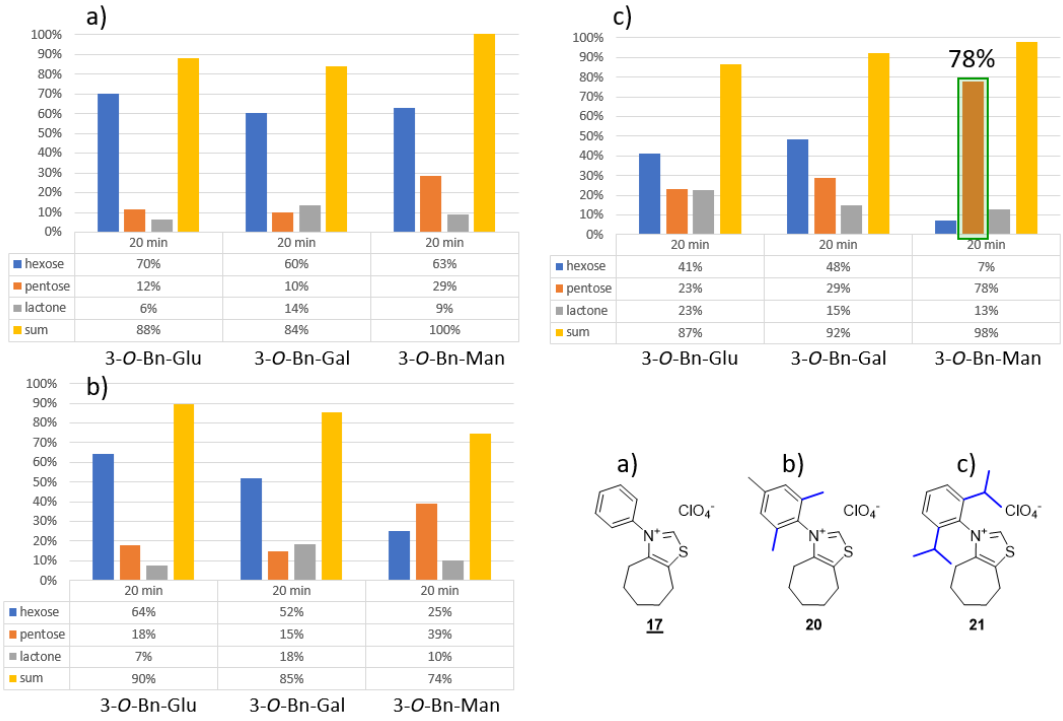


Figure 12: Influence of steric properties of aryl substituents on reactivity; a) phenyl catalyst 17, b) mesityl catalyst 20, c) dipp catalyst 21

The next family to be compared consists of three catalysts bearing substituents with increasing steric bulk in the order from **17** (phenyl catalyst) to **20** (mesityl catalyst) and **21** (dipp catalyst). Here, a more significant effect was observed with the different hexoses. Already with a mesityl substituent **20** the content of the benzyl pentose significantly increased, compared to the phenyl substituent by 30-50% relatively or 6-10% absolutely. This effect becomes even more pronounced with the dipp substituent **21**, where for the mannose derivative a content of pentose of 78% was determined which represents an unprecedentedly high selectivity for the overall project. Also, with the other sugars the highest pentose contents over the whole screening were determined with this catalyst, however again at lower levels. With this breakthrough closer investigations of this catalyst-substrate combination were of great interest to understand the reason behind this satisfyingly different behavior.

4.4.6 Closer investigation of dipp catalyst

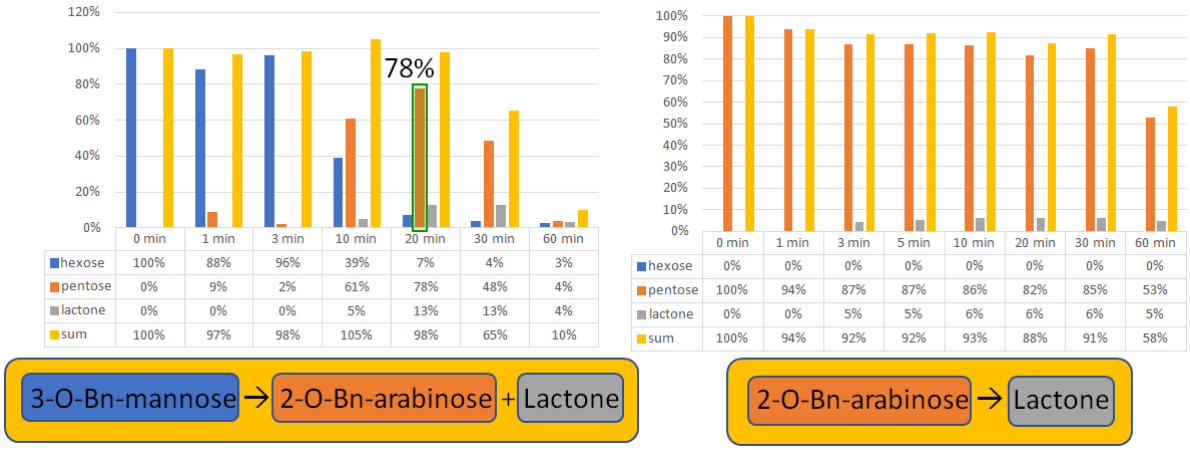
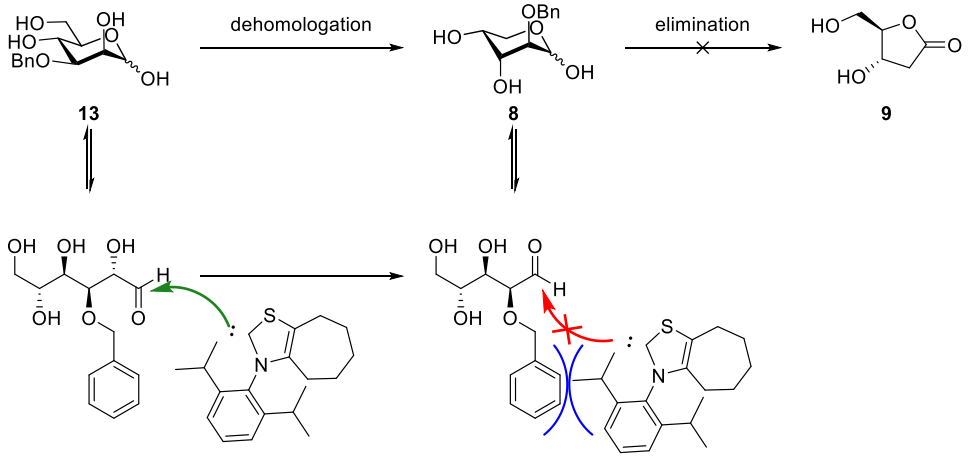


Figure 13: 3-*O*-Benzyl-D-mannose 13 and 2-*O*-benzyl-D-arabinose 8 subjected to dehomologation conditions with dipp catalyst 21

As mentioned in the last section, the combination of 3-*O*-benzyl-D-mannose **13** and dipp catalyst **21** gave an unprecedented high 2-*O*-benzyl-pentose content, while, at the same time, only small amounts of lactone were formed. In an attempt to understand this, 2-*O*-benzyl-arabinose **8**, the dehomologation product of 3-*O*-benzyl-D-mannose **13** (and 3-*O*-benzyl-D-glucose **7**) was subjected to the reaction conditions and investigated in a time-resolved screening. To our surprise, barely any lactone formation occurred (< 6%). This indicates that with the sterically demanding *N*-aryl substituent the initial attack of catalyst **21** on the carbonyl is still possible, thus leading to the desired dehomologation. However, steric demand of the dipp group prevents the second attack at 2-*O*-Bn-arabinose **8**, which is probably imposed by the bulky 2-*O*-benzyl group in position 2, thereby truly intercepting all further reactivity of this mechanism (Scheme 36).



Scheme 36: Steric clash preventing the second attack and hence the elimination

4.5 Next approaches for yet unresolved questions and possible further improvements

Thermal degradation

The loss of all observed species with extended reaction time poses a significant problem. Not only does it limit the interpretation of the later determined data points (does the degradation affect all species equally?), but also the general application of the dehomologation is limited to species that react fast enough. No new species were determined *via* this GC method, which would either imply that products with significantly different properties were formed or something else is happening. In the former case, a reasonable solution for this problem would be to search for catalysts, which are able to perform this reaction at lower temperatures than the harsh 130 °C. Another theory would be, that some of the corresponding analytes might be reacting with the formed formyl chalcone **2**, possibly after NHC activation. This formyl chalcone was so far not quantified, as significant overlaps with some of the sugar derived analytes in all tested analysis methods was unavoidable, including the finally employed GC protocol. Therefore, it was removed via extraction with Et_2O or SPE prior to derivatization. In case this proves to be true, a closer analysis of the decomposition products might confirm this reactivity and other catalysts or chalcone derivatives might be able to avoid it.

Catalyst screening becomes catalyst development

Following the discovery of the highly selective dipp catalyst, a more targeted catalyst screening incorporating *N*-aryl substituents with high steric demand is planned. Especially the combination with a triazolium based catalyst **49**, that led to clean lactone formation and showed hardly any loss in recovery, is of particular interest. One example for future design is represented by replacement of the phenyl groups adjacent to the carbene with dipp groups, leading to structure **50**. Along this line, we hope to achieve the same high reaction rates with low loss of recovery, however, thus intercepting the reaction at the dehomologation step for more examples (Figure 14).

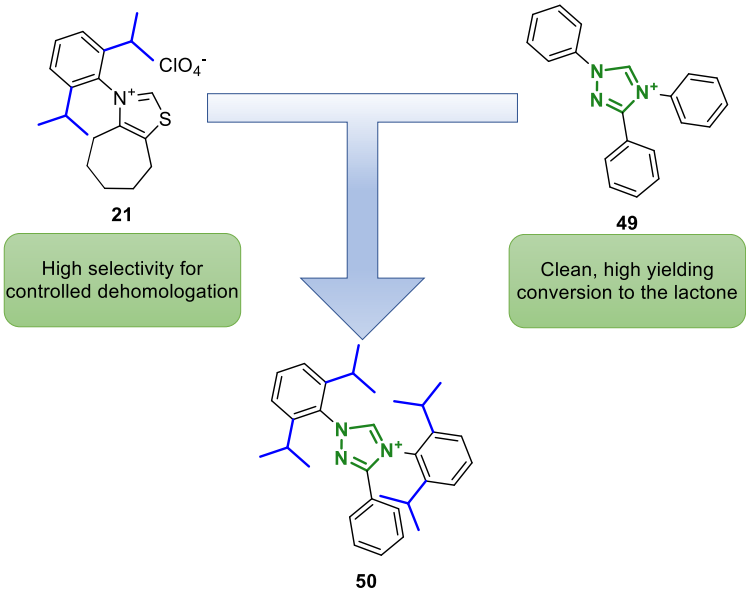


Figure 14: Future experience driven catalyst synthesis

Influence of relative orientation of 2,3 substituents on reactivity

Another aspect requiring further investigation is the significant difference in reactivity between the glucose and galactose derivatives (same O2/O3-stereochemistry) compared to the mannose structure. A significant difference in the open chain content would explain this behavior, as it is the open chain form actually participating in the reaction. These are, however, not trivial to determine with currently existing methods. Alternatively, the relative orientation of the hydroxyl group in 2-position and the benzyl group in 3-position might be reason for the different reactivity. The synthesis and screening of other sugars with *cis*-configuration might allude to these hypothesis (Figure 15). However independent, there must be another side-reactivity be going on, at least with (slow) 3-O-Bn-glucose, that needs to be elucidated and or prevented.

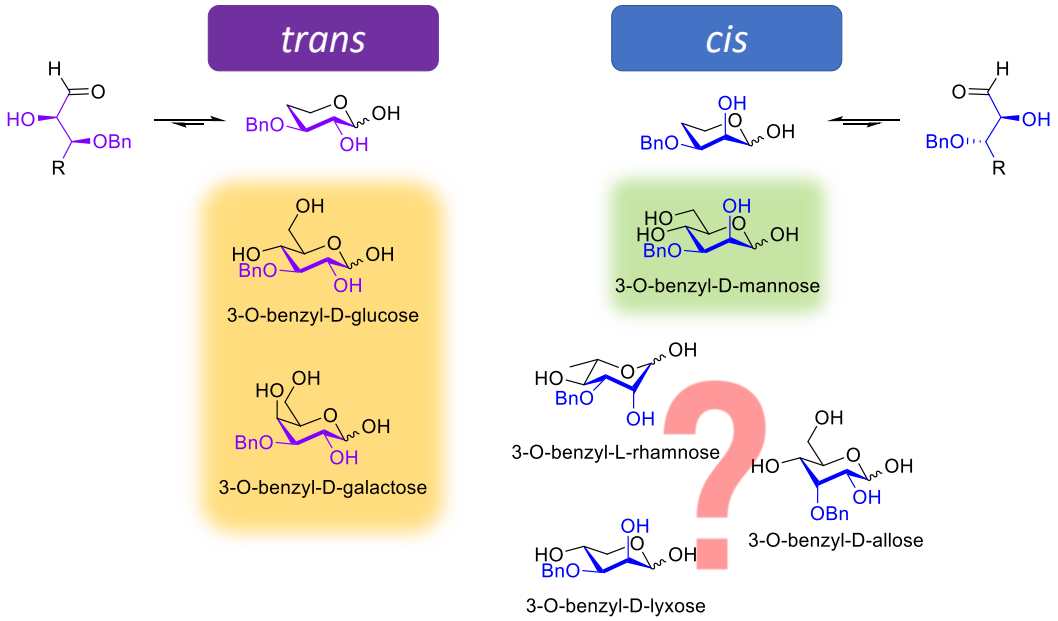


Figure 15: Does the relative 2,3-orientation of the substituents affect the difference in reactivity between mannose and glucose/galactose and to which extend does open chain content affect it?

4.6 Conclusion and Outlook

Three sugar derivatives were synthesized in 3 to 6 steps as representative substrates for the dehomologation. Additionally, 5 thiazolium-based precatalysts were prepared in 2 steps, partly already in a data-driven optimization effort. Each combination of sugar and catalyst was tested in the NHC catalyzed dehomologation of aldoses in a time-resolved and quantitative screening allowing to draw first structure/reactivity and structure/selectivity relations for this complex reaction.

Keeping the *N*-phenyl substitution as first reference point, installation of the 4-nitrophenyl substitution lead to essential loss of catalytic activity under the investigated conditions with all sugars. In contrast, the 4-methoxy catalyst gave a slightly faster conversion but still only comparable conversion to the pentoses, due to a slightly smaller selectivity between targeted dehomologation and follow-up lactone formation. The introduction of steric demand in the catalyst's *N*-substituent generally led to an increased conversion to dehomologated sugar, with the dipp-subsituted catalyst **21** outperforming all other catalysts tested so far in this project. With this catalyst yields up to 78% (based on GC) in case of the D-mannose derivative **13** were achieved. Remarkably, this catalyst was highly selective for the dehomolgation reaction and no significant conversion to lactone **9** of 2-*O*-Bn-arabinose **8** was found (neither in the cascade reaction nor in a separate control experiment starting from the already dehomogated compound); this coincides with the high recovery under otherwise constant reaction conditions. This breakthrough is assumed to be due to sufficient steric demand of catalyst's large dipp group to clash with the dehomologated sugar's benzyl group in position 2.

5 Experimental part

5.1 General methods

5.1.1 Reagents and solvents

All chemicals were used directly from commercial sources and used without further purification. Water-free solvents were available at the institute from a PureSolv EN 1-4 Enclosed solvent drying plant. Light petrol for column chromatography was distilled prior to use. MeCN was dried by refluxing it over CaH_2 for several hours, before collecting it by distillation. Amberlyst 15 was washed with the respective solvent prior to use. Ratios of liquids used as solvents or as eluents are given as volume ratios.

5.1.2 TLC

TLC analysis for reaction monitoring and analyzing fraction from column chromatography was performed on silica gel 60 F254-plates or HPTLC-plates (silica gel 60 F_{254} with concentration zone 20×2.5 cm) with LP/EtOAc, DCM/MeOH or $CHCl_3$/MeOH/H_2O as eluents. The spots were visualized using UV light (254 nm) followed by staining the plates with anisaldehyde solution (180 ml EtOH, 10 ml anisaldehyde, 10 ml H_2SO_4 conc., 2 ml AcOH), potassium permanganate solution (3.0 g $KMnO_4$, 20.0 g K_2CO_3, 250 mg KOH, 300 ml H_2O) or cerium molybdate solution ("Mostain", 21 g $(NH_4)_6Mo_7O_{24}{\cdot}4\ H_2O$, 1 g $Ce(SO_4)_2$ 31 ml H_2SO_4 conc., 500 ml H_2O).

5.1.3 Column chromatography

Generally, column chromatography was performed on a Büchi Sepacore Flash System with two Büchi Pump Modules C-605, a Büchi Pump Manager C-615, a Büchi UV Photometer C-635 and a Büchi Fraction Collector C-660 with silica gel from Merck (40-63 µm; self-packed columns). As eluent gradients of EtOAc in LP or MeOH in DCM were used.

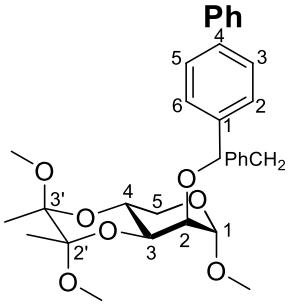
5.1.4 Melting points (m.p.)

