TECHNISCHE UNIVERSITÄT WIEN
Vienna | Austria

MASTER THESIS

INVESTIGATIONS IN THE *N*-HETEROCYCLIC CARBENE CONTROLLED DEHOMOLOGATION OF ALDOSES - SELECTIVITY AND REACTIVITY

Conducted to obtain the academic degree: **Master of Science (MSc.)**

Under the supervision of:

UNIV. PROF. DR. MARKO D. MIHOVILOVIC

DR. CHRISTIAN STANETTY

Institute of Applied Synthetic Chemistry

Submitted at:

TU WIEN

Faculty of Technical Chemistry

By:

CHRISTOPH SUSTER, BSC.

Matr. No: 01425589

Wassergrabenweg 6A, 2384 Breitenfurt

(O tempora, o mores!)

The good thing about science is that it is true whether or not you believe in it.

-Neil deGrasse Tyson

Acknowledgements

Conducting this thesis has been a remarkable time of my life, full of challenges and obstacles to overcome. During this time I certainly grew not only as a scientist but also as a human. It is undoubtedly due to the constant support of many people who I am lucky enough to have in my life, that I am now finally able to write these words. Words that conclude a period of my life that started with enormous self-doubt but turned into something I am very proud of. Seeing the outcome, I am now finally convinced of having made all the right decisions in dedicating myself to pursue an academic education in the field of chemistry.

First and foremost, I want to thank you, Christian! I can hardly believe that it was now nearly 5 years ago that I first walked into your office. Afraid of the oral exam I was about to have with you. When I left the office, I was already impressed. Not only did I leave smarter, but for the first time, I also considered synthetic chemistry a viable option for my future. However, when you offered me your supervision for my bachelor thesis, it was more your personality than my interest in the field that convinced me to agree. What happened since then is history, and I could not be happier. You are certainly the person I learned the most from, and your mentorship inside and outside chemistry has allowed me to grow as a chemist and as a person. Your enthusiasm for research and the high standards you live up to are an inspiration to me. I cannot put into words how thankful I am for the countless opportunities I got during the past years because of your constant support. Overall, I am very much looking forward to the years to come.

Next, I want to thank Marko Mihovilovic, Florian Rudroff, and Michael Schnürch, for all the input and feedback I received throughout this thesis. Your diverse fields of interest and the broad range of research topics allowed me to view chemistry from different perspectives, ultimately helping me to circumvent many issues I encountered during my research. Also, I very much appreciate that you always have an open ear for problems and the dedication to solve them.

I want to thank my parents Anna and Gerhard, and my brother Clemens, for providing a warm and welcoming home, allowing me to have a place to relax after hard workdays. Also, I am very grateful to my parents for all the mental and financial support I constantly receive. But besides all the classical “parental duties”, I cannot be thankful enough to you for raising me into the critically thinking person with a general interest in science that I am today.

Speaking of my family I further want to mention my “Großcousin” Michi and his girlfriend Manu. Over the last years you two have become an integral part of my life, always listening to my problems in an unbiased way, providing me guidance and an honest opinion. I very much enjoy our holidays together and I am looking forward to many more to come once we get this pandemic under control.

Of course, such a thesis would only be half the fun without a fantastic group of people that make the countless hours at the bench enjoyable. I was lucky enough to work with an extraordinary bunch of people, many of whom have become close friends. Dear *Anna, Astrid, Blanca, Charlie, Clemens, Dani, David, Dominik D, Dominik S, Drasi, Eleni, Farooq, Freddy, Heci, Hubert, Jakob, Johanna, Julia, Kathi O, Kathi S, Laszlo, Lydia, Nic, Nina, Rafaela, Rahele, Resi, Richi, Stefan, Thomas, and Tom*: It has

been and will continue to be an absolute pleasure to share the lab with you.

Thanks to the awesome G20 crew for all the fun games and bad jokes that certainly make the G20 the best lab on the floor. Also, thank you for letting me take over the DJ-duty from time to time and enduring my crazy music taste. Within the G20 I want to highlight Markus “Drasi” Draskovits for his endless patience and all the support and input I got during my research: You have been the best PhD/PostDoc I could have wished to work with.

Moreover, I want to thank the members of the “Cooking Group” for providing awesome food on a daily basis - certainly the healthy kind of nutrition every successful chemist needs.

Thanks to the “Laufgruppe” for making sure I stay in shape, and thank you for providing the healthy dose of workouts that every successful chemist needs.

Thanks to the people involved in the ‘weekly’ “Denksport” for allowing me to participate and learn a lot about high-level total synthesis, providing the mental training every successful chemist needs.

A very special mention goes to Viktor Savic for going through thick and thin with me. It is quite remarkable that our journey started 13 years ago in Rosensteingasse. You are one of the most talented chemists I have ever met and I highly appreciate that I can always count on you.

Also, I want to thank, Birgit, Lara, Nici, and Pontus for their friendship and countless hours of conversations.

Finally, it is time to thank Kathi Schlögl. Dear Kathi, thanks for being the awesome best friend that you are. You cannot imagine how proud I am to have you in my life and how much I enjoy working with you in the lab. You showed me what dedication and hard work mean when it comes to pursuing your goals. The high standards you live up to helped me tremendously to change a few things for the better. Even after 7 years I am yet to discover a flaw in your personality, and while the chemistry in the lab might suck from time to time, the chemistry between us has always been awesome. Thank you for your brutal honesty, and all the uncountable times you were there for me when I needed you. I am very happy to have you in my life, and I am glad that we will work together for the next years to come.

THANK YOU!

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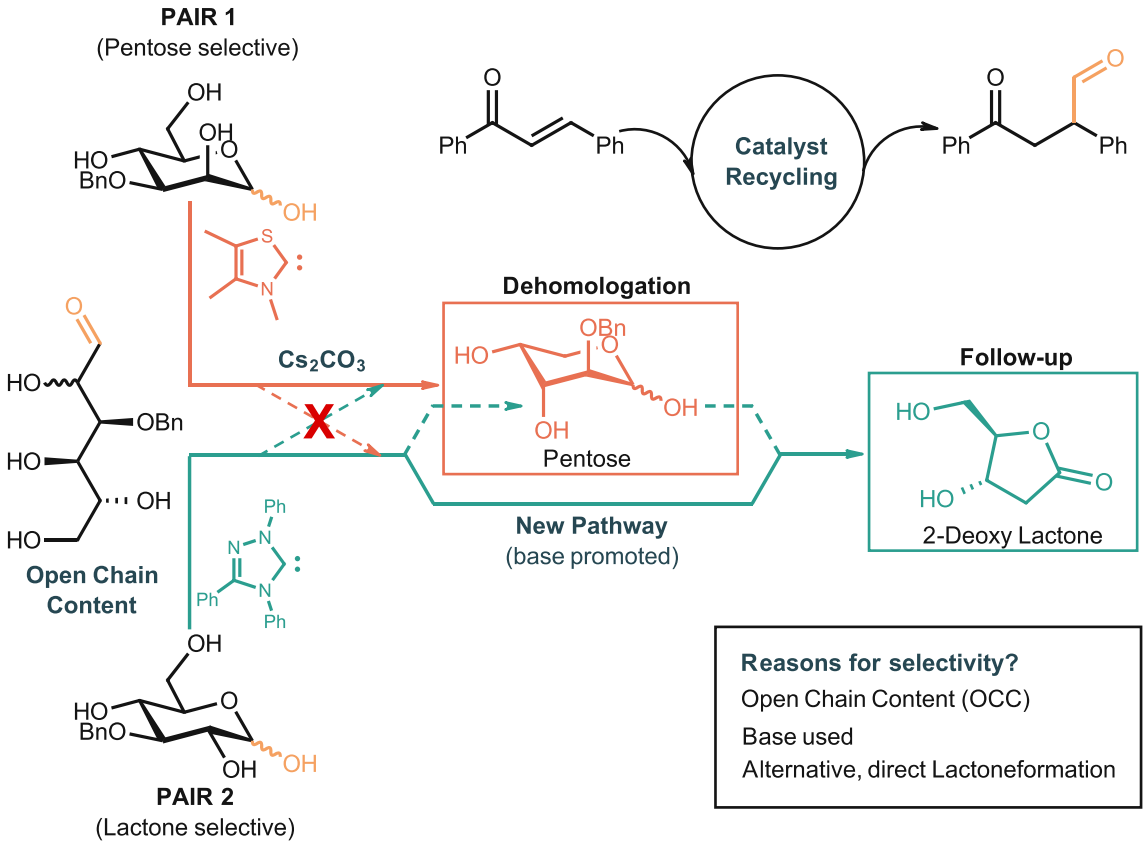
Abstract

Carbohydrates are the most abundant natural compounds class and are an important part of natures chiral-pool. However, while the realm of carbohydrate chemistry is well explored in terms of elaborate protection group chemistry and glycosylations, interconversions of carbohydrate structures (based on addressing their carbonyl moiety) are underrepresented.

In this light, *N*-heterocyclic carbenes (NHCs) are an interesting modern class of organocatalysts. Their unique reactivity profile, allowing for selective Umpolung chemistry of aldehydes with a precisely tunable catalytic profile, has earned them a place in the spotlight of recent research.

A cross-over between NHCs and carbohydrates has recently been reported, targeting the aldehyde moiety of reducing sugars in a sacrificial manner to liberate formaldehyde equivalents to formylate chalcones *via* a Stetter reaction. Our group envisioned a change of perspective and has already shown that this transformation could be used to dehomologate carbohydrates by strategic placement of protection groups to intercept the catalytic cycle. Two pairs of catalyst and sugar were identified exhibiting high selectivity for the dehomologated product or, alternatively, for 2-deoxy-lactones, presumably a follow-up product forming after additional redoxlactonisation, as expected possible follow-up reaction of the dehomologated sugar into.



However, the observed selectivity was not fully understood, and the method requires harsh and heterogeneous conditions, making the transformations somewhat unrobust provoking so far unidentified additional by-products. This thesis aimed at identifying some key influences on the selectivity and reactivity to obtain a deeper understanding of the full complexity of this new transformation. While preceding works focused on either the chalcone or the sugar side, individually,

this work attempts on shining light onto the reaction from a more general standpoint, simultaneously investigating both sides of the transformation to observe dependencies on one another.