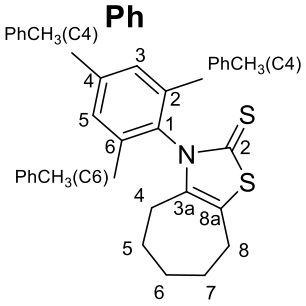
Melting points were determined with a Kofler-type Leica Galen III or a BÜCHI Melting Point B-545, with a heating rate of 1.0 °C and a 40%/90% threshold.

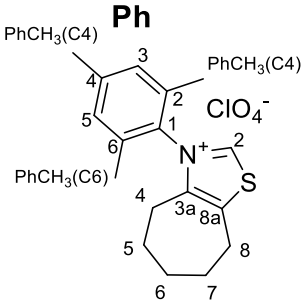
5.1.5 NMR

NMR spectra were recorded from $CDCl_3$, D_2O, CD_3OD or DMSO-d_6 solutions. For 400 MHz ^{1}H-NMR and 101 MHz ^{13}C-NMR an Avance UltraShield 400 spectrometer was used, for 600 MHz ^{1}H-NMR and 151 MHz ^{13}C-NMR an Avance III HD 600 spectrometer. All spectra were

calibrated to the solvent residual peak.[78] Chemical shifts (δ) are reported in ppm, coupling constants in Hz. Assignments were based on COSY, HSQC and HMBC experiments. The positions were labeled following IUPAC nomenclature, with some representative, more complex examples being given here:







5.1.6 Specific rotation

A modular circular polarimeter (Anton Paar MCP 500) with a 100 mm long cuvette of a 3 mm diameter was used for measuring the specific rotation of chiral compounds. Specific rotations were measured at 20 °C and a wavelength of 589 nm with the noted solvent of HPLC purity, or in the case of $CHCl_3$ of technical purity, and with the concentration being given in g/100 mL. The solutions of reducing sugars were prepared in advance, the respective time being given, to allow them to equilibrate between their anomeric forms.

5.1.7 GC

GC analysis was carried out on a Thermo Finnigan Focus GC/DSQ II equipped with a standard capillary column (BGB5, 30 m x 0.25 mm ID, 0.50 µm film) and an FID detector. Carrier gas: helium, injector: 230 °C; column flow: 2.0 mL/min; oven program: 50−180 °C (60 °C/min) → 180−310 °C (20 °C/min) → 310 °C (2 min). Analysis was carried out on the Chrom-Card data system by Thermo Fisher Scientific (GC OCX Ver: 6.2.0.0).

5.1.8 GC-MS

GC-MS spectra were measured on a Thermo Trace 1300 / ISQ LT (single quadrupole MS (EI)) using a standard capillary column BGB 5 (30 m x 0.25 mm ID). The standard method employed uses a temperature program of 2 min at 100 °C, ramping up to 300 °C at a rate of 35 °C, where it is kept for another 4 min.

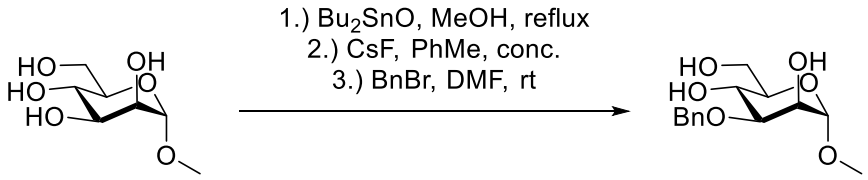
5.1.9 HR-MS

All HR-MS samples were dissolved in HPLC grade MeOH, MeCN or water. The analyses were carried out at the University of Natural Resources and Life Sciences, Vienna with an HTC PAL

system autosampler, an Agilent 1100/1200 HPLC with binary pumps, degasser and column thermostat and Agilent 6230 AJS ESI-TOF mass spectrometer. Analysis was performed with MassHunter Workstation Software – Qualitative Analysis version B.07.00. Measurements marked with a * were performed on a Q Exactive Focus, ESI, FIA injection, mobile phase 18% MeCN with 0.1% formic acid.

5.2 Synthesis of carbohydrate derivatives

5.2.1 Methyl 3-*O*-benzyl-α-D-mannopyranoside (23)



22
M = 194.18
$C_7H_{14}O_6$

23
M = 284.31
$C_{14}H_{20}O_6$

Methyl 3-*O*-benzyl-α-D-mannopyranoside **23** was prepared according to a modified literature procedure.[79]

Procedure:

A suspension of methyl α-D-mannopyranoside **22** (6.00 g, 30.9 mmol, 1.00 equiv.) and dibutyltin oxide (7.69 g, 30.9 mmol, 1.00 equiv.) in MeOH (anh., 60 ml) was stirred at reflux for 20 h under an Ar atmosphere. The solution turned clear and toluene (90 mL) and caesium fluoride (9.39 g, 61.8 mmol, 2.00 equiv.) were added, and the solvent was evaporated. The residue was kept at 50 °C/2.5 mbar for 2 h, before it was dissolved in DMF (anh., 42 ml). Molecular sieves (4 Å, 4.50 g) were added, followed by the addition of benzyl bromide (10.57 g, 61.8 mmol, 2.00 equiv.) and the mixture was stirred at room temperature for 25 h, when no further conversion was observed on TLC ($CHCl_3$:MeOH:H_2O = 7:3:0.5, anisaldehyde stain).

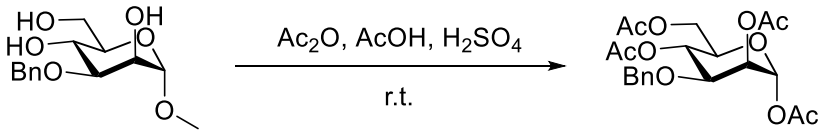
Workup:

The solvent was evaporated and the residue was co-evaporated with toluene two times. The residue was dissolved with DCM, the insoluble parts were washed with DCM until the product was extracted exhaustively ($CHCl_3$:MeOH:H_2O = 7:3:0.5, anisaldehyde stain). After separation of remaining solids the solution was concentrated *in vacuo*. Purification of product **23** was achieved by column chromatography using SiO_2 (180 g) and a gradient of MeOH in DCM from

4-8% to give the product in 5.71 g (65%) yield and 90% purity according to ^{1}H-NMR. Impurities were identified as various isomers of the product with the benzyl group in different positions. Spectral data[80] of the main component are in accordance with the literature.

Yield	5.71 g (65%) in 90% purity
Appearance	colorless oil
TLC	R_f ($CHCl_3$:MeOH:H_2O = 7:3:0.5, anisaldehyde stain): 0.60
^{1}H NMR (400 MHz, CD_3OD)	δ 7.43 (d, *J* = 7.2 Hz, 2H, PhH2/H6), 7.33 (t, *J* = 7.3 Hz, 2H, PhH3/H5), 7.27 (d, *J* = 7.1 Hz, 1H, PhH4), 4.72 (d, *J* = 11.8 Hz, 1H, PhC**H**H), 4.65 (d, *J* = 1.5 Hz, 1H, H1), 4.64 (d, *J* = 11.7 Hz, 1H, PhCH**H**), 3.95 (dd, *J* = 2.9, 1.8 Hz, 1H, H2), 3.84 (dd, *J* = 11.7, 2.2 Hz, 1H, H6a), 3.76 (t, *J* = 9.8 Hz, 1H, H4), 3.71 (dd, *J* = 11.9, 6.0 Hz, 1H, H6b), 3.58 (dd, *J* = 9.4, 3.2 Hz, 1H, H3), 3.51 (ddd, *J* = 9.5, 5.9, 2.3 Hz, 1H, H5), 3.36 (s, 1H, OCH_3).
^{13}C NMR (101 MHz, CD_3OD)	δ 140.0 (s, PhC1), 129.3 (d, PhC3/C5), 129.1 (d, PhC2/C6), 128.6 (d, PhC4), 102.7 (d, C1), 80.4 (d, C3), 74.6 (d, C5), 72.7 (t, Ph**C**H_2), 69.0 (d, C2), 67.7 (d, C4), 62.9 (t, C6), 55.2 (q, OCH_3).
HRMS (ESI$^+$)	calc. for $C_{14}H_{20}O_6Na$ $[M+Na]^+$: 307.1152, found: 307.1158 (– 1.86 ppm)

5.2.2 1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-α-D-mannopyranose (24)



23
M = 284.31
$C_{14}H_{20}O_6$

24
M = 438.43
$C_{21}H_{26}O_{10}$

1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-α-D-mannopyranose **24** was prepared according to a modified literature procedure.[79]

Procedure:

A solution of methyl 3-O-benzyl-α-D-mannopyranoside **23** containing ~10% of isomeric impurities (6.09 g, 21.4 mmol, 1.00 equiv.) in Ac_2O:AcOH:H_2SO_4 (50:20:0.5, 53 ml) was stirred at rt for 5 h, when TLC indicated full conversion (LP:EtOAc = 7:3, anisaldehyde stain).

Workup:

The reaction mixture was poured onto ice-water (200 mL) and then partitioned between DCM and $NaHCO_3$ solution (satd.). The aqueous layer was extracted with DCM. The organic layer was dried with Na_2SO_4 and concentrated affording 12.29 g of a yellowish oil. Purification of product **24** was achieved by column chromatography using SiO_2 (180 g) and a gradient of EtOAc in LP from 20-40% yielding 6.03 g (64%) of pure product according to ^{1}H-NMR. Spectral data[81] of the product are in accordance with the literature.

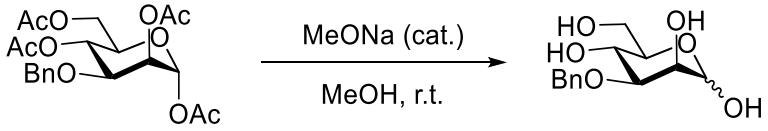
Yield	6.03 g (64%)
Appearance	colorless oil
TLC	R_f (LP:EtOAc = 7:3, anisaldehyde stain): 0.37
^{1}H NMR (400 MHz, CD_3OD)	δ 7.37 – 7.26 (m, 5H, Ph), 6.03 (d, *J* = 1.8 Hz, 1H, H1), 5.37 (dd, *J* = 3.2, 2.1 Hz, 1H, H2), 5.23 (appt. t, *J* = 10.1 Hz, 1H, H4), 4.65 (d, *J* = 11.8 Hz, 1H, PhC**H**H), 4.48 (d, *J* = 11.8 Hz, 1H, PhCH**H**), 4.22 (dd, *J* = 12.5, 4.9 Hz, 1H, H6a), 4.03 (dd, *J* = 12.1, 2.3 Hz, 1H, H6b), 4.03 – 3.97 (m, 1H, H5), 3.97 (dd, *J* = 9.8, 3.4 Hz, 1H, H3), 2.14, 2.13, 2.04, 2.01 (4×s, 4×3H, 4×$COCH_3$).

^{13}C NMR (101 MHz, CD_3OD) δ 172.4, 171.5, 171.4, 169.9 (4×s, 4×**C**OCH_3), 139.1 (s, PhC1), 129.4 (d, PhC3/C5), 129.1 (d, PhC2/C6), 128.9 (d, PhC4), 92.3 (d, C1), 75.9 (d, C3), 72.8 (t, $PhCH_2$), 72.0 (d, C5), 68.8 (d, C2), 68.2 (d, C4), 63.4 (t, C6), 20.8, 20.7, 20.64, 20.61 (4×q, 4×CO**C**H_3).

HRMS (ESI^+) calc. for $C_{21}H_{26}O_{10}Na$ $[M+Na]^+$: 461.1418, found: 461.1444 (– 5.51 ppm)

Optical rotation $[\alpha]_D^{20}$ = +0.65° (c = 1.2, $CHCl_3$) lit.[79] +2.8° (c = 1, $CHCl_3$)

5.2.3 3-*O*-Benzyl-D-mannopyranose (13)



24
M = 438.43
$C_{21}H_{26}O_{10}$

13
M = 270.28
$C_{13}H_{18}O_6$

3-*O*-Benzyl-D-mannopyranose **13** was prepared according to a modified literature procedure.[82]

Procedure:

1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-α-D-mannopyranose **24** (4.75 g, 10.8 mmol, 1.00 equiv.) was dissolved in methanol (anh., 48 ml) and NaOMe was added until a pH of ~ 10 was reached. The solution was stirred at room temperature for 2 h, when full conversion was observed by TLC ($CHCl_3$:MeOH:H_2O = 7:3:0.5, anisaldehyde stain).

Workup:

The reaction mixture was neutralized by addition of acidic ion exchange resin (Amberlyst 15), monitored using pH paper, the resin was filtered, washed with methanol and the filtrate was concentrated *in vacuo* yielding 2.96 g (quant.) of **13** as a colorless solid in an α:β ratio of ~7:3.

Yield	2.96 g (quant.)
Appearance	colorless solid
m.p.	50-52 °C (MeOH, Kofler)
TLC	R_f ($CHCl_3$:MeOH:H_2O=7:3:0.5, anisaldehyde stain) = 0.45
^{1}H NMR (400 MHz, CD_3OD)	α and β isomer were obtained in a ratio of ~ 7:3. δ 7.45 (d, *J* = 6.8 Hz, 2H, PhH2/H6), 7.33 (t, *J* = 7.3 Hz, 2H, PhH3/H5), 7.27 (d, *J* = 7.1 Hz, 1H, PhH4), 5.08 (d, *J* = 1.8 Hz, 0.7H, α H1), 4.74 (d, *J* = 11.6 Hz, 1H, PhC**H**H), 4.70 (d, *J* = 0.9 Hz, 0.3H, β H1), 4.66 (d, *J* = 11.7 Hz, 1H, PhCH**H**), 3.99 (d, *J* = 2.3 Hz, 0.3H, β H2), 3.96 (dd, *J* = 3.0, 2.0 Hz, 0.7H, α H2), 3.86 (dd, *J* = 11.8, 2.4 Hz, 0.3H, β H6a), 3.83 – 3.73 (m, 3.4H, α H4,

β H4, α H5, α H6a, α H6b, H6b β), 3.69 (dd, *J* = 8.9, 3.0 Hz, 0.7H, α H3), 3.38 (dd, *J* = 9.4, 3.1 Hz, 0.3H, β H3), 3.24 (ddd, *J* = 9.6, 5.8, 2.4 Hz, 1H, β H5).

^{13}C NMR (101 MHz, CD_3OD) α-isomer: δ 140.1 (s, PhC1), 129.3 (d, PhC3/C5), 129.1 (d, PhC2/6), 128.6 (d, PhC4), 95.8 (d, C1), 80.3 (d, C3), 74.1 (d, C5), 72.7 (t, $PhCH_2$), 69.9 (d, C2), 67.8 (d, C4), 63.0 (t, C6).

β-isomer: δ 140.1 (s, PhC1), 129.3 (d, PhC3/C5), 129.1 (d, PhC2/C6), 128.6 (d, PhC4), 95.6 (d, C1), 82.9 (d, C3), 78.1 (d, C4 or C5), 72.4 (t, Ph-CH_2), 70.0 (d, C2), 67.4 (d, C4 or C5), 63.0 (t, C6).

HRMS (ESI$^+$) calc. for $C_{13}H_{18}O_6Na$ $[M+Na]^+$: 293.0996, found: 293.1009 (– 4.43 ppm)

Optical rotation $[\alpha]_D^{20}$ = -0.80° (c = 1.0, MeOH, 12 h) lit.[83] -16° (c = 1.0, $CHCl_3$), lit.[79] +3.0° (c = 1, $CHCl_3$)

5.2.4 Methyl 6-*O*-(tert-butyldimethylsilyloxy)-α-D-galactopyranoside (26)

25
M = 194.18
$C_7H_{14}O_6$

26
M = 308.45
$C_{13}H_{28}O_6Si$

Methyl 6-*O*-(tert-butyldimethylsilyloxy)-α-D-galactopyranoside **26** was prepared according to a modified literature procedure.[70]

Procedure:

Methyl-α-D-galactopyranoside **25** (3.00 g, 15.5 mmol, 1.00 equiv.) was suspended in MeCN (anh., 62 ml) and first DABCO (3.73 g, 33.2 mmol, 2.15 equiv.) was added in one portion and then TBDMSCl (4.89 g, 32.4 mmol, 2.10 equiv.) was added slowly at rt and the mixture was stirred for 4.5 h. After that time full conversion was observed on TLC ($CHCl_3$:MeOH:H_2O = 7:3:0.5, anisaldehyde stain).

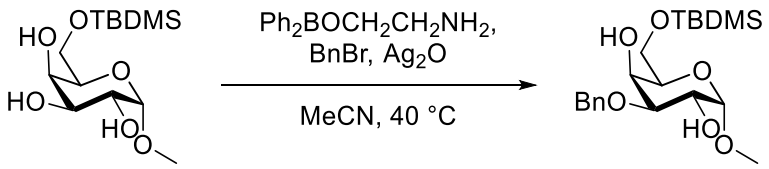
Workup:

MeOH (3.75 ml, 92.7 mmol, 6.00 equiv.) was added and the solution was stirred for another hour, before the solution was concentrated *in vacuo*. Purification of product **26** was achieved by column chromatography using dry loading with SiO_2 (90 g) and a gradient of MeOH in DCM from 0-20% and afforded the target compound in a yield of 3.74 g (79%) and pure according to ^{1}H-NMR. Spectral data[80] of the product are in accordance with the literature.

Yield	3.74 g (79%)
Appearance	colorless crystalline solid
m.p.	138.7-139.2 °C (MeOH) lit.[84] 136.0-137.0 °C
TLC	R_f ($CHCl_3$:MeOH:H_2O = 7:3:0.5, anisaldehyde stain) = 0.65
^{1}H NMR (400 MHz, CD_3OD)	δ 4.69 (d, *J* = 3.7 Hz, 1H, H1), 3.88 (d, *J* = 3.1 Hz, 1H, H4), 3.85 – 3.74 (m, 4H, H2, H5, H6a & H6b), 3.69 (dd, *J* = 10.1, 3.2 Hz, 1H, H3), 3.39 (s, 3H, OCH_3), 0.92 (s, 9H, $C(CH_3)_3$), 0.10 (s, 6H, $Si(CH_3)_2$).

	COSY-measurement in DMSO confirms the TBDMS group to be on O6 (see Figure 6).
^{13}C NMR (101 MHz, CD_3OD)	δ 101.5 (d, C1), 72.3 (d, C5), 71.6 (d, C3), 70.8 (d, C4), 70.3 (d, C2), 63.8 (t, C6), 55.5 (q, OMe), 26.3 (q, C(**C**H_3)$_3$), 19.1 (s, **C**$(CH_3)_3$), -5.2 (q, Si(CH_3)Me), -5.3 (q, SiMe(CH_3)).
HRMS (ESI$^+$)	calc. for $C_{13}H_{28}O_6NaSi$ $[M+Na]^+$: 331.1547, found: 331.1563 (– 4.77 ppm)
Optical rotation	$[\alpha]_D^{20}$ =+113° (c=1.1, $CHCl_3$) lit[85] +102° (c = 1.0, $CHCl_3$)

5.2.5 Methyl 6-*O*-(tert-butyldimethylsilyloxy)-3-*O*-benzyl-α-D-galactopyranoside (27)



26
M = 308.45
$C_{13}H_{28}O_6Si$

27
M = 398.57
$C_{20}H_{34}O_6Si$

Methyl 6-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-α-D-galactopyranoside **27** was prepared according to a literature procedure.[70]

Procedure:

Methyl 6-*O*-*tert*-butyldimethylsilyl-α-D-galactopyranoside **26** (3.30 g, 10.7 mmol, 1.00 equiv.), 2-aminoethyl diphenylborinate **30** (241 mg, 1.07 mmol, 0.10 equiv.) and Ag_2O (2.73 g, 11.8 mmol, 1.10 equiv.) were charged into a round bottom flask and dissolved in MeCN (anh., 107 ml). Benzyl bromide (2.99 g, 17.5 mmol, 1.50 equiv.) was added, and the reaction vessel was capped with a septum and purged with argon. The mixture was stirred vigorously for 28 h at 40 °C, when full conversion was observed by TLC analysis (LP:EtOAc = 7:3, anisaldehyde stain).

Workup:

The resulting mixture was diluted with DCM, filtered through a pad of Celite®, washed with DCM until the product was completely flushed through (checked using TLC, LP:EtOAc = 7:3, anisaldehyde stain). The filtrate was concentrated *in vacuo*. Purification of product **27** was achieved by column chromatography using dry loading with SiO_2 (180 g) and a gradient of EtOAc in LP from 20-40% and afforded the target compound in a yield of 3.16 g (74%) and pure according to ^{1}H-NMR.Spectral data[80] are in accordance with the literature.

Yield	3.16 g (74%)
Appearance	colorless crystalline solid
m.p.	73.5-73.6 °C (EtOAc)
TLC	R_f (LP:EtOAc = 7:3, anisaldehyde stain): 0.35
^{1}H NMR (400 MHz, CD_3OD)	δ 7.44 (d, *J* = 7.2 Hz, 2H, PhH2/H6), 7.32 (app. t, *J* = 7.3 Hz, 2H, PhH3/H5), 7.27 (d, *J* = 7.2 Hz, 1H, PhH4), 4.77 – 4.64 (m, 2H,

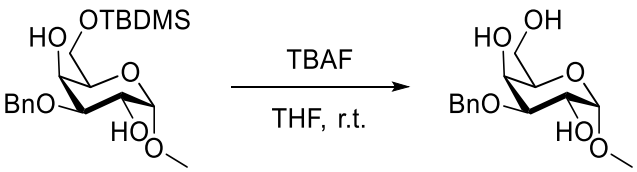
$PhCH_2$), 4.69 (s, 1H, H1), 4.02 (d, *J* = 2.8 Hz, 1H, H4), 3.95 (dd, *J* = 10.0, 3.9 Hz, 1H, H2), 3.82 (dd, *J* = 10.2, 5.9 Hz, 1H, H6a), 3.75 (dd, *J* = 10.2, 6.3 Hz, 1H, H6b), 3.68 (app. t, *J* = 6.1 Hz, 1H, H5), 3.60 (dd, *J* = 10.0, 3.1 Hz, 1H, H3), 3.38 (s, 3H, OMe), 0.91 (s, 9H, $C(CH_3)_3$), 0.09 (s, 3H, $Si(CH_3)Me$), 0.08 (s, 3H, $SiMe(CH_3)$).

^{13}C NMR (101 MHz, CD_3OD) δ 140.0 (s, PhC1), 129.3 (d, PhC3/C5), 129.1 (d, PhC2/C6), 128.6 (d, PhC4), 101.5 (d, C1), 79.3 (d, C3), 72.7 (t, $PhCH_2$), 72.2 (d, C5), 69.5 (d, C2), 67.8 (d, C4), 63.7 (t, C6), 55.5 (q, OMe), 26.4 (q, $C(\underline{\mathbf{C}}H_3)_3$), 19.1 (s, $\underline{\mathbf{C}}(CH_3)_3$), -5.2 (q, $Si(\underline{\mathbf{C}}H_3)Me$), -5.3 (q, $SiMe(\underline{\mathbf{C}}H_3)$).

HRMS (ESI$^+$) calc. for $C_{20}H_{34}O_6NaSi$ $[M+Na]^+$: 421.2017, found: 421.2042 (– 5.88 ppm)

Optical rotation $[\alpha]_D^{20}$ = +102° (c = 3.3, $CHCl_3$) lit.[86] +90° (c = 3.6, $CHCl_3$)

5.2.6 Methyl 3-*O*-benzyl-α-D-galactopyranoside (28)



27
M = 398.57
$C_{20}H_{34}O_6Si$

28
M = 284.31
$C_{14}H_{20}O_6$

Methyl 3-*O*-benzyl-α-D-galactopyranoside **28** was prepared according to a modified literature procedure.[87]

Procedure:

Tetrabutyl ammonium fluoride solution (1 M in THF, 14.8 ml, 14.8 mmol, 1.14 equiv.) was added slowly to a solution of 6-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-α-D-galactopyranoside **27** (5.19 g, 13.02 mmol, 1.00 equiv.) in THF (74 ml). The solution was stirred at rt under Ar for 3 h, when TLC (DCM:MeOH = 9:1, anisaldehyde stain) indicated complete conversion.

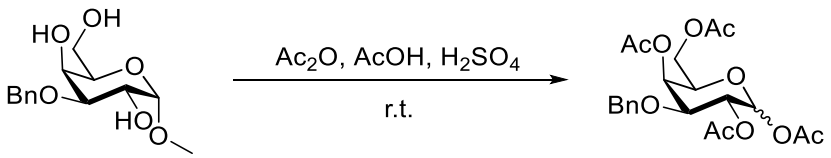
Workup:

The reaction mixture was evaporated. Purification of product **28** was achieved by column chromatography with SiO_2 (90 g) and a gradient of MeOH in DCM from 0-20% and afforded the target compound in a yield of 3.59 g (97%) and pure according to ^{1}H-NMR. Spectral data[80] of the product are in accordance with the literature.

Yield	3.59 g (97%)
Appearance	colorless oil
TLC	R_f (DCM:MeOH = 9:1, anisaldehyde stain) = 0.41
^{1}H NMR (400 MHz, CD_3OD)	δ 7.44 (d, *J* = 7.5 Hz, 2H, PhH2/H6), 7.32 (t, *J* = 7.5 Hz, 2H, PhH3/5), 7.27 (d, *J* = 6.7 Hz, 1H, PhH4), 4.74 (d, *J* = 11.9 Hz, 1H, PhC**H**H), 4.71 (d, *J* = 3.9 Hz, 1H, H1), 4.66 (d, *J* = 11.9 Hz, 1H, PhCH**H**), 4.06 (d, *J* = 2.9 Hz, 1H, H4), 3.95 (dd, *J* = 10.0, 3.8 Hz, 1H, H2), 3.76 – 3.66 (m, 3H, H5, H6a, H6b), 3.62 (dd, *J* = 10.0, 2.9 Hz, 1H, H3), 3.39 (s, 3H, OMe).

^{13}C NMR (101 MHz, CD_3OD)	δ 139.9 (s, PhC1), 129.3 (d, PhC3/C5), 129.0 (d, PhC2/C6), 128.6 (d, PhC4), 101.5 (d, C1), 79.1 (d, C3), 72.5 (t, $PhCH_2$), 72.1 (d, C5), 69.5 (d, C2), 68.0 (d, C4), 62.7 (d, C6), 55.6 (q, OMe).
HRMS (ESI^+)	calc. for $C_{14}H_{20}O_6Na$ $[M+Na]^+$: 307.1152, found: 307.1167 (-4.72 ppm)
Optical rotation	$[\alpha]_D^{20}$ = +167° (c = 0.6, EtOH), lit.[86] +141.43° (c = 3.21, $CHCl_3$)

5.2.7 1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-D-galactopyranose (29)



28
M = 284.31
$C_{14}H_{20}O_6$

G5
M = 438.43
$C_{21}H_{26}O_{10}$

1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-D-galactopyranose **29** was prepared according to a modified literature procedure.[79]

Procedure:

A solution of methyl 3-*O*-benzyl-galactopyranoside **28** (2.29 g, 8.06 mmol, 1.00 equiv.) in Ac_2O:AcOH:H_2SO_4 (50:20:0.5, 20 ml) was stirred at rt for 6 h, when TLC indicated full conversion (LP:EtOAc =7:3, anisaldehyde stain).

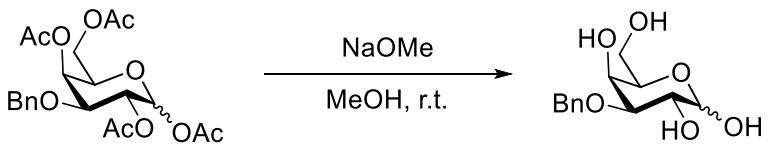
Workup:

The reaction mixture was poured into ice-water (150 mL), and, after the ice had melted, was separated between DCM and $NaHCO_3$ solution (satd.). The aqueous layer was extracted with DCM until no further product was detected in the extract using TLC (LP:EtOAc =7:3, anisaldehyde stain). The organic layer was dried using Na_2SO_4 and concentrated *in vacuo*. Purification of product **29** was achieved by column chromatography with SiO_2 (90 g) and a gradient of EtOAc in LP from 30-40% yielding 3.11 g (88%) of pure product according to ^{1}H-NMR in an α:β ratio of ~ 7:2.

Yield	3.11 g (88%)
Appearance	colorless oil
TLC	R_f (LP:EtOAc =7:3, anisaldehyde stain) = 0.56
^{1}H NMR (400 MHz, $CDCl_3$)	~7:2 ratio of α:β δ 7.40 – 7.23 (m, 5H, PhH2-H6), 6.35 (d, *J* = 3.7 Hz, 0.78H, α H1), 5.62 (d, *J* = 1.9 Hz, 0.78H, α H4), 5.60 (d, *J* = 8.5 Hz, 0.22H, β H1), 5.54 (dd, *J* = 3.4, 1.2 Hz, 0.22H, β H4), 5.26 (dd, *J* = 10.4, 3.8 Hz, 1H, α H2, β H2), 4.73 (d, *J* = 11.6 Hz, 1H, PhC**H**H), 4.47 (d, *J* = 11.8 Hz, 0.78H, α PhCH**H**), 4.41 (d, *J* = 12.2 Hz, 0.22H, β PhCH**H**), 4.25 (dd, *J* = 6.6, 1.3 Hz, 0.78H, α H5), 4.21 – 4.02 (m, 2H, α H6a, α H6b, β H6a, β H6b), 3.91 (dd, *J* = 10.5, 3.3 Hz, 1H,

	α H3, β H5), 3.61 (dd, *J* = 10.0, 3.4 Hz, 0.22H, β H3), 2.18 – 1.98 (8×s, 8×3H, CH_3CO).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 170.67, 170.65, 170.4, 170.0, 169.5, 169.4, 169.1 (8×s, 4×α & 4×β C=O), 137.6 (s, α PhC1), 137.3 (s, β PhC1), 128.6-127.8 (6×d, PhC2-C6), 92.3 (d, β C1), 90.1 (d, α C1), 76.7 (d, β C3), 73.1 (d, α C3), 72.1 (d, β C5), 71.8 (t, α Ph-CH_2), 71.6 (t, β Ph-CH_2), 69.5 (d, β C2), 69.2 (d, α C5), 68.4 (d, α C2), 66.7 (d, α C4), 65.8 (d, β C4), 62.1 (t, α C6), 61.8 (t, β C6), 21.04, 20.99, 20.92, 20.90, 20.87, 20.8 (8×q, 4×α & 4×β **C**H_3CO).
HRMS (ESI$^+$)	calc. for $C_{21}H_{26}O_{10}$ $[M+Na]^+$: 461.1418, found: m/z = 461.1442 (– 5.1 ppm)
Optical rotation	$[\alpha]_D^{20}$ = +91° (c = 1.0, $CHCl_3$), lit.[88] +64° (c = 1.0, $CHCl_3$)

5.2.8 3-*O*-Benzyl-D-galactopyranose (14)



29
M = 438.43
$C_{21}H_{26}O_{10}$

14
M = 270.28
$C_{13}H_{18}O_6$

3-*O*-Benzyl-D-galactopyranose **14** was prepared according to a modified literature procedure.[82]

Procedure:

1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-D-galactopyranose **29** (2.14 g, 4.87 mmol, 1.00 equiv.) was dissolved in MeOH (anh., 21 ml) and NaOMe was added until a pH of ~ 10 was measured using pH-paper. The solution is then stirred at room temperature for 2 h, when full conversion was observed by TLC ($CHCl_3$:MeOH:H_2O=7:3:0.5, anisaldehyde stain).

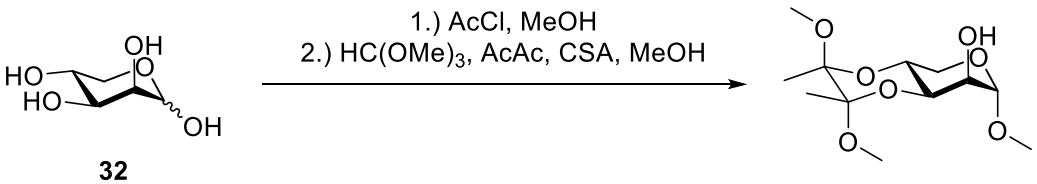
Workup:

Acidic ion exchange resin (Amberlyst 15) was added for neutralization (monitored using pH paper) and subsequently removed by filtration and washed with methanol. The solution was dried over Na_2SO_4 and concentrated *in vacuo* to yield 1.34 g of **14** as a colorless oil and pure as a mixture of 4 anomers in a ratio of ~60:30:7:3 according to NMR.

Yield	1.34 g (quant.)
Appearance	colorless oil
TLC	R_f ($CHCl_3$:MeOH:H_2O=7:3:0.5, anisaldehyde stain) = 0.45 & 0.50
^{1}H NMR (600 MHz, D_2O)	The ratios of the two dominant species, the α-pyranose (~30%) form and the β-pyranose form (~60%), were assigned: 7.39 – 7.25 (m, 5H, PhH), 5.14 (d, *J* = 3.9 Hz, 0.3H, α H1), 4.63 (dd, *J* = 11.7, 6.9 Hz, 0.3H, α PhCH2a), 4.53 (t, *J* = 12.0 Hz, 0.3H, β PhCH2a), 4.44 (d, *J* = 7.4 Hz, 0.6H, β H1), 4.01 (dd, *J* = 3.2, 1.2 Hz, 0.3H, α H4), 3.98 (dd, *J* = 3.1, 1.1 Hz, 0.6H, β H4), 3.90 (ddd, *J* = 6.7, 5.0, 1.2 Hz, 0.3H, α H5), 3.78 – 3.74 (m, 0.3H, α H2), 3.65 – 3.57 (m, 2.1H, α H3, α H6a, α H6b, β H6a, β H6b),

	3.52 – 3.47 (m, 0.6H, β H5), 3.44 (dd, *J* = 9.9, 7.4 Hz, 0.6H, β H2), 3.40 (dd, *J* = 9.9, 3.1 Hz, 0.6H, β H3).
^{13}C NMR (151 MHz, D_2O)	δ 137.4 (d, α PhC4), 137.2 (d, β PhC4), 128.9, 128.8, 128.64, 128.58, 128.56, 128.3, 128.2 (10×d, 10×PhC2-C6), 96.3 (d, β C1), 92.1 (d, α C1), 79.9 (d, β C3), 76.6 (d, α C3), 75.0 (d, β C5), 71.0 (t, β PhCH2), 71.0 (t, α PhC2), 70.9 (d, β C2), 70.3 (d, α C5), 67.4 (d, α C2), 66.0 (d, α C4), 65.2 (d, β C4), 61.1 (t, α C6), 60.9 (t, β C6).
HRMS (ESI$^+$)	**c**alc. for $C_{13}H_{18}O_6Na$ $[M+Na]^+$: 293.0996, found: 293.1005 (– 3.1 ppm)
Optical rotation	$[\alpha]_D^{20}$ = +64.1° (c = 1.0, H_2O, 12 h), lit.[89] +72° (c = 0.5, H_2O)

5.2.9 Methyl 3,4-*O*-(1,2-dimethoxy-1,2-dimethyl-1,2-ethanediyl)-α-D-lyxopyranoside (33)



32
M = 150.13
$C_5H_{10}O_5$

33
M = 278.30
$C_{12}H_{22}O_7$

Methyl 3,4-*O*-(1,2-dimethoxy-1,2-dimethyl-1,2-ethanediyl)-α-D-lyxopyranoside **33** was prepared according to a modified literature procedure.[90]

Procedure:

Acetyl chloride (3.63 g, 46.4 mmol, 1.16 equiv.) was added dropwise to a solution of D-lyxose **32** (6.00 g, 40.0 mmol, 1.00 equiv.) in MeOH (anh., 180 ml), and the resulting solution was refluxed for 1 h until TLC ($CHCl_3$:MeOH:H_2O = 7:3:0.5, anisaldehyde stain) indicated full conversion. The reaction was cooled to rt and quenched by adding $NaHCO_3$ until the evolution of gas stopped, then the solution was filtered through Celite® and the solvent was removed *in vacuo*.