Within this thesis, an in-depth investigation of the influence of the carbohydrate starting materials' open-chain content was conducted, suggesting that the initial mutarotation-step is rate determining.

Another issue in the optimised conditions was the heterogeneity of the base K_2CO_3 which caused irregularities in the reaction outcomes. To this end, the influence of different bases on the reaction's selectivity was studied, and a reaction-protocol using soluble bases was developed, which will likely prevent reproducibility problems in future investigations.

Further, the transformation was surveyed for the existence of side-reactions tentatively consuming catalytically active species. Strategies to prevent side-reactions using specially designed Michael acceptors gave rise to a novel cyclisation reaction, for which proof of concept was delivered. This novel approach is currently under further investigation.

While no NHC-activated side-reaction could be directly identified, strong evidence for an alternative mechanism to form redoxlactonisation product was gathered based on several experiments to elucidate the mechanism. This reaction pathway was proven to be a co-existing mechanism most-likely playing a significant role in the observed selectivity, giving rise to completely new explanations for selectivity control.

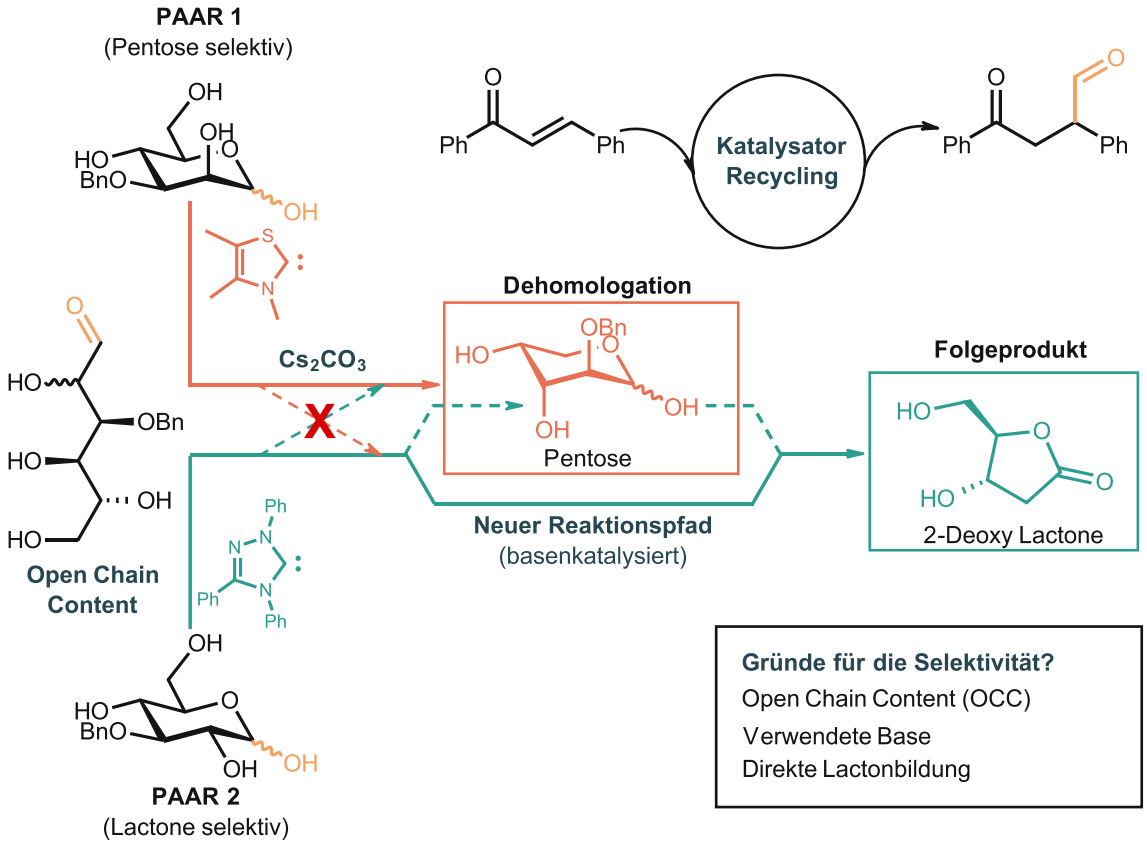
Results compiled within this thesis contributed to the overall understanding of this novel carbohydrate methodology and allowed further hypothesis-driven investigations to develop a general and practical synthetic protocol.

Kurzfassung

Kohlenhydrate sind die häufigsten Naturstoffe und ein wichtiger Bestandteil des natürlichen chiralen Substanzpools. Die Chemie der Zucker ist ein vielseitiges Feld, das in Gebieten wie Schutzgruppentechnik und Glykosylierungen sehr gut erfoscht ist, jedoch sind Zuckerinterkonversionen in der Literatur deutlich unterrepräsentiert, vor allem Reaktionen, die direkt die Carbonylfunktion adressieren, sind selten.

In diesem Zusammenhang sind *N*-heterocyclische Carbene (NHCs) eine interessante neue Entwicklung im Bereich der Organokatalyse. Diese weisen ein sehr besonderes Reaktivitätsprofil auf, welches selektiv für die Umpolung von Aldehyden verwendet werden kann. Im Vergleich zu klassischen Umpolungsreaktionen kann das Katalyseprofil bei NHCs sehr genau eingestellt und leicht verändert werden, weshalb NHCs seit einigen Jahren in den Focus der Organokatalyseforschung gerückt sind.

Kürzlich wurde ein Cross-Over zwischen NHCs und Kohlenhydraten publiziert, in dem die Aldehydefunktionalität von reduzierenden Zuckern verwendet wurde um unter Verbrauch des Zuckers Formaldehydequivalente zu erzeugen, welche dann *in-situ* dazu verwendet wurden Chalcone zu formylieren. Unsere Forschungsgruppe hatte die Idee, einen Perspektivenwechsel zu vollziehen, und konnte zeigen, dass der Zuckerabbau durch strategische Platzierung von Schutzgruppen gestoppt werden kann, wodurch dehomologierte Zucker gewonnen werden konnten. Die Forschungsarbeit ergab zwei Zucker und Katalysator Paare, die jeweils selektiv zum direkten Abbauprodukt führten oder eine bekannte Redoxlactonisierung eingingen, um selektiv 2-Deoxy-Lactone zu bilden.



Jedoch war zu diesem Zeitpunkt nicht klar, was die Gründe für die Selektivität waren. Zusätzlich waren harsche und heterogene Reaktionsbedingungen erforderlich, weshalb die Transformation unrobust

und anfällig für nicht näher definierte Nebenreaktionen war. Diese Arbeit versuchte wichtige Einflüsse auf die Selektivität und Reaktivität besser zu verstehen sowie ein generell besseres Verständnis über die komplexen Zusammenhänge dieser neuartigen Transformation zu erlangen. Während Vorarbeiten jeweils nur entweder die Zucker oder die Chalcone für ihre Untersuchungen im Blick hatten, wurde in dieser Arbeit versucht, die Gesamtheit der Vorgänge zu beleuchten indem beide Seiten der Transformation gemeinsam betrachtet wurden.

In der Arbeit ist eine ausführliche Analyse des Einflusses des Anteils an offenkettigen Anteilen von Zuckern enthalten, welche nahelegt, dass der initiale Mutarotationsschritt geschwindigkeitsbestimmend ist.

Ein großes Problem der bisherigen Reaktionsbedingungen war die Verwendung von K_2CO_3 als unlösliche Base, welche Unregelmäßigkeiten im Reaktionsausgang verursacht hat. Im Zuge der Studie wurden mehrere Basen auf deren Einfluss auf die Selektivtät der Reaktion untersucht und es konnte eine lösliche Base identifiziert werden, die das Heterogenitätsproblem löst.

Weiters wurde ein spezielles Augenmerk auf die Identifikation von Nebenreaktionen gelegt, welche den Katalysator verbrauchen. Um solche Nebenreaktionen zu unterbinden wurde verschiedene Strategien untersucht und im Zuge dessen konnte eine neuartige Cyclisierungsreaktion gefunden werden, welche Gegendstand von Folgeuntersuchungen sein wird.

Der wichtigste Fund war jedoch die Identifikation eines bisher unbekannten Reaktionswegs, durch den das Lacton-Nebenprodukt auf direktem Weg geformt wird. Eingehende Untersuchungen konnten zeigen, dass dieser Reaktionspfad in direkter Konkurrenz zur Dehomologisieurng steht und ganzheitlich neue Wege liefert die Selektivitätsphänomene der Reaktion zu erklären.

Generell wurde in dieser Arbeit zu einem besseren Verständnis dieser neuartigen Zuckermethodik beigetragen und es konnten wichtige neue Ansätze geliefert werden um die Methode in eine generelle synthetische Anwendung zu entwickeln.

General Remarks

Compounds actively handled during the experimental work of this thesis are referenced in text and schemes as bold Arabic numbers in square brackets in order of their appearance.
Literature references are given with superscript Arabic numbers in order of their appearance. Mentionings of the corresponding authors of certain publications are giving in italic letters.
D. Glöcklhofer conducted the synthesis of 3-OBn-mannose **[5]** used in this thesis within the Advanced Laboratory Course in Synthetic Chemistry at TU Wien under the experimental supervision of the author of this thesis.

Abbreviations

COSY	Correlated Spectroscopy - NMR
DCM	Dichloromethane
DBA	Dibenzalacetone
DBU	Diazabicycloundecen
DIEA	Diisopropylethylamin (Hünig-base)
DiiPrPh	2,6-Diisopropylphenyl
DMAP	Dimethylaminopyridine
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EWG	Electron withdrawing group
GC	Gas-chromatography
GC-MS	Gas-chromatography with Mass-spectrometry detector
HMBC	Heteronuclear Multiple Bond Correlation - NMR
HOMO	Highest obtained molecular orbital
HSQC	Heteronuclear Single Quantum Coherence - NMR
LG	Leaving group
LP	Light petrol
LUMO	Lowest unobtained molecular orbital
MeCN	Acetonitrile
Mes	Mesityl
MPLC	Medium pressure liquid chromatography
NHC	N-Heterocyclic carbene
HPLC	High-performance liquid chromatography
Nuc	Nucleophile
OCC	Open chain content
Ph	Phenyl
r.d.s.	Rate determining step
rt	Room temperature
TBAF	Tetrabutylammonium fluoride
SET	Single-electron-transfer
s.m.	Starting material

^{t}Bu	Tert. butyl
TBDMS	Tetrabutyldimethyl silyl
THF	Tetrahydrofuran
TIPDS	Tetraispropyl disilyl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
µW	Microwave

A. Introduction

A.1. *N*-Heterocyclic Carbenes (NHCs)

A.1.1. Structural Motifs

N-Heterocyclic carbenes (NHCs) are heterocyclic structures that contain at least one nitrogen atom and beare a divalent carbon atom that has an incomplete 6-valence-electron-shell. Molecules containing such a carbon atom are called carbenes. Their unsaturation in valence electrons forces a state where the carbene carbon can only form two bonds. Such arrangements are inherently unstable, rendering them transient reaction intermediates if no stabilising forces act on the molecule.