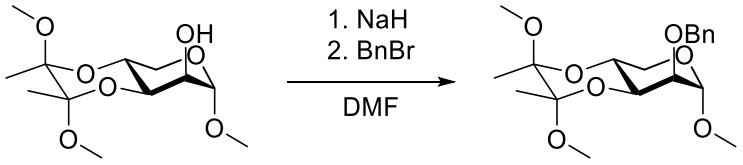
The residue was dissolved in MeOH (anh., 150 ml) and trimethyl orthoformate (anh., 29.0 g, 273 mmol, 6.83 equiv.) and butanedione (11.9 g, 138 mmol, 3.45 equiv.) were added slowly. Camphorsulfonic acid (3.20 g, 13.8 mmol, 0.345 equiv.) was added and the solution was refluxed for 2.5 h when full conversion was observed by TLC ($CHCl_3$:MeOH:H_2O = 7:3:0.5, anisaldehyde stain).

Workup:

The reaction was quenched by adding Et_3N (2.83 g, 28.0 mmol, 1.00 equiv.). After the removal of the solvent *in vacuo*, the residue was diluted with EtOAc, washed with Na_2CO_3 (sat), water and brine, dried over Na_2SO_4, and the solvent was removed yielding an orange oil. Purification of product **33** was achieved by column chromatography with SiO_2 (180 g) and a gradient of EtOAc in LP from 5-70% and afforded the target compound in a yield of 7.66 g (69%) and in 90% purity according to ^{1}H-NMR. The impurity appears to be the *cis*-isomer **34** of the formed diketal, which would lead to the same final target compound in the reaction sequence; hence, no further efforts were undertaken for separation. Spectral data[90] of the main component are in accordance with the literature.

Yield	7.66 g (69%)
Appearance	orange oil
TLC	R_f (LP:EtOAc = 2:1, anisaldehyde stain) = 0.27
^{1}H NMR (400 MHz, $CDCl_3$)	δ 4.68 (bs, 1H, H1), 4.20 – 4.13 (m, 1H, H4), 3.94 – 3.89 (m, 2H, H2 & H3), 3.65 – 3.58 (m, 2H, H5a, H5b), 3.36 (s, 3H, OCH_3(C1)), 3.26, 3.25 (2×s, 2×3H, OCH_3(C2') & OCH_3(C3')), 1.31, 1.27 (2×s, 2×3H, 2×CH_3).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 101.28 (d, C1), 100.68, 99.93 (2×s, C2' & C3'), 69.80 (d, C2), 68.73 (d, C3), 62.98 (d, C4), 60.61 (t, C5), 55.06 (q, O**C**H_3(C1)), 48.19, 48.06 (2×q, O**C**H_3(C2') & O**C**H_3(C3')), 17.89, 17.87 (2×q, **C**H_3(C2') & **C**H_3(C3')).
HRMS (ESI$^+$)	calc. for $C_{12}H_{22}O_7Na$ $[M+Na]^+$: 301.1256, found: 278.1366 (0.52 ppm)

5.2.10 Methyl 2-*O*-benzyl-3,4-*O*-(1,2-dimethoxy-1,2-dimethyl-1,2-ethanediyl)-α-D-lyxopyranoside (35)



33
M = 278.30
$C_{12}H_{22}O_7$

35
M = 368.43
$C_{19}H_{28}O_7$

Methyl 2-benzyl-3,4-*O*-(1,2-dimethoxy-1,2-dimethyl-1,2-ethanediyl)-α-D-lyxopyranoside **35** was prepared according to a standard procedure.

Procedure:

Methyl 3,4-BDA-lyxoside **33** (1.39 g, 4.99 mmol, 1.00 equiv., 90% purity) was dissolved in DMF (anh., 5.6 ml). A continuous flow of Ar was applied through the solution and the solution was cooled to 0 °C. As NaH (60% dispersion in mineral oil, 599 mg, 15.0 mmol, 3.00 equiv.) was added portion wise, the formation of H_2 gas was observed. After stirring at 0 °C for 30 minutes, BnBr (1.71 g, 5.99 mmol, 1.20 equiv.) was added slowly. The mixture was allowed to reach room temperature and was stirred for 1.45 h with full conversion and only very minor sideproduct formation being observed on TLC (LP:EtOAc = 8:1, anisaldehyde stain).

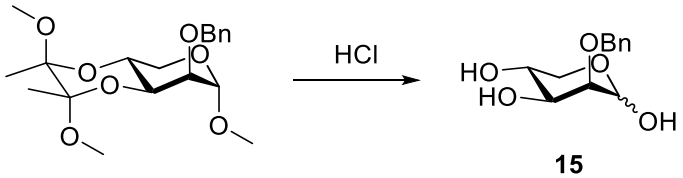
Workup:

MeOH (2 ml, 10 equiv.) was added slowly. The mixture was distributed between aqueous NH_4Cl solution (10%) and Et_2O. The aqueous phase was extracted with Et_2O twice. The combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was evaporated yielding 2.34 g of crude material. Purification of product **35** was achieved by column chromatography with SiO_2 (30 g) and a gradient of EtOAc in LP from 5-20% and afforded the target compound in a yield of 1.48 g (81%) and in 85% purity according to ^{1}H-NMR (interpreted as the same isomerism as in the starting material).

Yield	1.48 g (81%)
Appearance	yellow oil

TLC	R_f (LP:EtOAc = 8:1, anisaldehyde stain) = 0.45
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.45 (d, *J* = 7.0 Hz, 2H, PhH2/H6), 7.34 (t, *J* = 7.3 Hz, 2H, PhH3/H5), 7.27 (t, *J* = 7.2 Hz, 1H, PhH4), 4.96 (d, *J* = 11.9 Hz, 1H, PhC**H**H), 4.67 (d, *J* = 11.8 Hz, 1H, PhCH**H**), 4.64 (d, *J* = 1.6 Hz, 1H, H1), 4.33 (td, *J* = 10.6, 5.4 Hz, 1H, H4), 4.01 (dd, *J* = 10.3, 2.9 Hz, 1H, H3), 3.71 (t, *J* = 1.8 Hz, 1H, H2), 3.68 (dd, *J* = 10.2, 5.3 Hz, 1H, H5a), 3.60 (dd, *J* = 10.6 Hz, 1H, H5b), 3.32 (s, 3H, OCH_3(C1)), 3.30, 3.29 (2×s, 2×3H, OCH_3(C2') & OCH_3(C3')), 1.36, 1.31 (2×s, 2×3H, CH_3(C2') & CH_3(C3')).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 138.6 (s, PhC1), 128.1, 128.0, 127.4 (3×d, PhC2-C6), 100.6, 100.0, 99.4 (3×d, C1, C2', C3'), 75.7 (d, C2), 73.3 (t, $PhCH_2$), 69.4 (d, C3), 63.3 (d, C4), 60.8 (t, C5), 54.6 (q, O**C**H_3(C1), 47.80, 47.76 (2×q, O**C**H_3(C2') & O**C**H_3(C3')), 17.8, 17.7 (2×q, **C**H_3(C2') & **C**H_3(C3')).
HRMS (ESI$^+$)	calc. for $C_{19}H_{28}O_7Na$ $[M+Na]^+$: 391.1727, found: 391.172 (1.97 ppm)

5.2.11 2-*O*-Benzyl-D-lyxose (15)



35
M = 368.43
$C_{19}H_{28}O_7$

15
M = 240.26
$C_{12}H_{16}O_5$

2-*O*-Benzyl-D-lyxose **15** was prepared analogous to a literature procedure.[90]

Procedure:

A solution of methyl 2-benzyl-3,4-BDA-lyxoside lyxopyranoside **35** (1.20 g, 3.25 mmol, 1.00 equiv.) in aqueous HCl (2 N, 8.1 ml) was heated for 7.5 h at 80 °C until only very little starting material was observed by TLC (DCM:MeOH = 10:1, anisaldehyde stain).

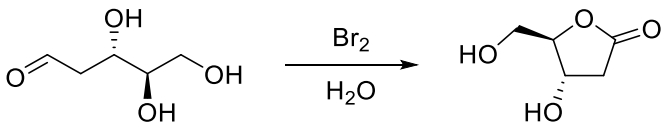
Work-up:

After cooling to rt, $NaHCO_3$ was added until the evolution of gas stopped and the solution tested neutral by pH paper. The solvent was removed *via* freeze drying and the obtained material was purified by column chromatography using dry loading with SiO_2 (45 g) and a gradient of MeOH in DCM from 0-20% and afforded the target compound **15** in a yield of 581 mg (75%) pure and in as a mixture of 4 isomers in a ratio of ~85:15:15:5 according to ^{1}H-NMR.

Yield	581 mg (75%)
Appearance	brown oil
TLC	R_f (DCM:MeOH = 10:1, anisaldehyde stain) = 0.51
^{1}H NMR (400 MHz, CD_3OD)	4 isomers in a ratio of ~85:15:15:5 were obtained. In the following only the α anomer is assigned. δ 7.41 (d, *J* = 6.9 Hz, 2H, PhH2/6), 7.33 (m, 2H, PhH3/H5), 7.27 (d, *J* = 7.0 Hz, 1H, PhH4), 5.00 (d, *J* = 3.8 Hz, 1H, H1), 4.75 – 4.64 (m, 2H, $PhCH_2$), 3.86 (dd, *J* = 7.6, 3.2 Hz, 1H, H3), 3.78 (td, *J* = 7.5, 4.2 Hz, 1H, H4), 3.70 (dd, *J* = 11.2, 4.1 Hz, 1H, H5a), 3.63 (dd, *J* = 11.3, 7.6 Hz, 1H, H5b), 3.59 (app. t, *J* = 3.6 Hz, 1H, H2).

^{13}C NMR (101 MHz, CD_3OD)	δ 138.6 (s, PhC1), 127.9, 127.7, 127.2 (3×d, PhC2-C6), 92.9 (d, C1), 78.5 (d, C2), 72.7 (t, Ph-CH_2), 70.7 (d, C3), 68.1 (d, C4), 63.0 (t, C5).
HRMS (ESI^+)	calc. for $C_{12}H_{16}O_5Na$ $[M+Na]^+$: 263.089, found: 263.0888 (0.67 ppm)
Optical rotation	$[\alpha]_D^{20}$ = -8.63° (c=1.0, MeOH, 12 h) lit.[89] -4° (c= 0.3, H_2O)

5.2.1 2-Deoxy-D-ribono-1,4-lactone (9)



51
M = 134.13
$C_5H_{10}O_4$

9
M = 132.12
$C_5H_8O_4$

2-*O*-Benzyl-D-lyxose **9** was prepared according to a modified literature procedure.[91]

Procedure:

2-Deoxy-D-ribose **51** (2.00 g, 14.9 mmol, 1.00 equiv.) was dissolved in H_2O (12 ml) in a round bottom flask. To this solution, Br_2 (4.0 ml, 77.6 mmol, 5.20 equiv.) was added, which led to the formation of a biphasic system. The flask was sealed and stirring was continued at rt for 24 h, when TLC ($CHCl_3$:MeOH:H_2O = 7:3:0.5, sm staining with anisaldehyde, product with potassium permanganate solution) showed complete conversion to the desired product.

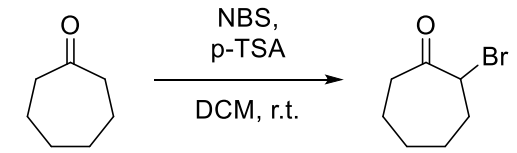
Work-up:

Ag_2CO_3 was added until the supernatant decolorized, which led to the formation of gas and a yellow-white precipitate. The reaction mixture was filtered through a bed of Celite and the solvent was lyophilized. The crude product was purified by column chromatography with SiO_2 (30 g) and a gradient of MeOH in EtOAc from 0-10% and afforded the target compound **9** in a yield of 1.50 g (76%) pure according to ^{1}H-NMR. Spectral data[92] are in accordance with the literature.

Yield	1.50 g (76%)
Appearance	colorless oil
TLC	R_f (DCM:MeOH=6:1, permanganate stain) = 0.48
^{1}H NMR (400 MHz, CD_3OD)	δ 4.43 (dt, *J* = 6.7, 2.2 Hz, 1H, H3), 4.37 (q, *J* = 3.2 Hz, 1H, H4), 3.76 (dd, *J* = 12.4, 3.2 Hz, 1H, H5a), 3.69 (dd, *J* = 12.4, 3.6 Hz, 1H, H5b), 2.91 (dd, *J* = 18.0, 6.7 Hz, 1H, H2a), 2.37 (dd, *J* = 18.0, 2.4 Hz, 1H, H2b).
^{13}C NMR (101 MHz, CD_3OD)	δ 177.2 (s, C1), 88.8 (d, C4), 68.3 (d, C3), 61.1 (t, C5), 37.8 (t, C2).
Optical rotation	$[\alpha]_D^{20}$ = +4.7° (c=1.0, MeOH) lit.[93] +3.5° (c= 0.8, MeOH)

5.3 Synthesis of thiazolium catalysts

5.3.1 2-Bromoheptanone (42)



48
M = 112.17
$C_7H_{12}O$

42
M = 191.07
$C_7H_{11}BrO$

2-Bromoheptanone **42** was prepared according to a literature procedure.[76]

Procedure:

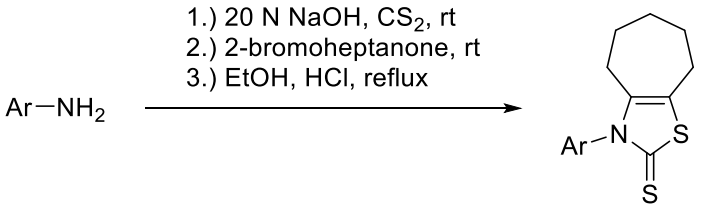
Under Ar atmosphere cyclohexanone **48** (5.00 g, 44.6 mmol, 1.00 equiv.) was dissolved in DCM (anh., 11 ml) in a three-neck round bottom flask. *p*-Toluenesulfonic acid monohydrate (0.85 g, 4.5 mmol, 0.100 equiv.) was added in one portion and *N*-bromosuccinimide (7.93 g, 44.6 mmol, 1.00 equiv.) was added in several small portions while cooling with ice-water, preventing the reaction from exceeding 5 °C. After slowly warming to rt, the reaction mixture was stirred for 20 h at this temperature, when GC-MS (sm with a retention of 2.99 min, dibrominated sideproduct with 3.71 min and dominantly the product with 4.25 min) and TLC (LP:EtOAc = 10:1, cerium molybdate stain) indicated significant product formation. The reaction was diluted to avoid further sideproduct formation and improve precipitation of the formed succinimide by first adding LP (25 ml) and stirring for another 5-10 min.

Workup:

The beige solid was filtered off and the filtrate was washed with aqueous $Na_2S_2O_3$ (satd., 2×75 ml), aqueous $NaHCO_3$ (satd., 2×75 ml) and brine (2x75 ml), dried over Na_2SO_4 and evaporated yielding 8.08 g (95%) of a slightly yellowish liquid. Analysis by ^{1}H-NMR confirmed predominant product formation with 12% of what is assumed to be the 2,7-dibrominated product. Distillation at 106 °C, 7 mbar afforded 6.48 g (76%) of the pure product **42** according to ^{1}H-NMR. Spectral data[63] of the main component are in accordance with the literature.

Yield	6.48 g (76 %)
Appearance	yellowish liquid
b.p.	106 °C, 7 mbar (lit.[94] 76-80°C, 1 mbar)
TLC	R_f (LP:EtOAc = 10:1, cerium molybdate stain): 0.61
GC-MS	t_R = 4.24 min, main fragments 192 (1.5, M^+), 190 (1.5, M^+), 111 (45), 93 (46), 55 (100).
^{1}H NMR (400 MHz, $CDCl_3$)	δ 4.37 (dd, *J* = 9.6, 5.1 Hz, 1H, H2), 2.92 – 2.80 (m, 1H, H7a), 2.56 – 2.42 (m, 2H, H7b), 2.42 – 2.28 (m, 1H, H3a), 2.13 – 1.86 (m, 4H, H3b, H4a, H6a), 1.81 – 1.64 (m, 2H, H5a), 1.63 – 1.47 (m, 4H, H5b, H6b), 1.44 – 1.31 (m, 2H, H4b).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 206.4 (s, C1), 53.9 (d, C2), 39.5 (t, C7), 34.4 (t, C3), 29.7 (t, C5), 27.0 (t, C4), 25.1 (t, C6).

5.3.2 General procedure of *N*-aryl-thiazole-2-thiole formation (procedure A)



The *N*-aryl-thiazole-2-thiole species **C3-7** were prepared according to a modified literature procedure.[63]

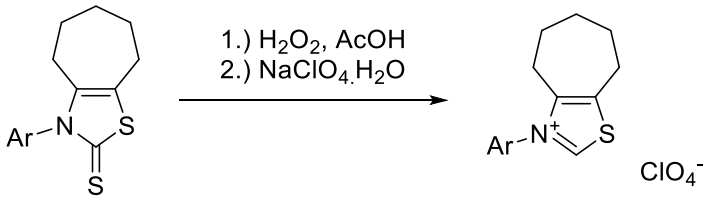
Procedure:

A solution of the respective aniline (1.00 equiv.) in DMSO (0.5 ml/mmol) was treated with aqueous NaOH solution (20 N, 1.00 equiv.). At 0 °C CS_2 (1.00 equiv.) was added dropwise and stirred for 1 h at room temperature. Then, 2-bromocycloheptanone **42** (1.00 equiv.) was added slowly at 0 °C, which led to a color change of the solution and the mixture was stirred for 20 h at rt.

Work up:

H_2O (1 mL/mmol) was added, the mixture was stirred for 10 min at 0 °C and the supernatant solution was decanted. Depending on the substrate either a slurry or a precipitate remained, that was suspended in EtOH (1 mL/mmol). Concentrated HCl (0.05 mL/mmol, 0.58 equiv.) was added dropwise and the mixture was heated to reflux for 1 h. After cooling to room temperature, the mixture was placed in the fridge, where crystals precipitated. The solid was collected by suction filtration, washed with small amounts of *n*-pentane before being dried by first purging with air and then under reduced pressure on the rotary evaporator. Purification by column chromatography was performed when products were not already obtained pure according to ^{1}H-NMR.

5.3.3 General procedure of oxidative desulfurization (procedure B)



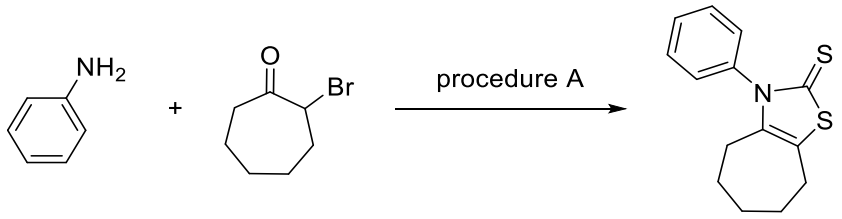
Procedure:

A solution or suspension of the thione (1.00 equiv.) in glacial acetic acid (4.1 ml/mmol sm) was cooled with a water bath, then H_2O_2 (30%, aqueous solution, 3.30 equiv.) was added dropwise and the reaction mixture was stirred for 1 h. The volatile components were removed under reduced pressure and the residue was dissolved in MeOH (0.69 ml/mmol sm). At temperature of 0 °C a mixture of sodium perchlorate monohydrate (4.10 equiv.) in MeOH/H_2O = 2/1 (3.61 ml/mmol sm) was added and the solution was stirred for 30 min.

Work up:

H_2O (50 mL) was added and the mixture was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification was performed by column chromatography or trituration when required.

5.3.4 3-Phenyl-3,4,5,6,7,8-hexahydro-2*H*-cyclohepta[*d*]thiazole-2-thione (43)

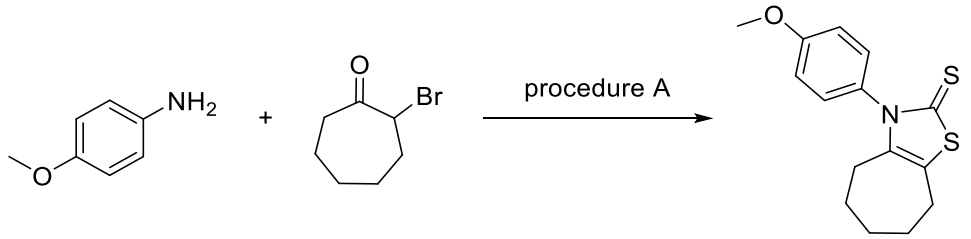


37	**42**	**43**
M = 93.13	M = 191.07	M = 261.40
C_6H_7N	$C_7H_{11}BrO$	$C_{14}H_{15}NS_2$

3-Phenyl-3,4,5,6,7,8-hexahydro-2*H*-cyclohepta[*d*]thiazole-2-thione **43** was prepared according to general **procedure A** from aniline **37** (487 mg, 5.23 mmol, 1.00 equiv.). It was further purified using column chromatography (SiO_2, 12 g, EtOAc in LP = 5-50%) yielding 228 mg (17%) of pure product according to ^{1}H-NMR.

Yield	228 mg (17%)
Appearance	bright beige solid
m.p.	197.2-197.6 °C (EtOAc)
TLC	R_f (LP:EtOAc = 5:1): 0.27
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.59 – 7.53 (m, 2H, PhH3/H5), 7.52 – 7.45 (m, 1H, PhH4), 7.22 (m, 2H, PhH2/H6), 2.66 – 2.53 (m, 2H, H8), 2.42 – 2.19 (m, 2H, H4), 1.87 – 1.73 (m, 4H, H6 & H7), 1.65 – 1.45 (m, 2H, H5).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 187.1 (s, C2), 141.7 (s, C3a), 138.6 (s, PhC1), 129.9 (d, PhC3/C5), 129.5 (d, PhC4), 128.4 (d, PhC2/C6), 124.2 (s, C8a), 30.7 (t, C6), 29.7 (t, C4), 27.1, 27.0 (2×t, C8 & C7), 25.8 (t, C5).
HRMS (ESI$^+$)	calc. for $C_{14}H_{16}NS_2$ $[M+H]^+$: 262.0719, found: 262.0725 (- 2.32 ppm)

5.3.5 3-(4-Methoxyphenyl)-3,4,5,6,7,8-hexahydro-2*H*-cyclohepta[*d*]thiazole-2-thione (**45**)



39
M = 123.16
C_7H_9NO

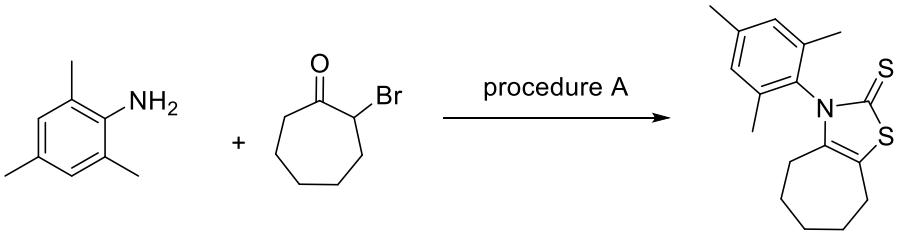
42
M = 191.07
$C_7H_{11}BrO$

45
M = 291.43
$C_{15}H_{17}NOS_2$

3-(4-Methoxyphenyl)-3,4,5,6,7,8-hexahydro-2*H*-cyclohepta[*d*]thiazole-2-thione **45** was prepared according to general **procedure A** from 4-methoxyaniline **39** (645 mg, 5.23 mmol, 1.00 equiv.) yielding 619 mg (41%) of pure product according to ^{1}H-NMR directly after precipitation.

Yield	619 mg (41%)
Appearance	beige solid
m.p.	119.2-120.1 °C (H_2O)
TLC	R_f (LP:EtOAc = 5:1, potassium permanganate stain): 0.23
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.12, 7.03 (2×d, *J* = 8.5 Hz, 2×2H, PhH2/H6 & PhH3/H5), 3.85 (s, 3H, OCH_3), 2.64 – 2.57 (m, 2H, H8), 2.34 – 2.26 (m, 2H, H4), 1.82 – 1.71 (m, 4H, H6 & H7), 1.65 – 1.53 (m, 2H, H5).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 187.3 (s, C2), 160.0 (d, PhC4), 142.1 (s, C3a), 131.2 (s, PhC1), 129.4, 115.0 (2×d, PhC2/C6, PhC3/C5), 123.8 (s, C8a), 55.5 (q, OCH_3), 30.7 (t, C6 or C7), 29.7 (t, C4), 27.1, 27.0 (2×t, C8 & C6 or C7), 25.8 (t, C5).
HRMS (ESI$^+$)	calc. for $C_{15}H_{18}NOS_2$ $[M+H]^+$: 292.0824, found: 292.0829 (- 1.63 ppm)

5.3.6 3-Mesityl-3,4,5,6,7,8-hexahydro-2*H*-cyclohepta[*d*]thiazole-2-thione (46)



40
M = 135.21
$C_9H_{13}N$

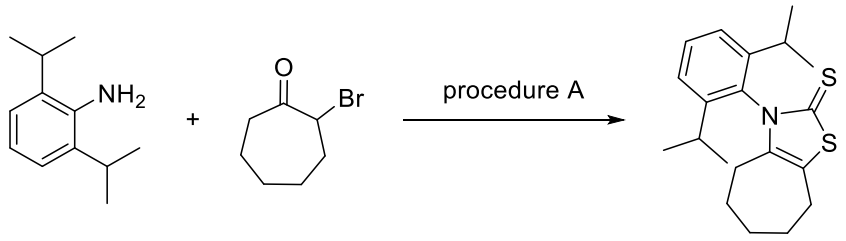
42
M = 191.07
$C_7H_{11}BrO$

46
M = 303.48
$C_{17}H_{21}NS_2$

3-Mesityl-3,4,5,6,7,8-hexahydro-2*H*-cyclohepta[*d*]thiazole-2-thione **46** was prepared according to general **procedure A** from 2,4,6-trimethylaniline **40** (707 mg, 5.23 mmol, 1.00 equiv.) yielding 596 mg (38%) of pure product according to ^{1}H-NMR directly after precipitation. Spectral data[63] of the product are in accordance with the literature.

Yield	596 mg (38%)
Appearance	beige solid
m.p.	135.3-137.0 °C (*n*-pentane)
TLC	R_f (LP:EtOAc = 5:1, potassium permanganate stain): 0.33
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.00 (s, 2H, Ph H3/5), 2.66 – 2.60 (m, 2H, H8), 2.33 (s, 3H, PhC**H$_3$**(C4)), 2.24 – 2.16 (m, 2H, H4), 2.01 (s, 6H, PhCH_3(C2/C6)), 1.85-1.74 (m, 4H, H6 & H7), 1.62-1.53 (m, 2H, H5).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 185.4 (s, C2), 140.8 (s, C3a), 139.6 (d, PhC4), 135.7 (s, PhC1), 134.2 (d, Ar C2/6), 129.7 (d, Ar C3/C5), 124.5 (s, C8a), 31.1 (t, C6 or C7), 28.9 (t, C4), 27.5 (t, C8), 27.4 (t, C6 or C7), 26.5 (t, C5), 21.4 (q, PhC4-CH_3), 17.8 (q, PhC2/C6-CH_3).
HRMS (ESI^+)	calc. for $C_{17}H_{22}NO_2$ $[M+H]^+$: 304.1188, found: 304.1203 (- 4.93 ppm)

5.3.7 3-(2,6-Diisopropylphenyl)-3,4,5,6,7,8-hexahydro-2*H*-cyclohepta[*d*]thiazole-2-thione (47)



41
M = 177.29
$C_{12}H_{19}N$

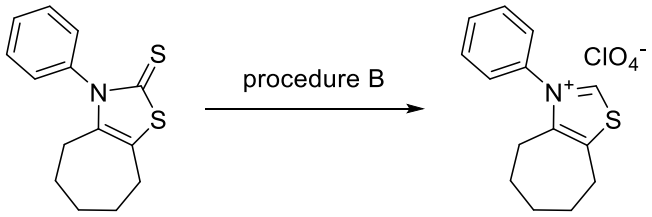
42
M = 191.07
$C_7H_{11}BrO$

47
M = 345.56
$C_{20}H_{27}NS_2$

3-(2,6-Diisopropylphenyl)-3,4,5,6,7,8-hexahydro-2*H*-cyclohepta[*d*]thiazole-2-thione **47** was prepared according to general **procedure A** from 2,6-diisopropylaniline **41** (928 mg, 5.23 mmol, 1.00 equiv.) yielding 972 mg (54%) of pure product according to ^{1}H-NMR directly after precipitation. Spectral data[63] of the product are in accordance with the literature.

Yield	972 mg (54%)
Appearance	slightly yellow solid
m.p.	165.0-165.1 °C (*n*-pentane)
TLC	R_f (LP:EtOAc = 10:1, potassium permanganate stain): 0.31
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.47 (t, J = 7.8 Hz, 1H, PhH4), 7.29 (d, J = 7.8 Hz, 2H, PhH3/H5), 2.68 – 2.62 (m, 2H, H8), 2.46 (sept, J = 6.8 Hz, 2H, Ph-CH), 2.26 – 2.14 (m, 2H, H4), 1.88 – 1.70 (m, 4H, H6 & H7), 1.59 – 1.50 (m, 2H, H5), 1.28 (d, J = 6.8 Hz, 6H, $CH(CH_3)_2$), 1.13 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 186.7 (s, C2), 146.4 (d, PhC2/C6), 141.8 (s, C3a), 133.7 (s, PhC1), 130.3 (d, PhC4), 124.6 (d, PhC3/C5), 124.0 (s, C8a), 31.0 (t, C6), 29.4 (t, C4), 28.8 (d, $\underline{\mathbf{C}}H(CH_3)_2$), 27.5 (t, C8), 27.2 (t, C7), 26.3 (t, C5), 24.4 (q, $CH(\underline{\mathbf{C}}H_3)_2$), 23.9 (q, $CH(\underline{\mathbf{C}}H_3)_2$).
HRMS (ESI^+)	calc. for $C_{20}H_{28}NS_2$ $[M+H]^+$: 346.1658, found: 346.1675 (- 5.11 ppm)

5.3.8 3-Phenyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate (17)



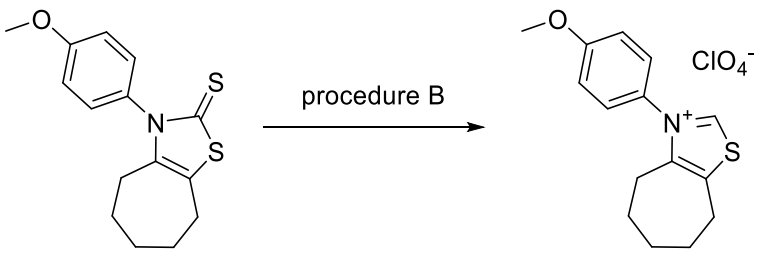
43
M = 261.40
$C_{14}H_{15}NS_2$

17
M = 329.80
$C_{14}H_{16}ClNO_4S$

3-Phenyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate **17** was prepared according to general **procedure B** from **43** (200 mg, 0.77 mmol, 1.00 equiv.). The product was not obtained pure after precipitation and purification *via* column chromatography with SiO_2 (12 g) and a gradient of MeOH in DCM from 0-20% and a second column using 5-10% afforded the target compound in a yield of 97 mg (39%) and pure according to ^{1}H-NMR.

Yield	97 mg (39%)
Appearance	brown oil
TLC	R_f (DCM:MeOH = 9:1, potassium permanganate stain): 0.28
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.54 (s, 1H, H2), 7.71 – 7.57 (m, 3H, PhH3/H5, PhH4), 7.54 – 7.48 (m, 2H, PhH2/H6), 3.13 – 3.01 (m, 2H, H8), 2.78 – 2.69 (m, 2H, H4), 2.02 – 1.83 (m, 4H, H6 & H7), 1.76 – 1.65 (m, 2H, H5).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 154.4 (d, C2), 148.5 (s, C3a), 140.3 (s, C8a), 136.9 (s, PhC1), 131.9 (d, PhC4), 130.6 (d, PhC3/C5), 126.2 (d, PhC2/C6), 30.8 (t, C6), 28.2 (t, C8), 28.0 (t, C4), 26.4 (t, C7), 25.2 (t, C5).
HRMS (ESI$^+$)*	calc. for $C_{14}H_{16}NS$ $[M\text{-}ClO_4]^+$: 230.0998, found: 230.0998 (± 0.00 ppm)

5.3.9 3-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate (**19**)



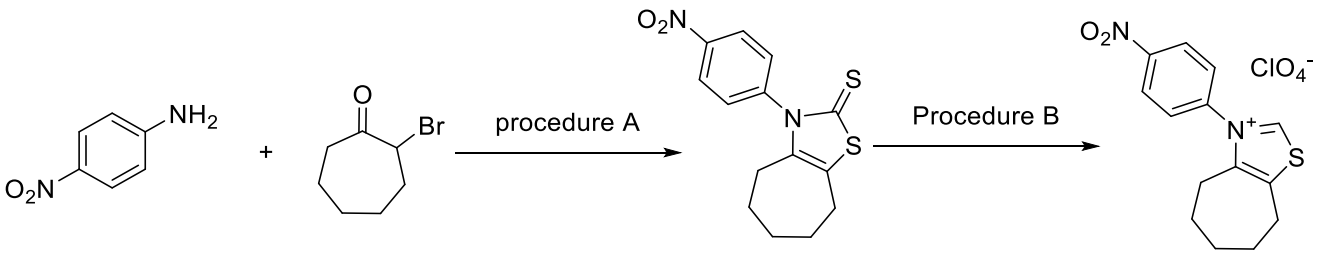
45
M = 291.43
$C_{15}H_{17}NOS_2$

19
M = 359.82
$C_{15}H_{18}ClNO_5S$

3-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate **19** was prepared according to general **procedure B** from **45** (475 mg, 1.63 mmol, 1.00 equiv.) yielding 512 mg (87%) of the target compound pure according to ^{1}H-NMR.