In a 6-valence-electron configuration, the electrons not involved in bond-formation can occupy either the same orbital (singlet state) or occupy different orbitals (triplet state). In a singlet carbene, the HOMO is a formally sp^2 hybridised lone-pair, and the LUMO is a *p*-orbital, hence giving it a strongly nucleophilic reaction profile. In contrast, triplet carbenes are electrophilic diradicals. (see *Figure 1*, *left*). While theories about carbenes existence date back into the mid-19th century, it took over 100 years before the first stable carbene was isolated in 1988 by *Bertrand*[1]. Followed by a seminal work of *Arduengo*[2], who reported a stabilised singlet carbene, that utilised the especially strong σ-electron-withdrawing and π-donating properties of nitrogen in a heterocyclic ring to stabilise the singlet state – the first isolated NHC (see *Figure 1*, *middle*). Arduengo used two sterically demanding *N*-adamantyl substituents on an imidazolium scaffold, next to the carbene carbon to help with steric shielding. Shortly after, it was realised that the shielding properties of adamantyls contributed only little to the stabilisation that was observed. The σ-withdrawing effects that inductively lower the energy of the HOMO, and the mesomeric donation of electron-density into the LUMO, by the two adjacent nitrogen atoms, together with electronic stabilisation of the aromaticity, outweigh the shielding effect by a lot and much simpler substituents, such as methyl, could be used to generate carbenes with sufficient lifetime, upon in-situ deprotonation of the corresponding azolium salt analogues[3]. Other heteroatoms, such as oxygen and sulfur, were shown to be applicable in NHC scaffolds (oxazolidine, thiazolidine). Ultimately, *Bertrand* showed that NHCs bearing only one heteroatom are feasible[4-6] *(see Figure 1*, *right*). Together with their unique reactivity modes (see *A.1.2 Reactivity*), these discoveries opened an entirely new field for organo-catalysis, which gained massive popularity within the past 30 years[7].

This rapid increase in applications for NHCs is based on their very simple but also diverse structural motifs. Their synthesis is based on established and robust heterocyclic chemistry, making it fast and easy to synthesise big libraries of NHC structures, mostly by altering the substrate and not the synthetic

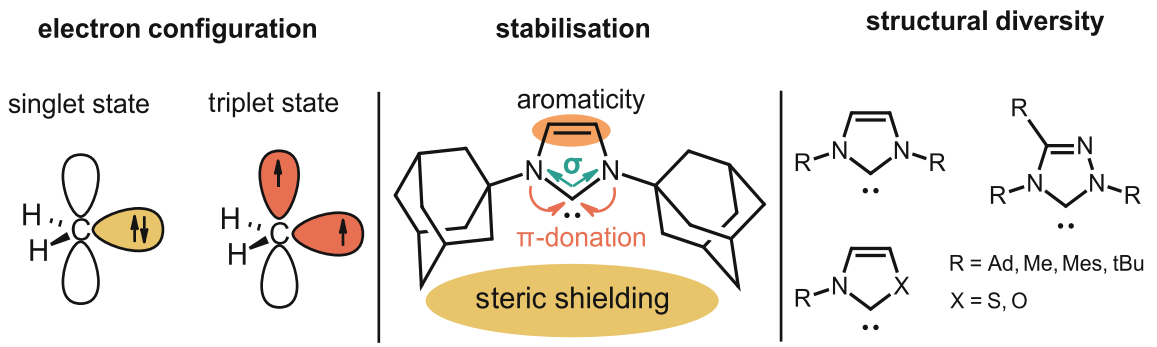


Figure 1. Left: electron configuration of carbenes. **Middle:** stabilising effects in NHCs. On the exemplary structure of the "Arduengo Carbene." **Right:** important catalytically active NHC-scaffolds.

strategy.

A.1.2. Reactivity of NHCs

A.1.2.1. General modes of reactivity

Due to their nucleophilic nature and tendency to donate electrons into σ-molecular orbitals, NHCs offer a very distinct set of reaction modes that can mainly be categorised into three groups (see *Figure 2*). The first two, coordination to transition metals and coordination to *p*-block elements, are related, while their reactivity as organocatalysts in mostly Umpolung chemistry stands out.

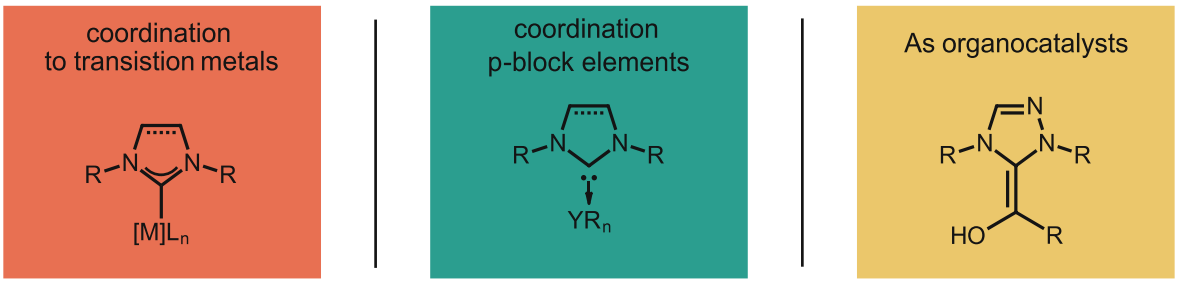


Figure 2. General concepts of reactivity for NHCs

A.1.2.2. Coordination to transition metals

The primary reactivity of singlet carbenes comes from the lone pair that is giving them a highly nucleophilic character. As this lone electron pair readily donates density into a σ-accepting orbital, NHCs are prone to coordinate on transition metals. Their empty *p*-orbital allows for efficient π-backbonding further enhancing the stability of the NHC-metal complexes[7]. Most applications for NHCs to date are within the realm of coordination chemistry. A widely recognised success story was the development of 2nd generation ruthenium-based (Hoveyda)-Grubbs catalysts for cross-metathesis. The generational leap between the nowadays commonly used 2nd generation, and their predecessors (Grubbs I), was the exchange of a phosphine- with an NHC ligand, that not only improved the affinity for olefins by 10^4 but also drastically increased the thermal stability of the catalytically active moiety, ultimately providing unrivalled catalyst efficiencies in the realm of cross-metathesis[8,9].

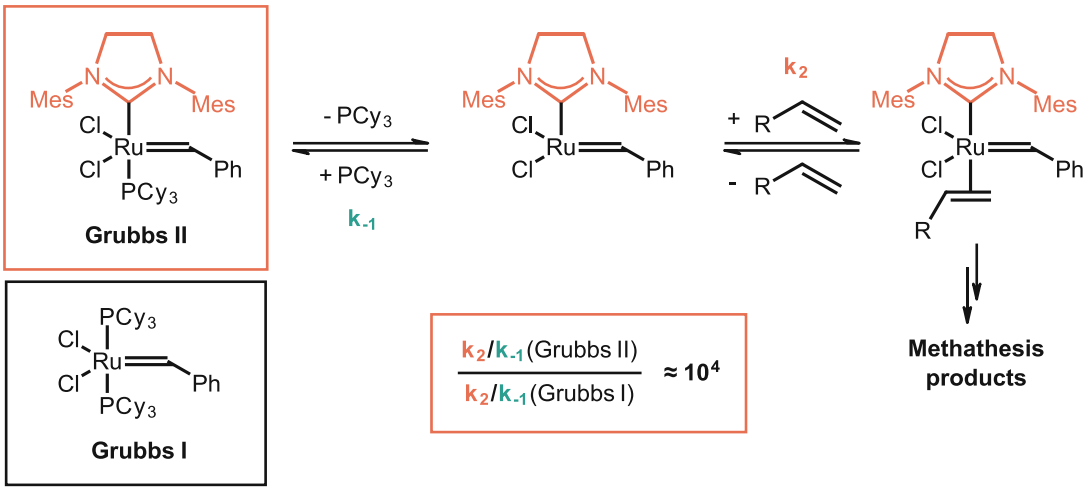


Figure 3. Formation of the initial catalyst-olefin complex with a 2nd generation Grubbs-catalyst. The olefin complex's reaction is about four orders of magnitudes more preferred over the re-formation of the σ-complex (k-1) than the 1st generation of Grubbs catalysts, with two PCy_3 ligands [7].

This increase in reactivity is caused by the high amount of donatable σ-electron density, from the NHC to the ruthenium metal centre, allowing for easier π-bonding with the π-acceptor ligands, like olefins. Generally, NHCs provide outstanding ligand properties, paving the way for novel reaction pathways and selectivities within classical transition metal catalysis. An excellent example of such a selective reaction is the formation of Z-alkenes *via* cross-metathesis, utilising a "3rd generation Grubbs catalyst". Such a catalyst bears a specially designed NHC-substitution pattern, thus enabling the synthesis of the thermodynamically unfavoured Z-isomere, concomitantly allowing the biomimetic synthesis of several natural products Z-alkenes are a common theme[10] (see *Figure 4* top).

Very soon, NHCs also started to infiltrate other fields that make use of transition metal catalysis. For example, classical cross-coupling reactions have seen a rapid uptake of novel catalysts featuring NHC-ligands such as the Pd-PEPPSI catalyst, that utilises the strong σ-donating properties of NHCs to form a very well activated metal centre, that is specially primed for oxidative addition into carbon-halogen bonds[7,11] (see *Figure 4* bottom). Additionally, the NHC ligand provides increased air stability to the complex, which improves the total number of achievable catalyst turnovers and allows easier preparative handling.

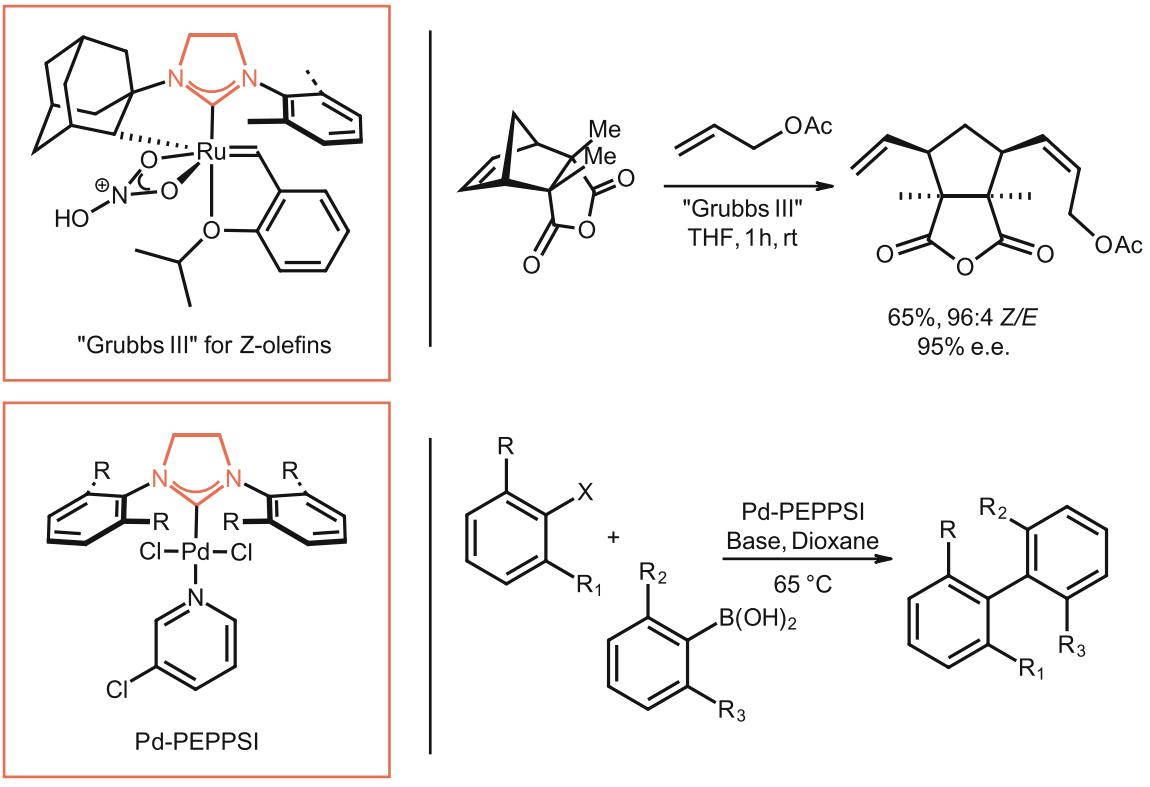


Figure 4. Unique reaction pathways only enabled by NHC-transition metal complex catalysis, exemplified with a Z-olefin selective metathesis reaction developed by *Grubbs*[10] (Top), and Pd-PEPPSI catalyst for cross-coupling reactions, displayed on a Suzuki-Miyaura reaction (bottom).

A.1.2.3. Coordination to p-block elements

As with transition metals, NHCs can also σ-donate into σ-accepting orbitals of *p*-block elements with low valencies, such as boron or phosphorous giving outstanding stabilisation to the zero-oxidation state of those elements. Ultimately, it results in a strong dative bond, which is why the formation of stable complexes exhibit different reaction profiles than comparable *p*-block adducts. For some interactions,

the dative bond can be viewed as a "normal" covalent bond. The extreme structural versatility of NHCs gives rise to fine tuneable adducts, which can be used as frustrated lewis acid pairs, active silicon reagents, or generally stabilise reactive species for improved reaction efficiency[7].

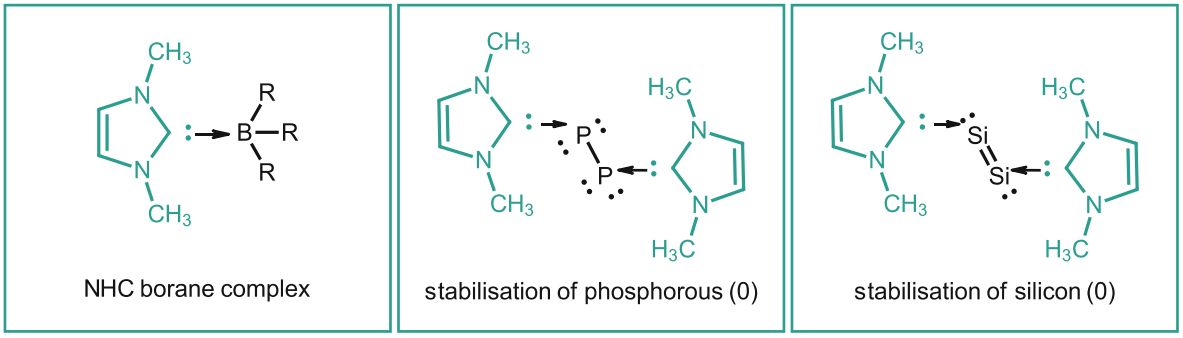


Figure 5. Overview of exemplary reactivity modes for NHCs and *p*-block elements, and their stabilisation of the zero-oxidation state.

A.1.2.4. Utilisation as organocatalysts

The high nucleophilicity of NHCs allows them to attack at carbonyl moeities, thus enabling two distinct reaction pathways. The carbene carbon can attack at an ester moiety, resulting in elimination of the alkoxy group, leaving behind an acyl azolium salt with increased electrophilicity compared to the ester. These high electrophilic properties enable a reaction with alcohols to undergo transesterification reactions. Such applications are nowadays commonly used in step-growth polycondensations or ring-opening polymerisations in the field of macromolecular chemistry (see *Figure 6*)[7].

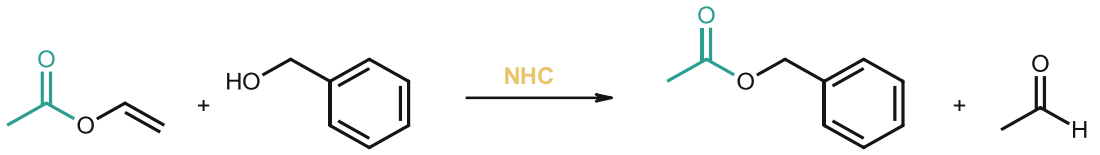


Figure 6. Transesterification using NHC catalysis.

The second and most diversely utilized option is the nucleophilic attack at an aldehyde function. Upon forming of the tetrahedral transition state, the strong negative mesomeric effect of the heterocyclic ring acidifies the aldehyde proton enough for it to be available for a proton shift. This effect stabilises the transition state as an enamine-like species that is nucleophilic at the former carbonyl carbon position. This intermediary reaction product is named 'Breslow intermediate' after Ronald Breslow, who proposed the existence of those moieties (see *Figure 7 top panel*).

As intrinsically nucleophilic species, the Breslow intermediates themselves can attack at electropositive positions of molecules leading to the ejection of the NHC, thus making it a catalytic moiety. Such reactions, where a carbon with initially partial positive charge attacks as a nucleophile, are called Umpolung reactions. The most prominent examples of Umpolung in 'classical' chemistry are benzoin condensations catalysed by cyanide or the Seebach-Umpolung (see chapter *A.2 Umpolung Chemistry*).

The first observation of NHC catalysed Umpolung was described by *Ukai* in 1943, where they reported the formation of dimeric benzoins when treating aldehydes with thiazolium salts. It took 15 more years until Breslow came up with the first mechanistic explanation, thus hinting on the existence of the 'Breslow Intermediate'.[12,13] Over the years the mechanistic understanding has grown dramatically, resulting in several reaction types based on the original Umpolung-idea. (see *Figure 7 bottom panel*).