Yield	512 mg (87%)
Appearance	brown oil
TLC	R_f (DCM:MeOH = 9:1, potassium permanganate stain): 0.36
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.50 (s, 1H, H2), 7.43, 7.05 (2×d, *J* = 8.6 Hz, 2×2H, PhH2/H6 & PhH3/H5), 3.87 (s, 3H, OCH_3), 3.18 – 2.96 (m, 2H, H8), 2.83 – 2.68 (m, 2H, H4), 1.96 – 1.81 (m, 4H, H6 & H7), 1.71 – 1.61 (m, 2H, H5).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 161.8 (s, PhC4), 154.4 (d, C2), 148.7 (s, C3a), 139.9 (s, C8a), 129.5 (s, PhC1), 127.5, 115.5 (2×d, PhC2/C6 & PhC3/C5), 56.0 (q, OCH_3), 30.8 (t, C6), 28.2 (t, C8), 27.9 (t, C4), 26.5 (t, C7), 25.2 (t, C5).
HRMS (ESI$^+$)	calc. for $C_{15}H_{18}NOS$ $[M\text{-}ClO_4]^+$: 260.1104, found: 260.1119 (– 5.99 ppm)

5.3.10 3-(4-Nitrophenyl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate (2-step procedure, 18)



38
M = 138.13
$C_6H_6N_2O_2$

42
M = 191.07
$C_7H_{11}BrO$

44
M = 306.40
$C_{14}H_{14}N_2O_2S_2$

18
M = 374.79
$C_{14}H_{15}ClN_2O_6S$

First step: 3-(4-Nitrophenyl)-3,4,5,6,7,8-hexahydro-2*H*-cyclohepta[*d*]thiazole-2-thione **44** was prepared according to general **procedure A** from 4-nitroaniline **38** (723 mg, 5.23 mmol, 1.00 equiv.). It was further purified using column chromatography yielding 361.0 mg **44** however still containing an unidentified impurity (^{1}H-NMR). The material was used without further purification in the next step.

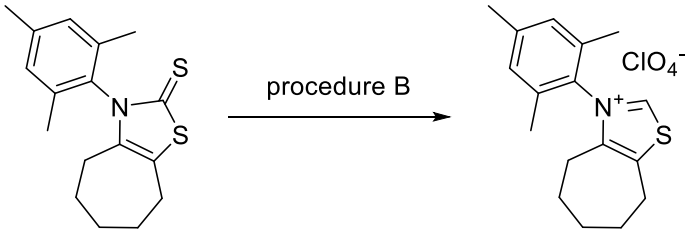
Yield	361.0 mg (containing an unidentified impurity <20 mol%)
Appearance	orange solid
TLC	R_f (LP:EtOAc = 5:1, potassium permanganate stain): 0.33
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.54 – 8.36, 7.52 – 7.40 (2×m, 2×2H, PhH2/H6, PhH3/H5), 2.63 (dd, *J* = 15.8, 9.2 Hz, 2H, H8), 2.31 (td, *J* = 11.4, 5.8 Hz, 2H, H4), 1.90 – 1.75 (m, 4H, H6 & 7), 1.64 (dt, *J* = 16.9, 5.4 Hz, 2H, H5).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 187.4 (s, C2), 148.0, 143.9 (2×s, PhC1 & PhC4), 140.6 (s, H3a), 130.1 (d, PhC2/C6), 125.5 (s, H8a), 125.2 (d, PhC3/C5), 30.5 (t, C6), 29.7 (t, C4), 27.1 (t, C8), 26.9 (t, C7), 25.8 (t, C5).
HRMS (ESI$^+$)*	calc. for $C_{14}H_{15}N_2O_2S_2$ $[M+H]^+$: 307.0568, found: 307.0568 (± 0.00 ppm)

3-(4-Nitroxyphenyl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate **18** was prepared according to general **procedure B** from the crude mixture of **44** (170.6 mg, stoichiometric calculations assuming a content of 1.63 mmol, 1.00 equiv.). Purification was achieved through trituration of the obtained crude oil with Et_2O resulting in the precipitation of

the target compound which was washed with $CHCl_3$ to yield 60 mg (29%) which were pure according to ^{1}H-NMR.

Yield	60 mg (29%)
Appearance	beige solid
m.p.	173-175 °C (Kofler, MeOH)
TLC	R_f (DCM:MeOH = 9:1, potassium permanganate stain): 0.36
^{1}H NMR (600 MHz, CD_3OD)	δ 10.08 (s, 1H, H2), 8.58 (d, *J* = 9.0 Hz, 2H, PhH2/H6 or PhH3/H5), 7.92 (d, *J* = 9.0 Hz, 2H, PhH2/H6 or PhH3/H5), 3.23 – 3.11 (m, 2H, H8), 2.90 – 2.74 (m, 2H, H4), 2.05 – 1.97 (m, 2H, H6), 1.94 – 1.88 (m, 2H, H7), 1.81 – 1.73 (m, 2H, H5).
^{13}C NMR (151 MHz, CD_3OD)	δ 149.6 (s, PhC1 or PhC4), 148.6 (s, C3a), 141.3 (s, PhC1 or PhC4), 140.1 (s, C8a), 127.8, 125.2 (2×d, PhC2/C6 & PhC3/C5), 30.3 (t, C6), 27.3 (t, C4), 27.1 (t, C8), 26.1 (t, C7), 24.6 (t, C5). C2 is not visible, presumably due to neighboring D exchange resulting in broadening of the signal.
HRMS (ESI^+)*	calc. for $C_{17}H_{22}NO_2$ $[M\text{-}ClO_4]^+$: 275.0849, found: 275.0848 (- 0.36 ppm)

5.3.11 3-Mesityl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate (20)



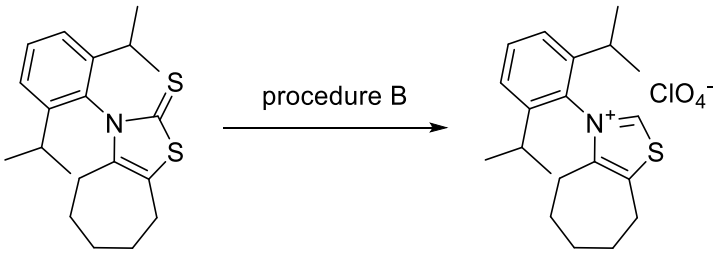
46
M = 303.48
$C_{17}H_{21}NS_2$

20
M = 371.88
$C_{17}H_{22}ClNO_4S$

3-Mesityl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate **20** was prepared according to general **procedure B** from **46** (700 mg, 2. 31 mmol, 1.00 equiv.) yielding 776 mg (90%) of the target compound pure according to ^{1}H-NMR directly upon precipitation. Spectral data[63] and m.p.[63] of the product are in accordance with the literature.

Yield	776 mg (90%)
Appearance	beige-brown solid
m.p.	135.6-135.7 °C (DCM) lit.[95] 134-136 °C
TLC	R_f (DCM:MeOH = 9:1, potassium permanganate stain): 0.43
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.61 (s, 1H, H2), 7.06 (s, 2H, Ph-H3/H5), 3.28 – 3.04 (m, 2H, H8), 2.58 – 2.48 (m, 2H, H4), 2.37 (s, 3H, $PhCH_3$(C4)), 2.00 – 1.93 (m, 8H, $PhCH_3$(C2/5), H6), 1.91 – 1.82 (m, 2H, H7), 1.70 – 1.61 (m, 2H, H5).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 155.5 (d, C2), 148.0 (s, C3a), 142.2 (s, PhC4), 141.1 (s, C8a), 134.1 (s, PhC2/C6), 132.9 (s, PhC1), 130.3 (d, PhC3/C5), 30.9 (t, C6), 28.3 (t, C8), 27.0 (t, C4), 26.8 (t, C7), 25.7 (t, C5), 21.3 (q, $PhCH_3$(C4)), 17.4 (q, $PhCH_3$(C2/C6)).
HRMS (ESI^+)	calc. for $C_{17}H_{22}NS^+$ $[M\text{-}ClO_4]^+$: 272.1467, found: 272.1479 (-4.22 ppm)

5.3.12 3-(2,6-Diisopropylphenyl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate (21)



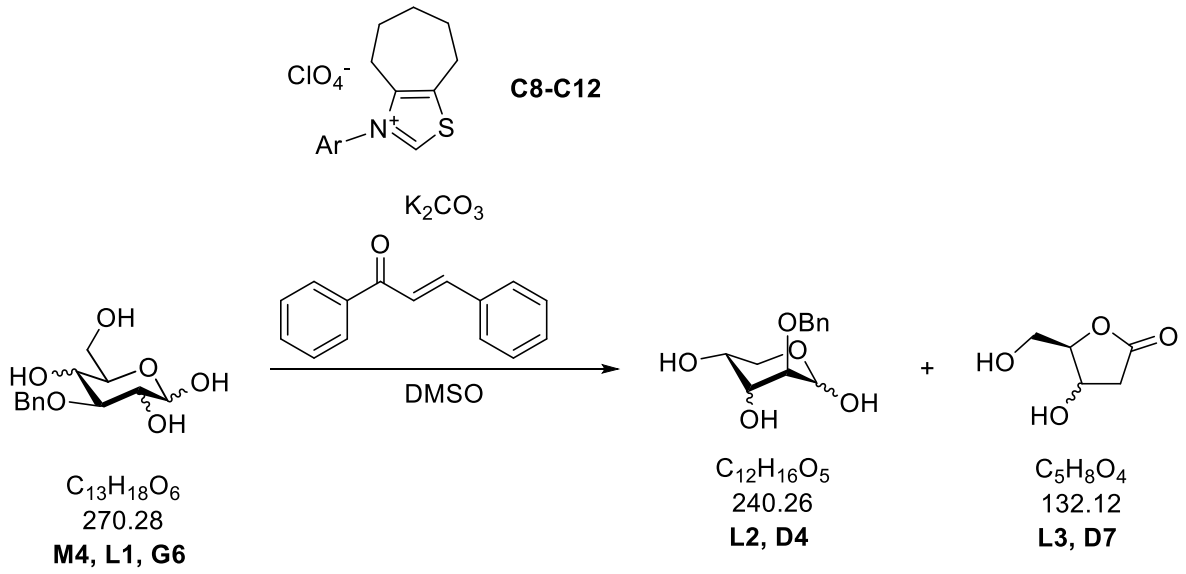
47
M = 345.56
$C_{20}H_{27}NS_2$

21
M = 413.96
$C_{20}H_{28}ClNO_4S$

3-(2,6-Diisopropylphenyl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate **21** was prepared according to general **procedure B** from **47** (700 mg, 2.03 mmol, 1.00 equiv.) yielding 696 mg (83%) of the target compound as beige form pure according to ^{1}H-NMR directly upon evaporation. Spectral data[63] of the product are in accordance with the literature.

Yield	696 mg (83%)
Appearance	beige foam
m.p.	96.7-97.2 °(DCM) lit.[95] 105-108 °C
TLC	R_f (DCM:MeOH = 9:1, potassium permanganate stain): 0.49
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.65 (s, 1H, H2), 7.59 (t, *J* = 7.9 Hz, 1H, Ph H4), 7.35 (d, *J* = 7.9 Hz, 2H, Ph H3/H5), 3.22 – 3.14 (m, 1H, H8), 2.59 – 2.46 (m, 1H, H4), 2.05 (sept, *J* = 6.8 Hz, 2H, C**H**$(CH_3)_2$), 1.99 – 1.92 (m, 1H, H6), 1.90 (q, *J* = 4.7, 4.1 Hz, 1H, H7), 1.62 (pent, *J* = 5.1 Hz, 1H, H5), 1.16 (d, *J* = 6.9 Hz, 6H, C**H**$_3$-CH).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 155.4 (d, C2), 148.8 (s, C3a), 145.0 (s, PhC2/C6), 141.2 (s, C8a), 132.6 (d, PhC4), 132.2 (s, PhC1), 125.3 (d, PhC3/C5), 30.9 (t, C6), 28.9 (d, **C**H$(CH_3)_2$), 28.3 (t, C8), 27.4 (t, C4), 26.7 (t, C7), 25.6 (t, C5), 24.9, 23.3 (2×q, 2×CH(**C**H$_3)_2$).
HRMS (ESI$^+$)	calc. for $C_{10}H_{28}NS$ $[M\text{-}ClO_4]^+$: 314.1937, found: 314.1951 (-4.61 ppm)

5.4 General procedure for NHC-catalyzed dehomologation



Dehomologation:

Stock solutions of the sugars **M4**, **L1** and **G6** (0.80 mol/l), the catalysts **C8-C12** (0.20 mol/l) and chalcone (1.6 mol/l) in DMSO were prepared.

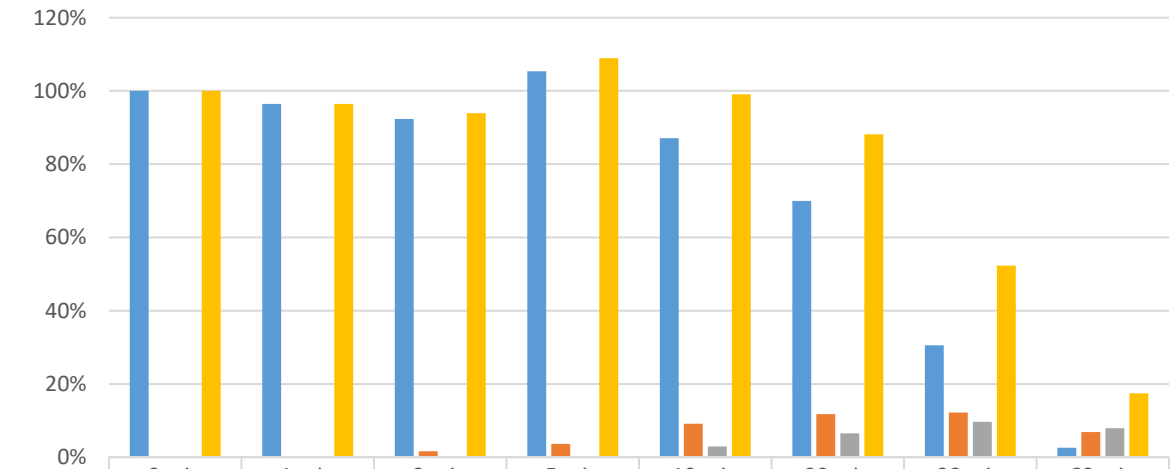
Potassium carbonate (4.4 mg, 0.032 mmol, 0.20 equiv.) was charged into a microwave vial. 200 µl each of the benzylated-sugar stock solution (43.2 mg, 0.16 mmol, 1.00 equiv.), the catalyst stock solution (0.04 mmol, 0.25 equiv.) and the chalcone (66.6 mg, 0.32 mmol, 2.00 equiv.), as well as DMSO (dry, 1.4 mL) were added. The microwave vial was capped and the reaction mixture was set under Ar atmosphere *via* Schlenk technique. After stirring for 2 min at rt a t0 sample was taken to later correct for the actual initial benzyl hexose concentration. The reaction mixture was heated in a heating block at 130°C for 60 minutes with samples of roughly 0.2 ml being taken and transferred to an extra vial after 1 min, 3 min, 5 min, 10 min, 20 min, 30 min and 60 min and were either directly derivatized or stored at -18 °C until further processing (<14 h).

Derivatization:

Exactly 125 µl from each vial were transferred to an Eppendorf vial, a solution of erythritol in H_2O (60 µl, 100 mmol/l, 0.012 mmol) was added (as silylation standard) and volatiles were removed in the speed vac (0.7 mbar, 26.5 °C, ~ 2 h). For each of the samples obtained in this manner the following procedure was applied:

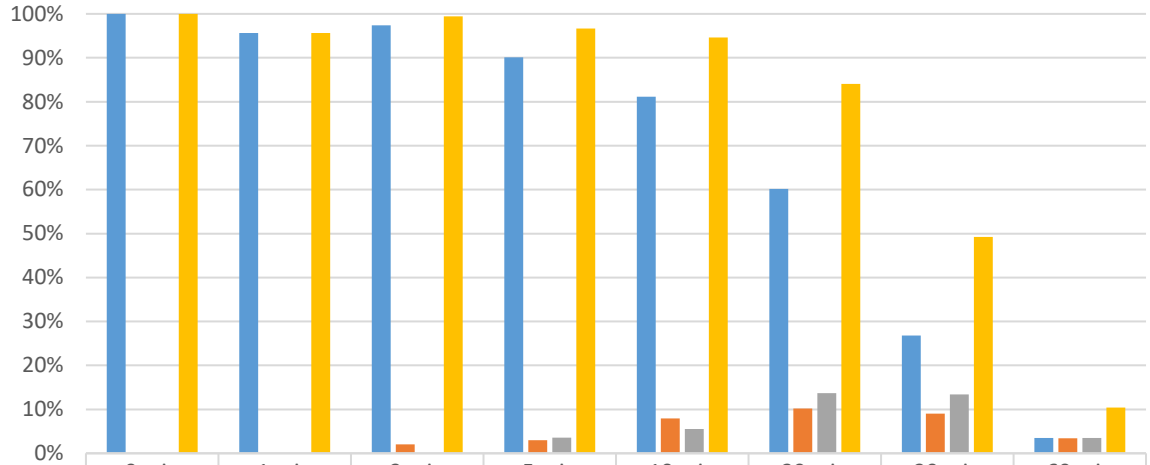
The residue was transferred in MeCN:H_2O=1:4 (2×0.5 mL), onto a short pipette column of dry C18 silica gel (~100 mg). The vial was once rinsed with MeCN (0.2 ml) onto the column and eluted with MeCN:H_2O 1:4 (0.5 ml). The obtained eluent was concentrated *in vacuo*. A solution of *O*-methylhydroxylamin in pyridine (anh., 200 µl, 40 mg/ml) was added to the residue and heated to 70 °C for 1 h. Next, a solution of DMAP in pyridine (anh., 200 µl, 1.5 mg/ml) was added as well as BSTFA (+1% TMSCl, 200 µl). The mixture was stirred at 70 °C for another 2 h. After cooling to rt, EtOAc (400 µl) was added, resulting in a maximum concentration of starting material derived components of 10 mM and 6 mM of erythritol. 600 µl were taken out and diluted with a solution of methylbenzoate in EtOAc (600 µl, 2 mM), The sample was filtered via syringe filter and subjected to GC analysis.