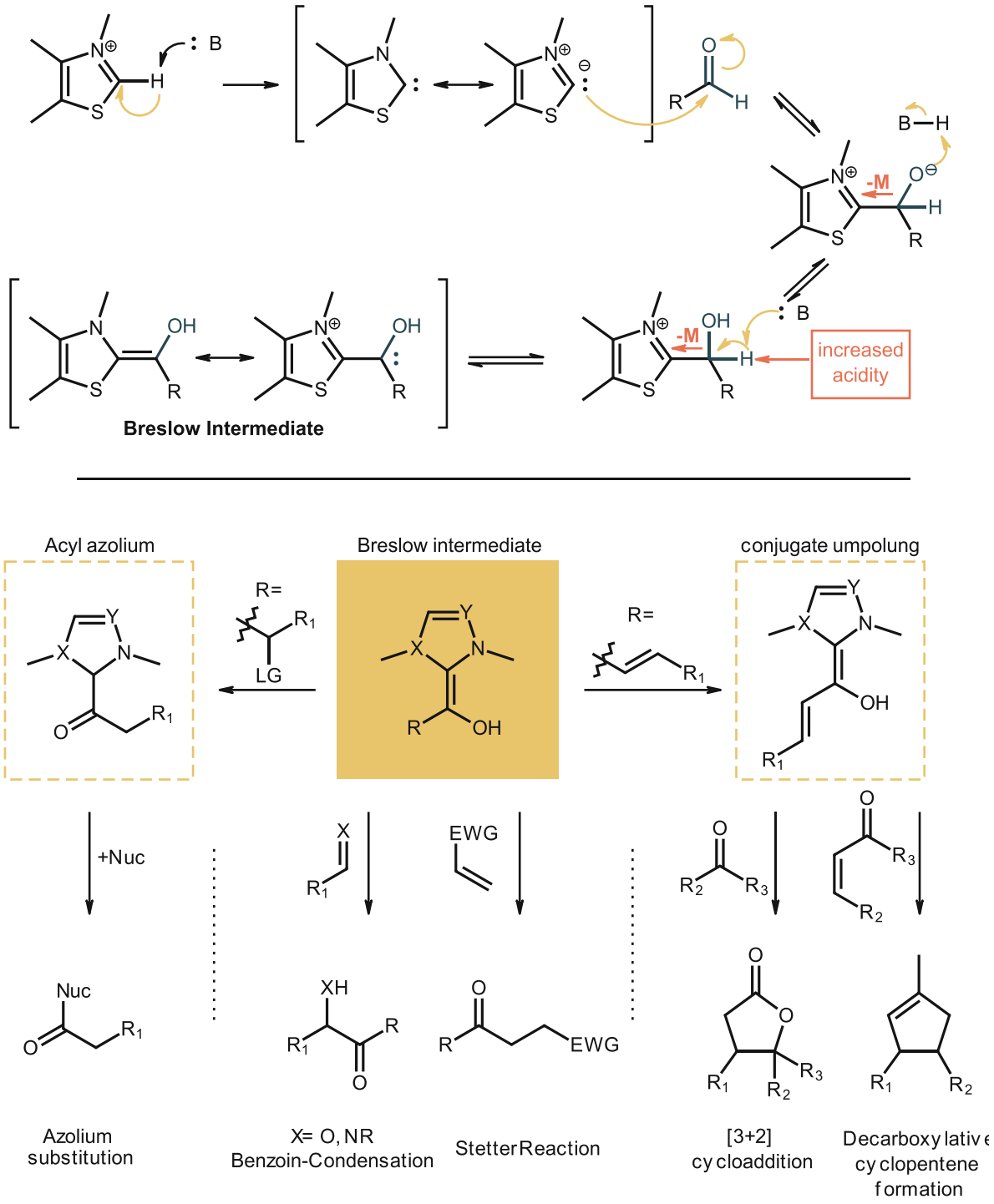


Figure 7. Top: Formation of the Breslow intermediate form a pre-catalyst salt. The strong negative mesomeric effect, applied by the NHC heterocycle, is indicated by the orange arrows. **Bottom:** Follow up reactions of the Breslow intermediate.[7]

The most straight forward reactions are benzoin condensation and Stetter reaction. In that cases the Breslow intermediate directly acts as a nucleophile, attacking either another aldehyde moiety, resulting in the reversible formation of benzoins, or undergoes irreversible conjugate addition with a Michael acceptor (generally α,β-unsaturated carbonyl compounds) in the so-called Stetter reaction (see *Figure 7 bottom-middle*). Those two reactions are by far the most studied and best understood reactions of NHC-organocatalysis, with a broad understanding of rational catalyst design and prediction of reaction

outcome[14,15]. (see *A.2.3 Examples of Umpolung Reactions*)
Throughout the years, asymmetric variants of the benzoin condensation, as well as the Stetter reaction, were developed, using chiral NHC catalysts. The stereoinduction in the product molecule is caused by the asymmetric formation of the Breslow intermediate and, concomitantly, a preferred attack direction onto the electrophile.
The mechanistically more elaborate reactions require a particular structural motif of the attacked aldehyde. In case the aldehyde is α,β-unsaturated, conjugate Umpolung is feasible, where the double bond of the aldehyde forms a π-system with the NHC adduct, that can attack as a nucleophile at another carbonyl carbon, in a conjugate -Baylis-Hillman- fashion (see *Figure 7 bottom-right*). Depending on the attacking electrophile the Breslow intermediate can undergo [3+2] cycloaddition or decarboxylative formation of cyclopentene.
If the initially attacked aldehyde has a leaving group in α-position, eliminating it can restore the original polarity of the carbonyl, which has an excellent leaving group in the NHC-adduct. Therefore, resulting nucleophilic attack at the activated carbonyl centre is possible *via* standard S_N2T mechanism.[7,13]

A.2. Umpolung Chemistry

A.2.1. Definition

Umpolung reactions (Umpolung = German for 'give reverse polarity') are reactions where organic molecules react with each other in a reverse manner, compared to their innate polarity driven reactivity[15]. Originally the term, introduced by *Wittig*[16], included only transformations in which acyl anions occurred, but with seminal works published by *Eschenmoser*[17], *Stork*[18] and *Seebach*[19], the definition was soon expanded to be a general chemical concept[20]. With the stellar rise of NHC-Umpolung chemistry, in the early 1990s, the field soon became one of the most prominent and most versatile in all of organocatalysis[4,15].

A.2.2. Concept

In molecules that have heteroatoms with lone electron pairs integrated into their structure, like oxygen or nitrogen, the possibility to donate electrons exists. Consequently, the carbons in the backbone of the molecule follow an alternating pattern of being able to donate or to accept electrons – natural polarisation[20]. In Umpolung reactions, this innate pattern is reversed *via* the additions of different groups to the hetero functionality. Such reversions can be achieved catalytically (e.g. CN^-, NHCs) or via stochiometric functionalisation, e.g. as dithio acetals (see *Figure 8*).

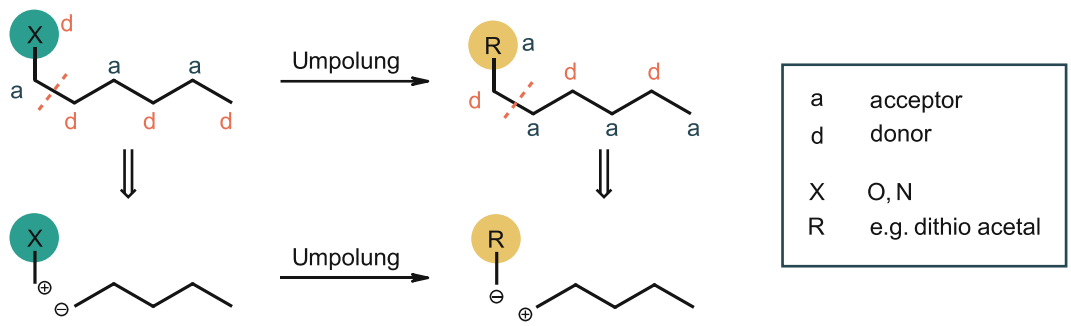


Figure 8. Concept and effect of Umpolung shown on an exemplary retrosynthetic disassembly[20].

Generally, Umpolung chemistry is most often applied to aldehydes, as they have a proton that can become acidic, thus giving chemists a way of creating carbon nucleophiles upon deprotonation. As already described in a previous chapter (see *A.1.2.4 Utilisation as organocatalysts*) when using NHCs for Umpolung reactions, their strong negative mesomeric effect is crucial to enable the deprotonation at the carbonyl centre. A mechanistically equivalent reaction is represented by the Umpolung with cyanide anions, that have a negative inductive effect (as used in the classical benzoin condensation – see chapter *A.2.3.1 The Benzoin* Condensation). Interestingly, the formation of the carbon nucleophile proceeds in an intramolecular fashion, as the attacked carbonyl abstracts the former aldehyde proton.

A.2.3. Examples of Umpolung Reactions

A.2.3.1. The Benzoin Condensation

The benzoin condensation was the first-ever reported reaction that made use of the Umpolung concept. Although not understood at the time, *Wöhler* and *Liebig*[21] reported the dimerisation of benzaldehyde into the α-hydroxy ketone (benzoin) upon addition of cyanide anions, already in 1832.

Looking at the mechanism today, it is clear that the reaction represents an addition. Therefore, the term "condensation" is wrong but still sees widespread use within the synthetic community.

Mechanistically, an aldehyde undergoes an S_N2T reaction with cyanide, forming an intermediary cyanohydrin, that can attack at an electrophilic position – making use of the Umpolung concept. This attacked species can either be the same aldehyde (homo-benzoin reaction), or a different aldehyde (cross-benzoin reaction). In such a setting with two aldehydes, there are four reactions products possible, of which usually only one is desired. All benzoin reactions are reversible, meaning that the formed acyloin species are in equilibrium with the starting materials concomitantly driving the reaction to form only the most favoured product[22].

In the classical cyanide catalysed version of the reaction, control over the selectivity is futile and relies mostly on one of the aldehyde species not being able to undergo Umpolung. Other drawbacks of this method are its limitation to aromatic aldehydes as substrates and the missing possibility of controlling

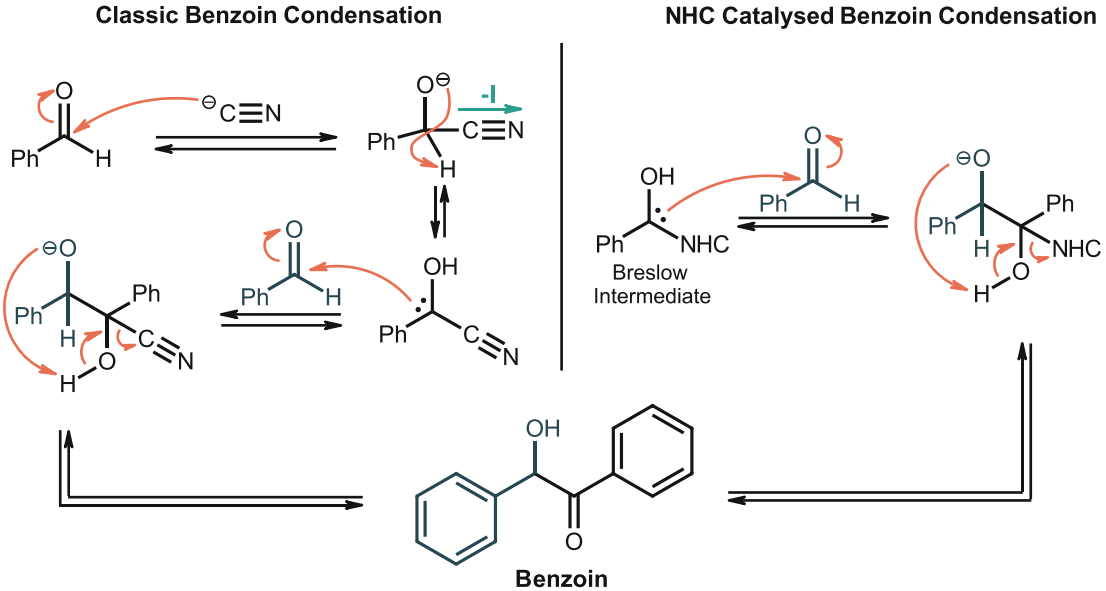


Figure 9. Benzoin Condensation is shown on the Homo-Benzoin Reaction with benzaldehyde. The classical method using cyanide anions is drawn on the left, while the modern variant utilising NHC catalysts is shown on the right. The formation of the Breslow intermediate is shown in *Figure 7* (top).

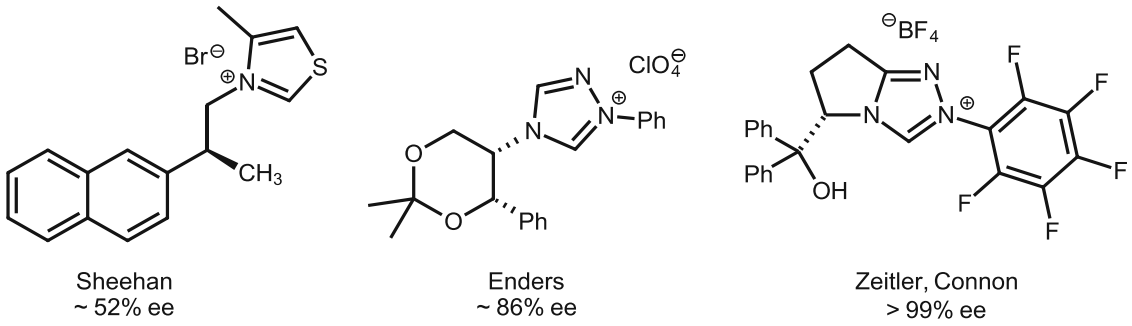


Figure 10. Development of different chiral catalysts for the stereoselective Benzoin Condensation. Starting from *Sheehan*[27] to *Enders*[28] and the first nearly perfect enantioselective catalyst by *Zeitler and Connon*[29]

the reaction outcome.

In 1943 *Ukai* reported that the dimerisation was also achieved using thiazolium salts under basic conditions, the first NHC catalysed version of the benzoin condensation. Intensive research in this field led to an immense expansion in the scope of benzoin reactions. The first impact NHCs had was the possibility of activating aliphatic aldehydes, as the -M effect of the NHC is stronger than the -I effect of cyanide electron-withdrawing properties of a phenyl ring were no longer required[23]. Further, the scope of coupling partners was extended, as *Suzuki*[24] was able to show the first selective intramolecular addition to an aromatic ketone while suppressing the homo-benzoin pathway.

Soon, examples of catalyst-driven divergence for Cross-Benzoin selectivity were published, using the fact that thiazolium-based NHCs had higher selectivity for aliphatic aldehydes triazolium salts showed affinity to aromatic aldehydes[23,25,26].

Perhaps the most significant advantage of the NHC catalysed variant over the classical method, is the possibility to induce stereochemistry. *Sheehan*[27] developed the first catalyst that gave mediocre enantiomeric excess in 1966. In the 1990s, *Enders*[28] found triazolium salts to be beneficial for stereo induction compared to imidazolium or thiazolium salts and drastically increased enantioselectivity to reach values up to 86% (e.e.). Computer-aided catalyst design then led to the development of bifunctional NHCs that incorporate a hydrogen bond donor, thus stabilising secondary interactions in the transition state further, allowing for almost perfect enantioselectivity[29].

A.2.3.2. The Retro Benzoin Reaction

The benzoin condensation's reversibility is exploited in the retro benzoin reaction, where α-hydroxy ketones are cleaved into two carbonyl species in the presence of a Umpolung reagent. As the retro benzoin reaction is just the reverse of the normal benzoin condensation, substrates formed *via* benzoin condensation hardly undergo a Retro benzoin reaction. However, as described in the previous chapter (*A.2.3.1 The Benzoin* Condensation), it is very hard, to couple aldehydes to ketones *via* benzoin

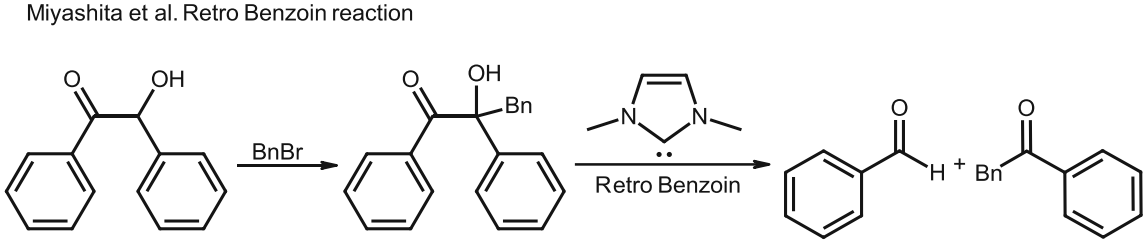


Figure 11. An early example of a Retro benzoin reaction, reported by *Miyashita*[22]

condensations. Therefore, the formal product of such an aldehyde-ketone coupling readily undergoes retro benzoin reaction to give the corresponding aldehyde and ketone. *Miyashita*[22] showed that α-benzyl benzoins – synthesised *via* α-alkylation of benzoin – can be cleaved into benzaldehyde and phenyl acetophenone (see *Figure 11).*

A.2.3.3. Stetter Reaction

Named after *Hermann Stetter*[32], who first reported this type of transformation in 1976, the Stetter reaction is a 1,4-Michael addition onto an α,β-unsaturated carbonyl function, where a carbon nucleophile originates from an Umpolung of an aldehyde. In contrast to the benzoin condensation, the nucleophilic attack is irreversible (see *Figure 12 top left*). The irreversible nature leads to the withdrawal of the Stetter product from the reaction equilibrium, while homo-benzoin products can still revert into starting material. In the long run, the Stetter product is always preferred over the acyloin species. While Stetter discovered the reaction under NHC catalysis, it can also be performed with cyanide catalysis.

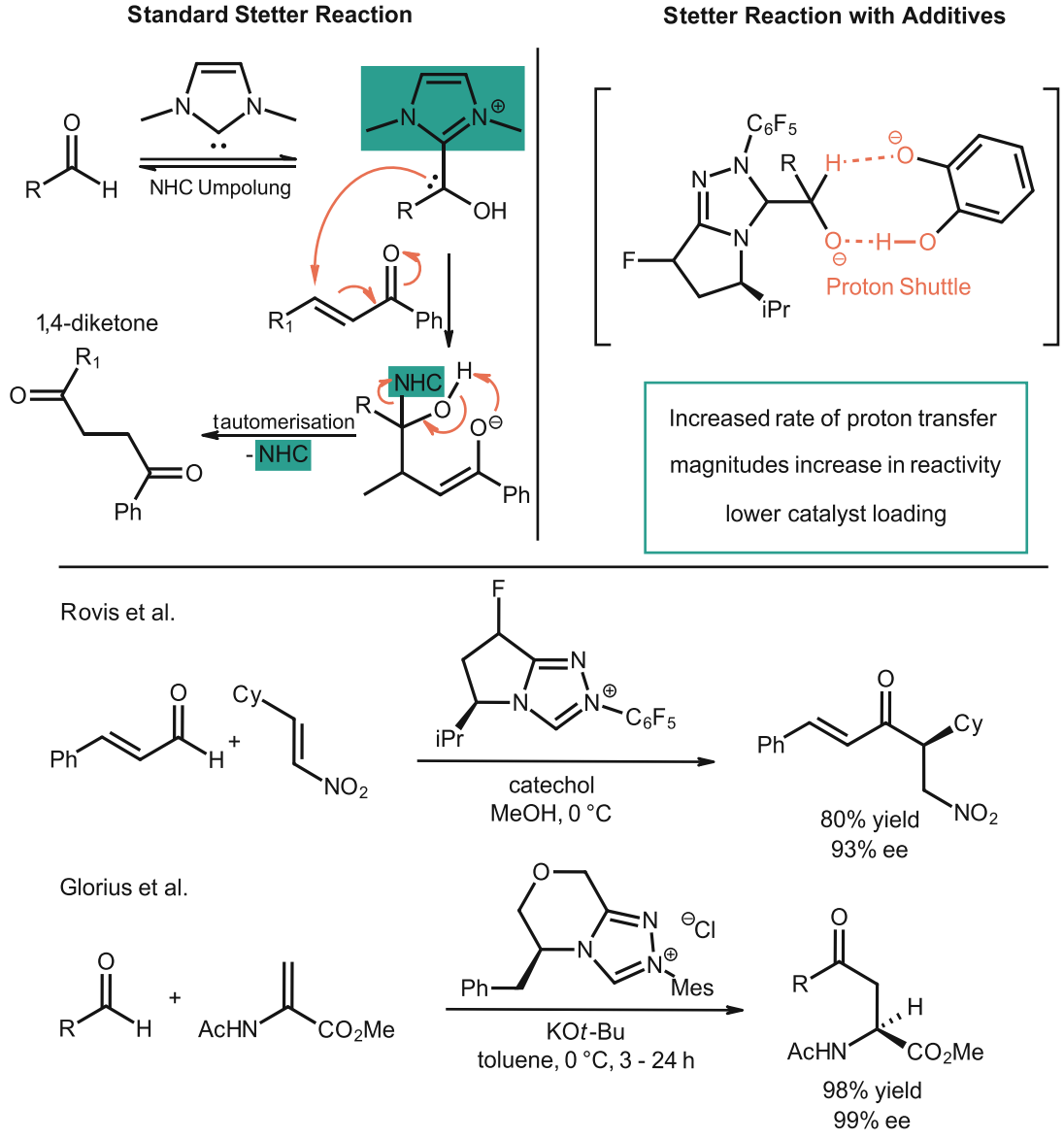


Figure 12. Mechanism of the Stetter reaction to form 1,4-diketones (top-left). Increase of reaction speed by enhancing the proton transfer with catechol (top-right). Exemplary stereo selective versions of Stetter reactions by Rovis[30] and *Glorius*[31] (bottom)

The Stetter reaction concept was generalised to all common Michael acceptors – like α,β-unsaturated esters, ketones, nitriles or sulfones[15].

As for the benzoin condensations, scientific focus in the development of the Stetter reaction was directed towards catalyst design for enantioselective versions. However, general low reactivity and chemoselectivity problems hampered the progress[33]. A partial success was the use of intramolecular Stetter reactions, as their innate higher reactivity circumvented many issues. The intramolecular reactions first allowed for efficient catalyst design, and the gained knowledge was applicable also for intermolecular reactions. In 2008 *Enders*[34] reported the first generally usable intermolecular enantioselective Stetter reaction on chalcones, with e.e.-values of up to 78%.