5.4.1 Time-resolved screening of 3-*O*-benzyl-D-glucose 7 with phenyl catalyst 17



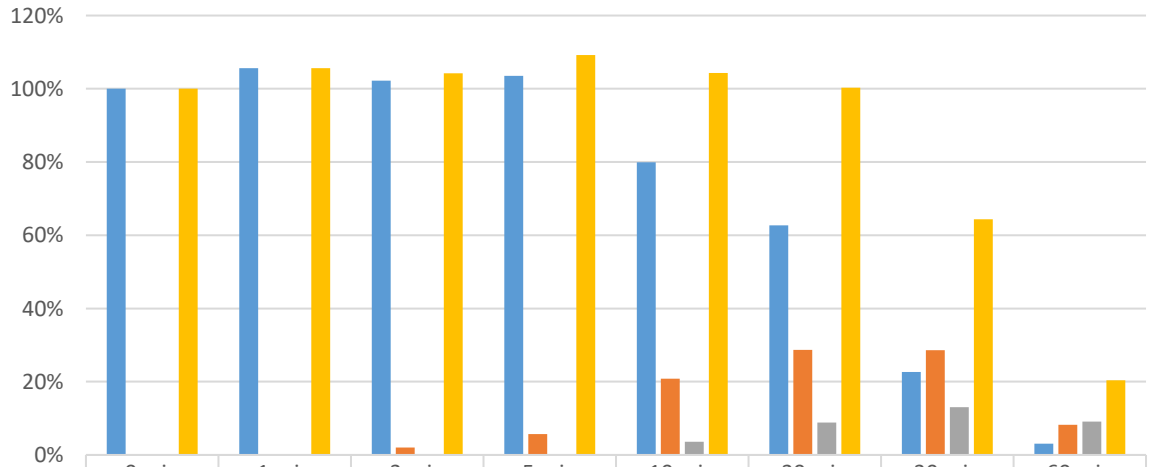
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	96%	92%	105%	87%	70%	31%	3%
pentose	0%	0%	2%	4%	9%	12%	12%	7%
lactone	0%	0%	0%	0%	3%	6%	10%	8%
sum	100%	96%	94%	109%	99%	88%	52%	17%

5.4.2 Time-resolved screening of 3-*O*-benzyl-D-galactose 14 with phenyl catalyst **17**



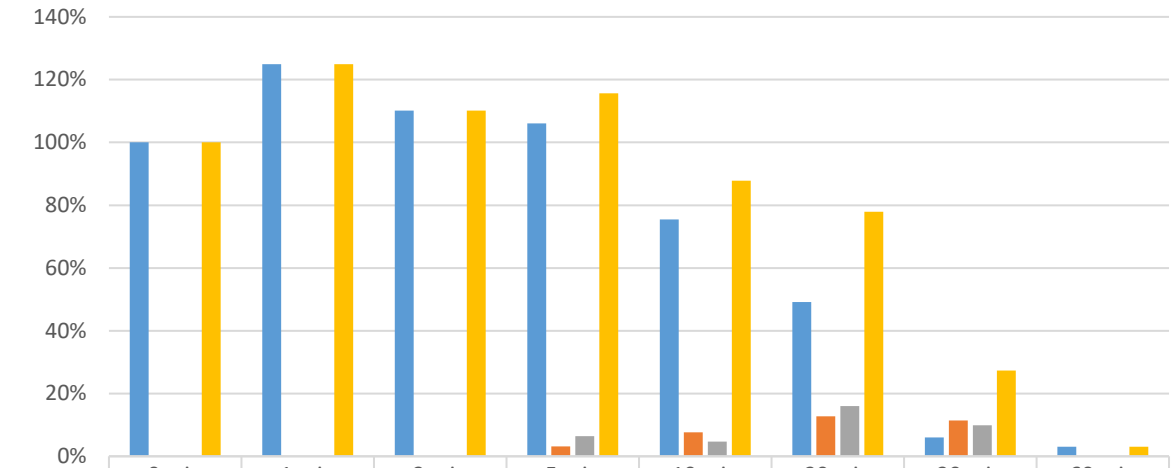
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	96%	97%	90%	81%	60%	27%	3%
pentose	0%	0%	2%	3%	8%	10%	9%	3%
lactone	0%	0%	0%	4%	6%	14%	13%	4%
sum	100%	96%	99%	97%	95%	84%	49%	10%

5.4.3 Time-resolved screening of 3-*O*-benzyl-D-mannose 13 with phenyl catalyst **17**



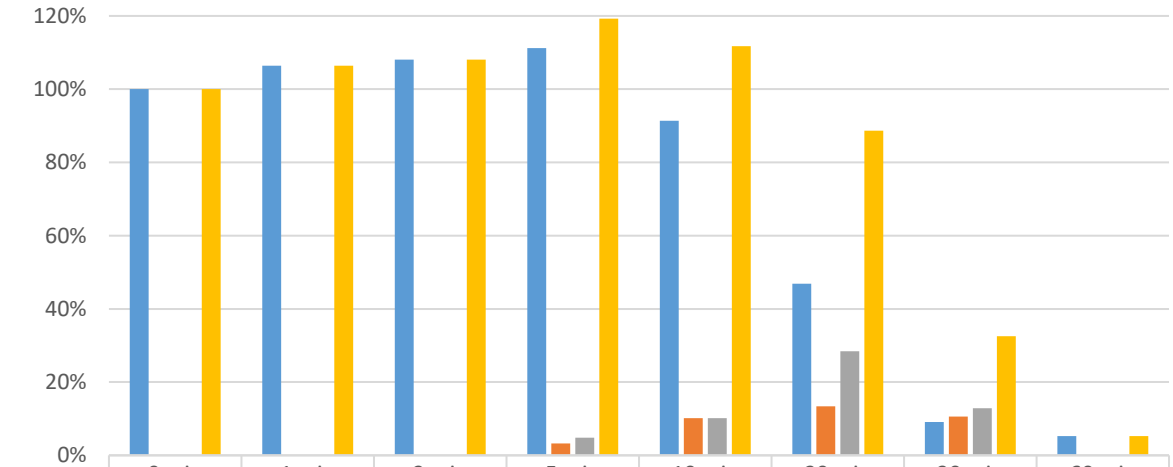
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	106%	102%	104%	80%	63%	23%	3%
pentose	0%	0%	2%	6%	21%	29%	29%	8%
lactone	0%	0%	0%	0%	4%	9%	13%	9%
sum	100%	106%	104%	109%	104%	100%	64%	20%

5.4.4 Time-resolved screening of 3-*O*-benzyl-D-glucose 7 with 4-methoxyphenyl catalyst 19



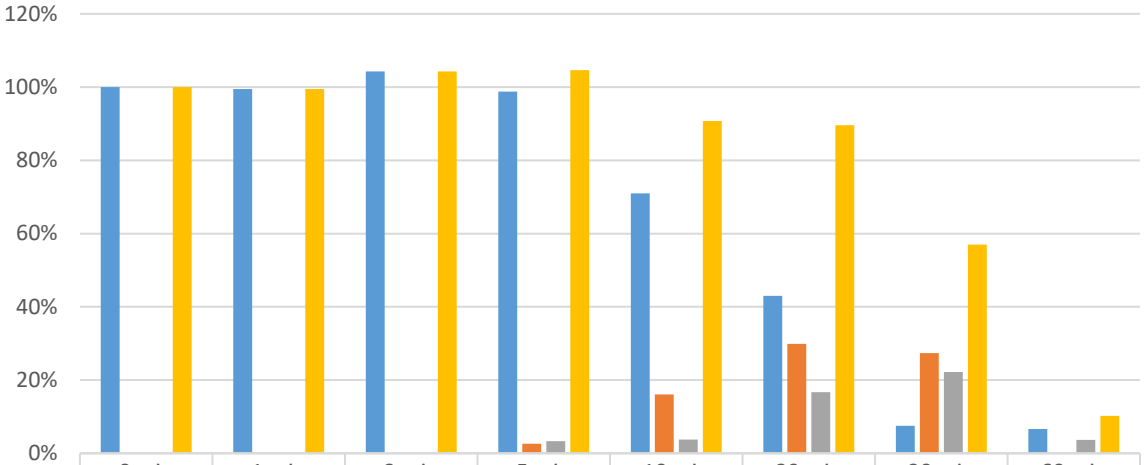
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	125%	110%	106%	76%	49%	6%	3%
pentose	0%	0%	0%	3%	8%	13%	11%	0%
lactone	0%	0%	0%	6%	5%	16%	10%	0%
sum	100%	125%	110%	116%	88%	78%	27%	3%

5.4.5 Time-resolved screening of 3-*O*-benzyl-D-galactose 14 with 4-methoxyphenyl catalyst 19



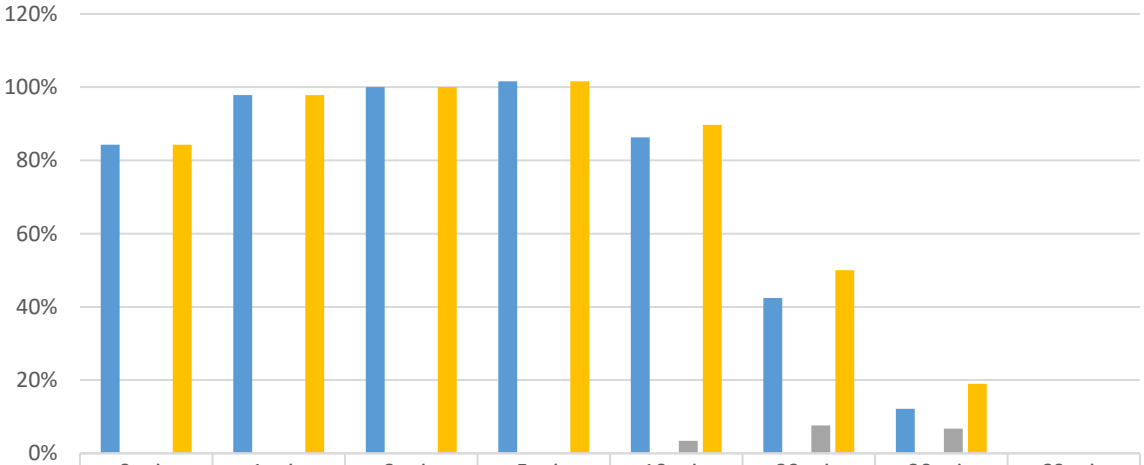
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	106%	108%	111%	91%	47%	9%	5%
pentose	0%	0%	0%	3%	10%	13%	11%	0%
lactone	0%	0%	0%	5%	10%	28%	13%	0%
sum	100%	106%	108%	119%	112%	89%	33%	5%

5.4.6 Time-resolved screening of 3-*O*-benzyl-D-mannose 13 with 4-methoxyphenyl catalyst 19



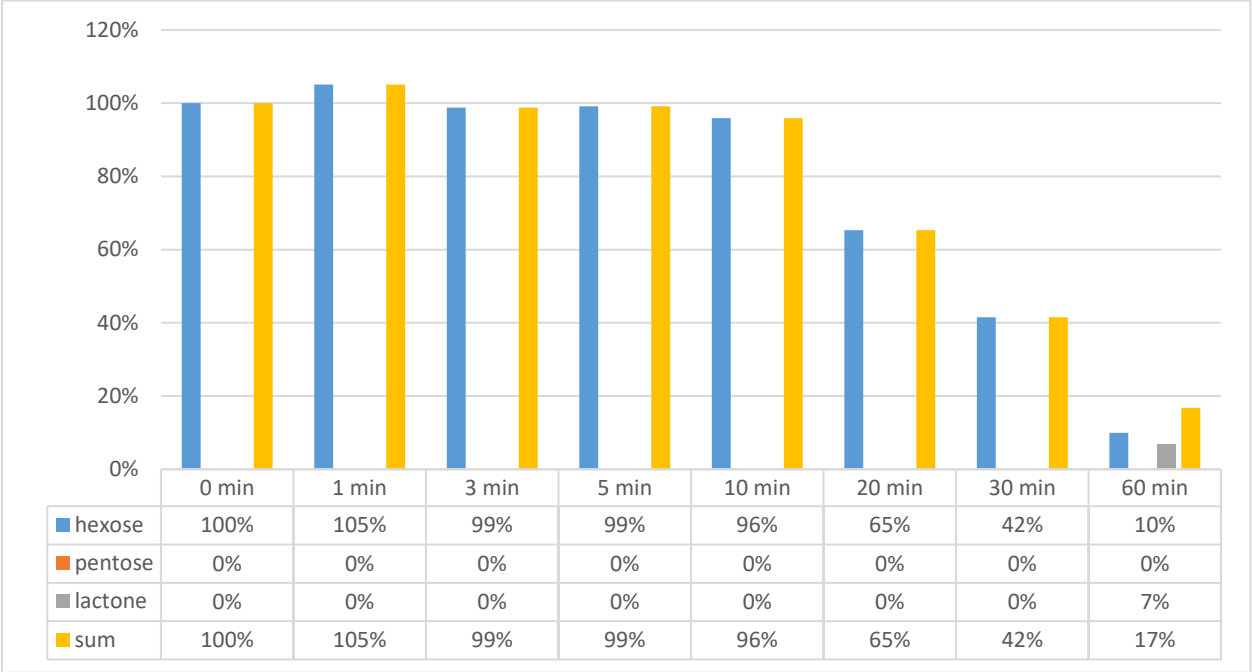
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	99%	104%	99%	71%	43%	7%	7%
pentose	0%	0%	0%	3%	16%	30%	27%	0%
lactone	0%	0%	0%	3%	4%	17%	22%	4%
sum	100%	99%	104%	105%	91%	90%	57%	10%

5.4.7 Time-resolved screening of 3-*O*-benzyl-D-glucose 7 with 4-nitrophenyl catalyst 18



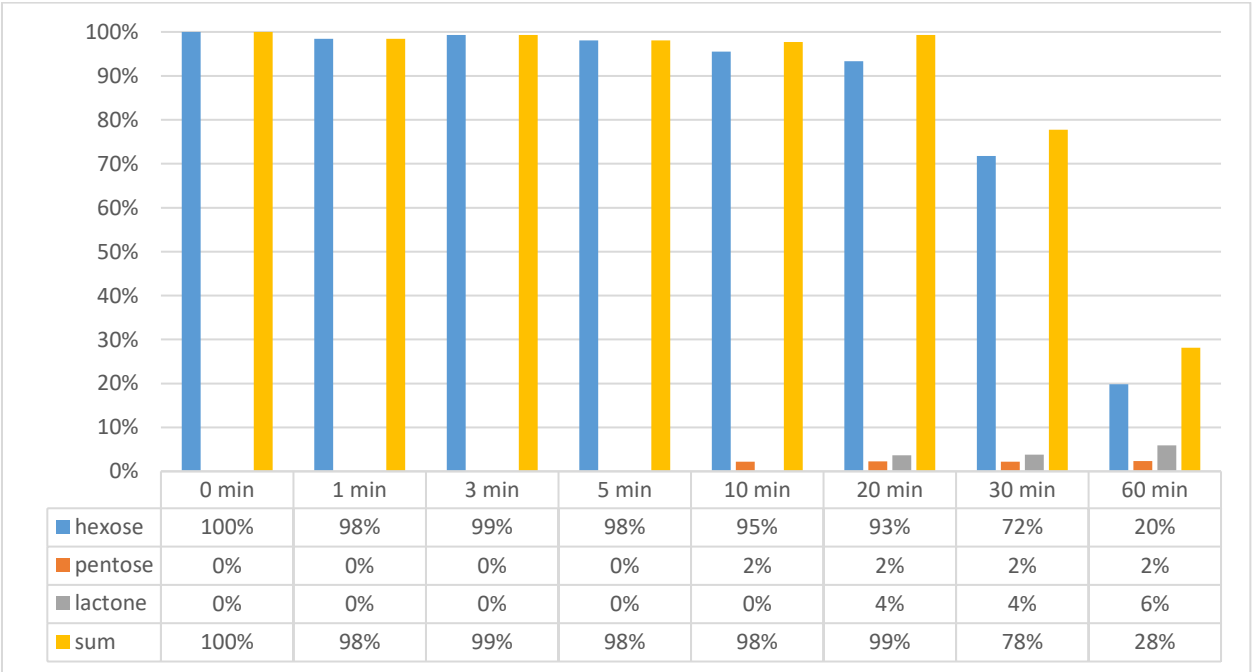
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	84%	98%	100%	102%	86%	42%	12%	0%
pentose	0%	0%	0%	0%	0%	0%	0%	0%
lactone	0%	0%	0%	0%	3%	8%	7%	0%
sum	84%	98%	100%	102%	90%	50%	19%	0%