Further development of specially designed substrates and catalysts together with additives (e.g. catechol) have increased the reactivity while maintaining good enantioselective capabilities of this transformation. For example, *Glorius*[31] used dehydroamino esters with aldehydes to access α-amino acid derivates in highly enantiopure fashion. (see *Figure 12 bottom*)

The remarkable increase in reactivity when adding catechol to the reaction mixture was found by *Rovis*[30], who earlier reported that the presence of heteroatoms in proximity to the aldehyde drastically increased the yield of certain Stetter transformations[35]. They investigated the underlying reasons and ruled out the natural Lewis acidity of lone electron-pairs of heteroatoms. Ultimately, they were able to show that heteroatoms helped with the proton transfer upon Umpolung, which was discovered to be rate determining for most Stetter type reactions. They were able to utilise the di-phenolic species catechol to enhance the general reactivity of Stetter reactions and proofed its effect *via* measurement of the kinetic isotopic effect. (see *Figure 12 top-right*).

A.3. Carbohydrates

A.3.1. Structure and Chemical Properties

A.3.1.1. General Structure and Important Nomenclature

Carbohydrates (also called "sugars") are the most abundant and the most diverse class of natural products[36]. Their common structural motif is a polyhydroxy substitution pattern on a carbonyl-containing chain. Sugars can form oligomeric or polymeric structures built up from elementary building blocks – the so-called monosaccharides.

These monosaccharides can be classified based on their carbonyl function and chain length. Carbohydrates bearing an aldehyde are called aldoses while ketones are referred to as ketoses. Aldoses are also referred to as "reducing sugars" as their aldehyde moiety can be easily oxidised (vide infra). The simplest carbohydrate - glyceraldehyde - has a carbon chain length of 3 and is classified as triose. Equally are the carbohydrates with four carbons called tetroses and the pattern continues for: pentoses (5), hexoses (6), heptoses (7) and so on.

Except for a few special cases, all non-carbonyl carbons of sugars are substituted with one hydroxy group, creating stereocenters along the chain. The high amount of chiral carbons allows for an enormous pool of possible structures. Even for simplistic aldoses, the number of different structures is 2^{n-2} (n is the number of carbons). Within a set of equal carbon chain length, always two sugars represent an enantiomeric pair with the same relative, but inverted absolute stereochemistry, the D- and the L-form. The absolute stereo configuration of the carbon furthest away from the carbonyl function

determines if the structure is a D- or an L-sugar. By definition L (*laevo* - Latin for" left") gets assigned if the deterministic hydroxyl function is pointing to the left in the Fisher projection, while D (*dexter* - Latin for" right") is assigned if it is facing to the right side[37]. In the Fischer projection, the carbon chain of the sugar is drawn downwards in a straight line. The atom with the highest oxidation state (carbonyl function) points upward, the substituents along the chain get projected onto the drawing plane and therefore face right or left (see *Figure 13*).

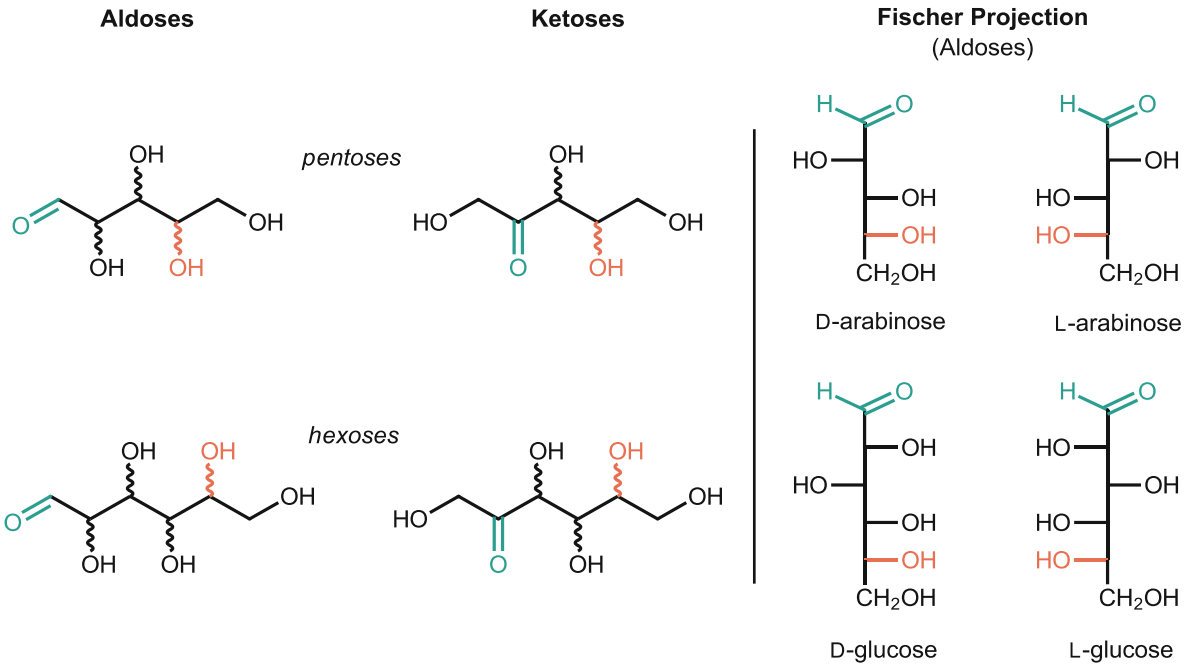


Figure 13. General structure of hexoses and pentoses (left) and a few examples of monosaccharide structures in Fischer projection (right). The chiral centre that is deciding between D- and L- form is marked in orange, while the carbonyl function that discriminates between ketoses and aldoses is marked in turquoise

Sugars that have the same absolute stereo conformation in all but one stereocenter are called epimers. The standard set of monosaccharides is formally described by the permutative addition of CH_2OH-units to glyceraldehyde next to the carbonyl moiety, forming the so-called "family tree of sugars".

A.3.1.2. Intramolecular Hemiacetal Formation – The Cyclic Forms

Their structure, containing a carbonyl and hydroxy functional groups, gives sugars the innate possibility to undergo intramolecular cyclisation *via* hemiacetal formation forming predominantly 5 or 6 membered rings that incorporate an oxygen atom. Energetically it is beneficial for carbohydrates to undergo this reversible cyclisation reaction. Therefore, most carbohydrates exist predominantly in the cyclic form. For example, glucose in aqueous solution has an open-chain content of smaller than 10^{-3} % and even the tetroses with a relatively high open-chain content, equilibrate at around 90% cyclic form. Depending on the ring-size the cyclic carbohydrate forms are called furanoses (5-membered) or pyranoses (6-membered), derived from the Hantzsch-Widman nomenclature of the corresponding heterocycles (furan and pyran). The cyclisation itself introduces a new stereocenter to the molecule next to the endocyclic oxygen called the anomeric centre. Upon hemiacetal formation, both enantiomeric forms of the anomeric centre can be formed, and the reversible nature of this transformation allows for equilibration of the anomeric forms, the so-called mutarotation (see *Figure 14*).

A specific stereo-descriptor describes the anomeric form based on the anomeric carbon configuration

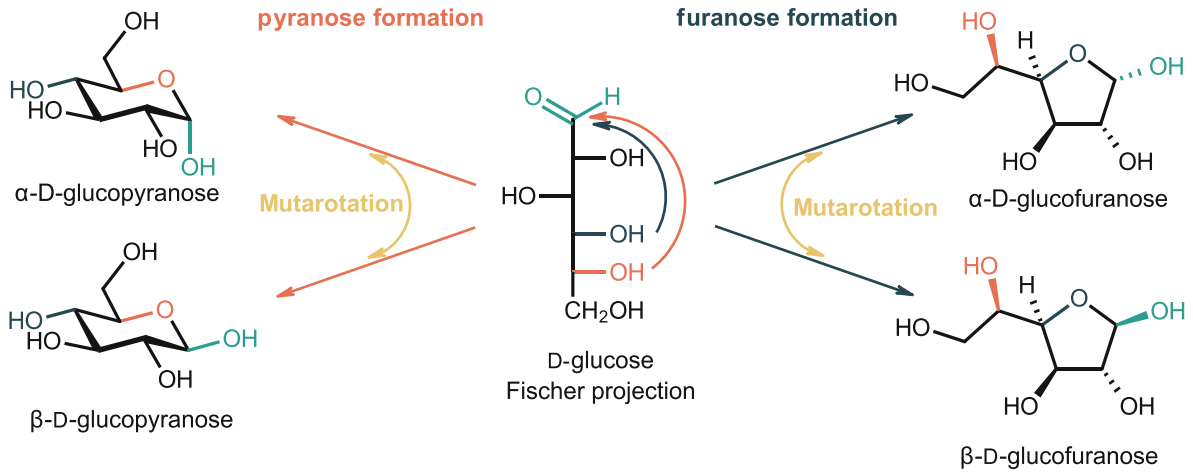


Figure 14. Intramolecular cyclisation to form hemiacetals of D-glucose.

relative to the position defining the absolute configuration (D- and L- descriptor). For a matching configuration "α" is used while "β" stands for different absolute configuration of the two centres.

A.3.1.3. Oligosaccharides

In nature, carbohydrates are most often found as oligomers, featuring intricate patterns of different monomers and linking. Oligomers are linked *via* glycosidic bonding of the anomeric carbon to a hydroxy group of another monomer unit, forming an acetal. The acetal bond is more stable than the hemiacetal of monosaccharides. The amount of possible complexity rises from the fact that each link can be α or β and the anomeric carbon can be linked to any hydroxy-function of the other monomeric unit. For a hexose-dimer, already 10 different possibilities exist. Building up larger structures, the possibility of permutations becomes unmeasurably large.

Oligosaccharides play a role in all parts of life, from building up the DNA-backbone, helping with protein-folding, and acting as a protective shield on cell-membranes in lipopolysaccharides. The complexity of interactions has hampered biological understanding. The ever-growing field of glycobiology investigates the role of carbohydrates, especially oligosaccharides. Research often requires chemical methods to recreate specific glycosylation patterns; this, however, is challenging[37,38].

A.3.2. Assembly of Saccharides

A.3.2.1. Glycosylation

Most synthetic efforts regarding carbohydrates are about the selective formation of glycosyl bonds, driven by high demand for novel biological research to obtain various natural oligosaccharide fragments[39,40].

In a glycosylation reaction, the anomeric position of a saccharide (glycosyl donor) reacts with an alcohol moiety (glycosyl acceptor). For example, other sugar molecules could build up more complex oligosaccharides in such a transformation.