5.4.8 Time-resolved screening of 3-*O*-benzyl-D-galactose 14 with 4-nitrophenyl catalyst 18



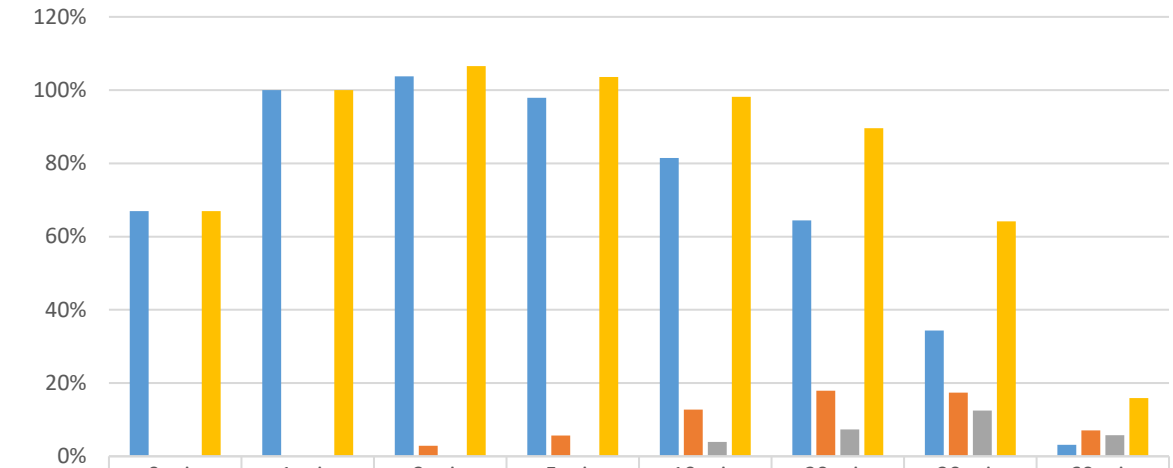
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	105%	99%	99%	96%	65%	42%	10%
pentose	0%	0%	0%	0%	0%	0%	0%	0%
lactone	0%	0%	0%	0%	0%	0%	0%	7%
sum	100%	105%	99%	99%	96%	65%	42%	17%

5.4.9 Time-resolved screening of 3-*O*-benzyl-D-mannose 13 with 4-nitrophenyl catalyst 18



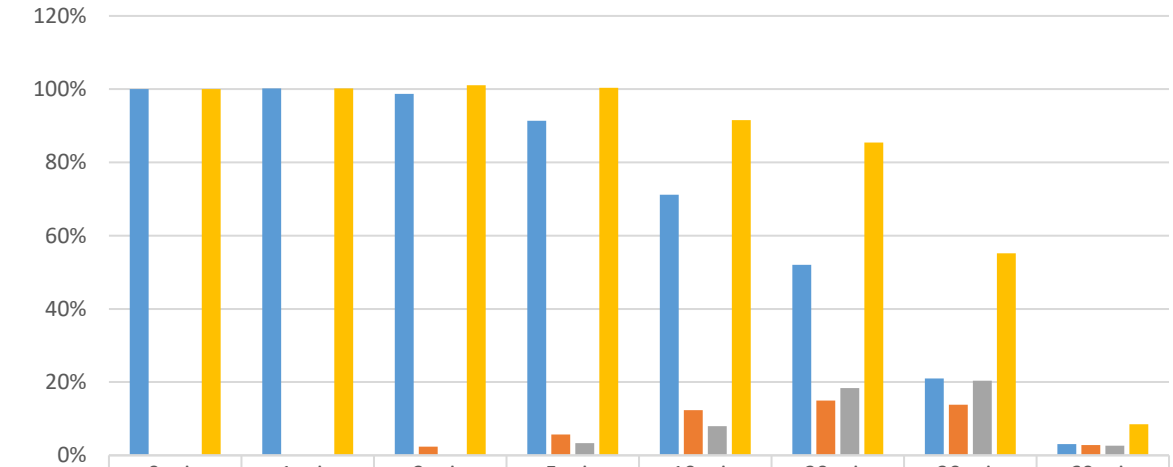
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	98%	99%	98%	95%	93%	72%	20%
pentose	0%	0%	0%	0%	2%	2%	2%	2%
lactone	0%	0%	0%	0%	0%	4%	4%	6%
sum	100%	98%	99%	98%	98%	99%	78%	28%

5.4.10 Time-resolved screening of 3-*O*-benzyl-D-glucose 7 with mesityl catalyst 20



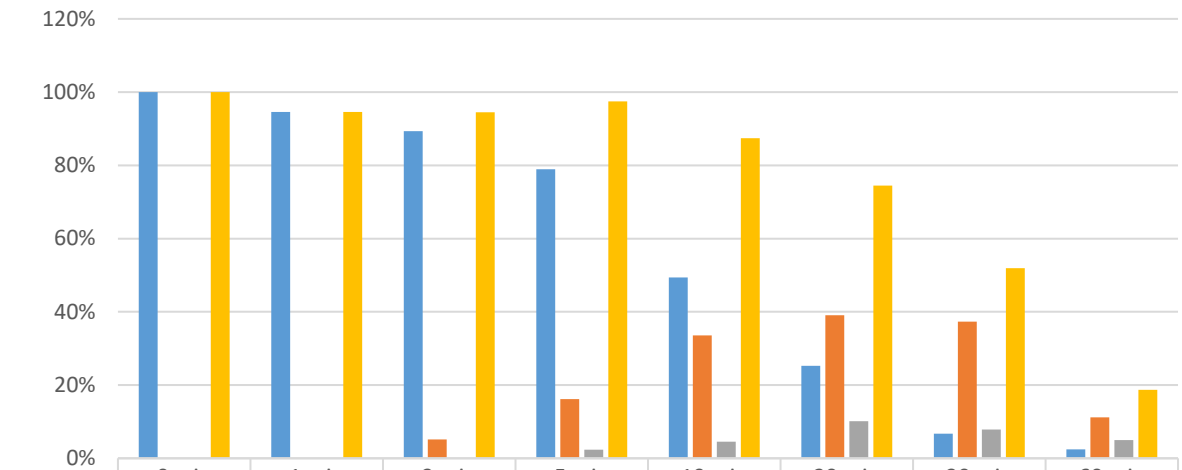
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	67%	100%	104%	98%	81%	64%	34%	3%
pentose	0%	0%	3%	6%	13%	18%	17%	7%
lactone	0%	0%	0%	0%	4%	7%	13%	6%
sum	67%	100%	107%	104%	98%	90%	64%	16%

5.4.11 Time-resolved screening of 3-*O*-benzyl-D-galactose 14 with mesityl catalyst 20



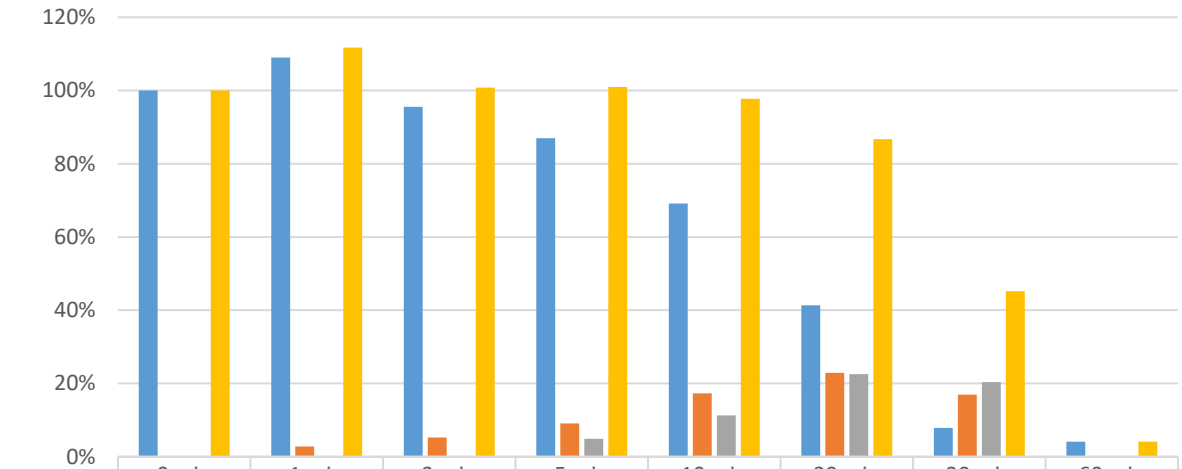
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	100%	99%	91%	71%	52%	21%	3%
pentose	0%	0%	2%	6%	12%	15%	14%	3%
lactone	0%	0%	0%	3%	8%	18%	20%	3%
sum	100%	100%	101%	100%	92%	85%	55%	9%

5.4.12 Time-resolved screening of 3-*O*-benzyl-D-mannose 13 with mesityl catalyst 20



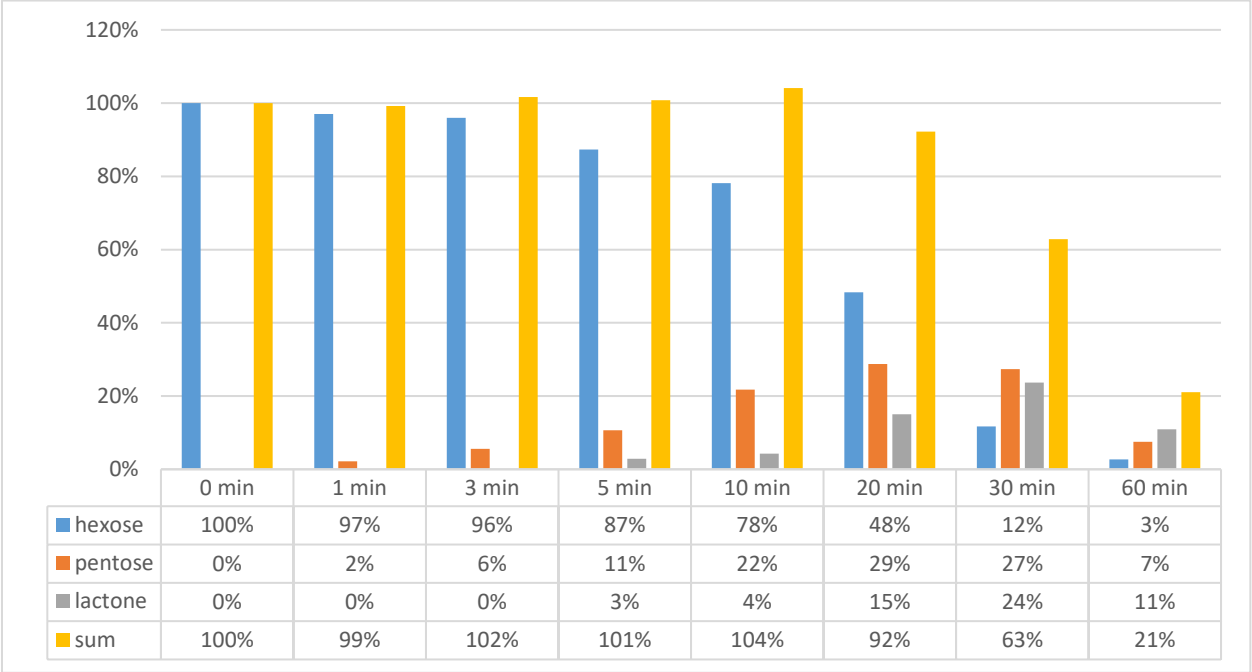
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	95%	89%	79%	49%	25%	7%	2%
pentose	0%	0%	5%	16%	34%	39%	37%	11%
lactone	0%	0%	0%	2%	4%	10%	8%	5%
sum	100%	95%	94%	97%	87%	74%	52%	19%

5.4.13 Time-resolved screening of 3-*O*-benzyl-D-glucose 7 with dipp catalyst 21



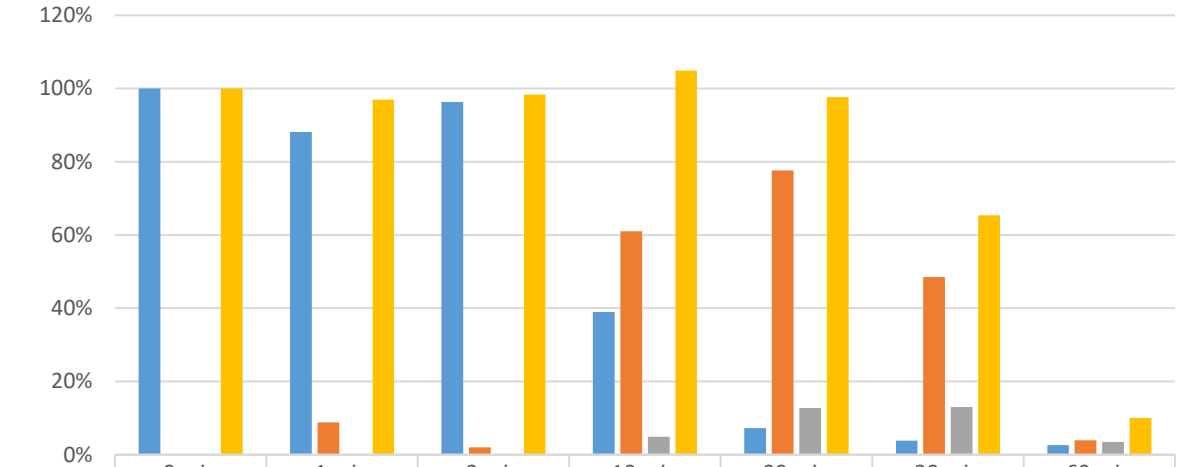
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	109%	96%	87%	69%	41%	8%	4%
pentose	0%	3%	5%	9%	17%	23%	17%	0%
lactone	0%	0%	0%	5%	11%	23%	20%	0%
sum	100%	112%	101%	101%	98%	87%	45%	4%

5.4.14 Time-resolved screening of 3-*O*-benzyl-D-galactose 14 with dipp catalyst 21



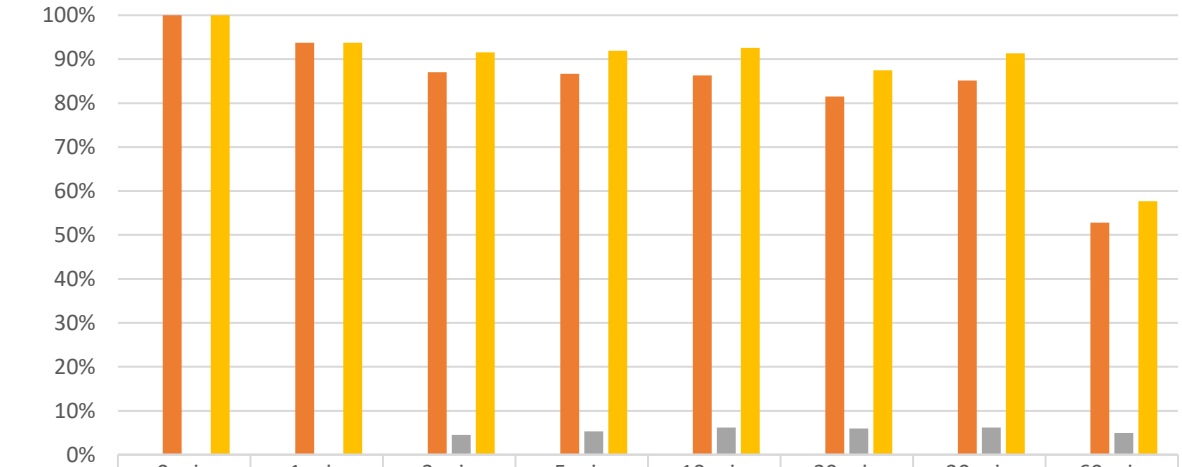
	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	100%	97%	96%	87%	78%	48%	12%	3%
pentose	0%	2%	6%	11%	22%	29%	27%	7%
lactone	0%	0%	0%	3%	4%	15%	24%	11%
sum	100%	99%	102%	101%	104%	92%	63%	21%

5.4.15 Time-resolved screening of 3-*O*-benzyl-D-mannose 13 with dipp catalyst 21



	0 min	1 min	3 min	10 min	20 min	30 min	60 min
hexose	100%	88%	96%	39%	7%	4%	3%
pentose	0%	9%	2%	61%	78%	48%	4%
lactone	0%	0%	0%	5%	13%	13%	4%
sum	100%	97%	98%	105%	98%	65%	10%

5.4.16 Time-resolved screening of 2-*O*-Benzyl-D-arabinose 8 with dipp catalyst 21



	0 min	1 min	3 min	5 min	10 min	20 min	30 min	60 min
hexose	0%	0%	0%	0%	0%	0%	0%	0%
pentose	100%	94%	87%	87%	86%	82%	85%	53%
lactone	0%	0%	5%	5%	6%	6%	6%	5%
sum	100%	94%	92%	92%	93%	88%	91%	58%

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