Mechanistically, an oxocarbenium ion gets formed upon activation of a leaving group at the anomeric centre, that can be attacked by a lone electron-pair of a hydroxyl function of the acceptor[41]. Without any other influences, such a reaction is described as an S_N1 reaction, where no stereocontrol is possible. The resulting glycosides are a statistical mixture of α- and β- linked products, thus proving to be a synthetic challenge. Another problem is regioselectivity, as carbohydrates incorporate multiple hydroxy

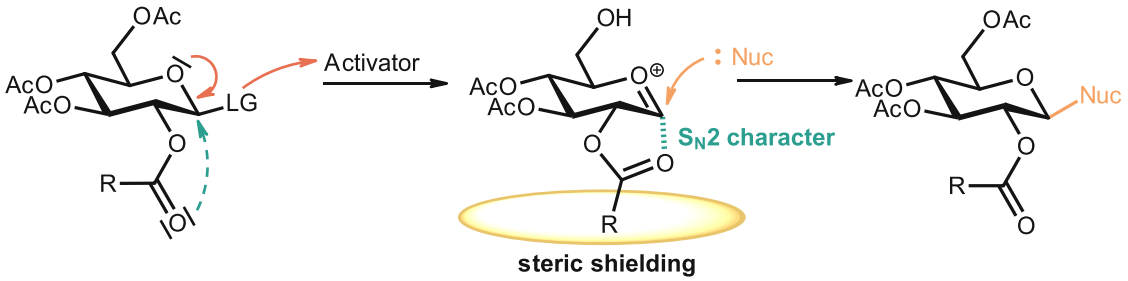


Figure 15. Glycosylation general mechanism of a glycosylation reaction

functions within their structure, elaborate protection group strategies are needed (see *A.3.2.2 Protection Group Strategies*). Both of those problems were the focus of carbohydrate research for several decades. Today chemists are equipped with a useful toolbox of methods that allow for regio- as well as -stereoselectivity[36,41,42] (see *Figure 15*).

The stereoselectivity can be controlled *via* the installation of specific substituents close to the anomeric centre. For example, sterically demanding groups like pivalate esters or alkyl phosphates shield the oxocarbenium ion from one side, thus directing the attack to occur from the opposite direction. Generally, the reaction shows characteristics of both a dissociative mechanism (S_N1-type) and an associative (S_N2-type) reaction, based on the interactions with solvent and counterions.[41,43-45].

One of the oldest syntheses for glycosides is the *Koenings-Knorr* reaction[46], where a halogen leaving group (usually bromine is used) gets activated and withdrawn from the reaction equilibrium, by forming a precipitating silver(I) salt (see *Figure 16*).

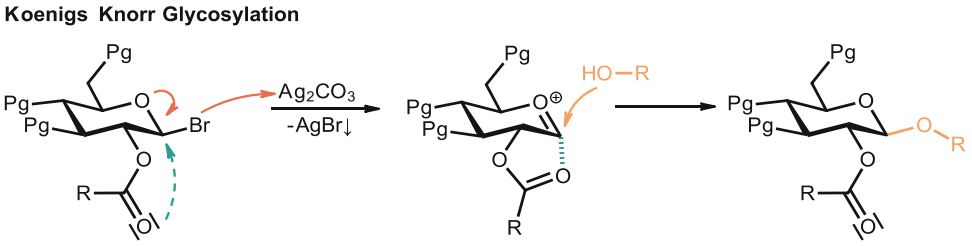


Figure 16. Koenigs Knorr glycosylation, with silver carbonate.

A.3.2.2. Protection Group Strategies

Before even performing glycosylations, another challenge arises - the regioselectivity. Protection groups on donor and acceptor are needed, to ensure a selective reaction of the donor with a specific acceptor position, while also preventing homo-glycosylation.

With a multitude of very similar hydroxy-functions present, elaborate protection group strategies are needed. Most of the time, they need to discriminate between different relative stereo-relations or utilize the different reactivities of primary and secondary alcohols. Even the site-selective introduction of a specific protection group in a carbohydrate structure can be complicated.

Typical challenges and their solution are presented based on two examples related to work that was performed by the author of this thesis in the Bioorganic Synthetic Chemistry group at TU Wien. Especially the differentiation between the endo-cyclic positions is difficult, as the hydroxy-functions are all secondary. Methods that can discriminate based on relative stereochemistry need to be applied to manage this challenging task. For example, the site-selective introduction of a benzyl group to the *O*3 position of mannose makes use of such a method by *Taylor*[47], that uses borinic acid catalysis. The

reaction allows to activate an equatorial hydroxy function of a *cis*-diol for substitution. This reactivity gives rise for an efficient route towards 3*O* substituted *manno* or *galacto*-building blocks (see *Figure 17* top). This route was used to synthesise 3-OBn-mannose, an important starting material for this thesis. (see *A.5.3.1*).

For most applications where complex oligosaccharides need to be synthesised, the protection groups also need to be orthogonal to each other, to allow for sequential deprotection. Such an orthogonal protection strategy was recently demonstrated on thio manno-heptoses by *Suster and Stanetty*[48] (see *Figure 17* bottom) and is discussed as a typical approach towards the goal of differentiated carbohydrate building blocks.

First, an exo-cyclic bridging TIPDS group is introduced selectively to the primary position. The magnitudes higher reactivity of primary alcohols than secondary ones allows for a chemoselective introduction of the TIPDS group[49,50]. Next, the relative stereochemistry within the mannose scaffold is exploited, by a cyclic orthoester formation, that is only possible on a *cis*-diol like the *O2* and *O*3 positions of mannose. The steric strain resulting from a cyclisation on a *trans*-diol (like between *O3* and *O*4) is

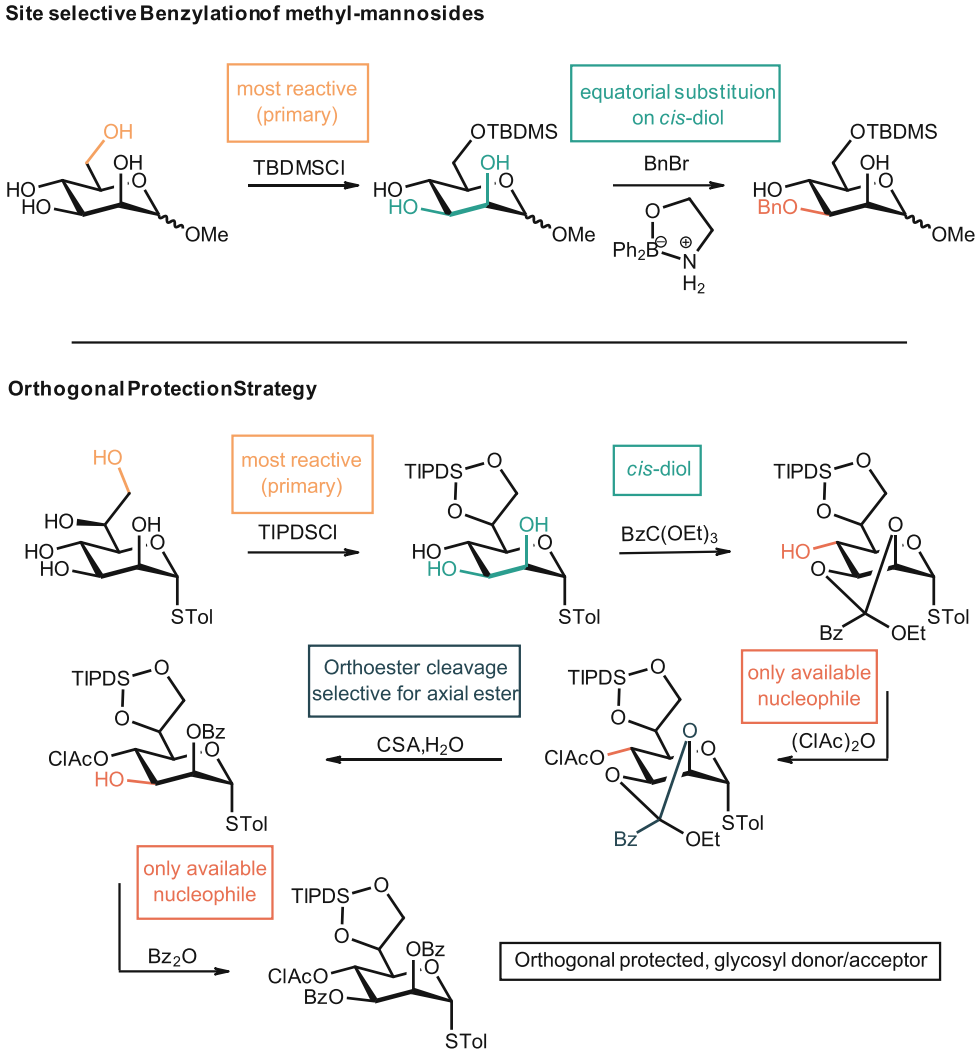


Figure 17. Top: Site-selective *O*3 benzylation of mannose using borinic acid catalysed alkylation by *Taylor*. **Bottom:** Examplatory strategy, using reactivity differences and relative stereochemistry of five hydroxy functions, introduces an orthogonal set of protection groups to *manno*-heptoses. This strategy was recently used in the Bioorganic Synthetic Chemistry Group at TU Wien[48]

very high, and the reaction path therefore unfavourable. This procedure leaves a sugar scaffold with only one hydroxy function behind (*O*4 position), that can then be protected orthogonally, for example with a labile chloroacetate ester. The next step is the hydrolysis of the orthoester moiety in slightly acidic conditions to introduce another ester function at the diol's axial position – the *O*2 position. The remarkable stereoselectivity of this transformation comes from a better stabilised transition state when the ester is oriented axially[51]. The choice of introduced orthoesters inherently influences the type of ester-group that is introduced in the orthoester hydrolysis. Last, there is again only one hydroxy function unprotected, allowing for orthogonal esterification of the *O*3 position.
The involvement of the introduced groups in glycosylation (regarding stereoselectivity) causes try-and-error to be an innate feature of glycosylations, making it hard to develop generalised protection procedures[41,48].

A.3.3. Aldehyde-Derived Reactivity of Aldoses

Apart from the important field of oligosaccharide synthesis, the chemical structure also presents a very selective reactivity site for other purposes – the aldehyde. The reactivity derived from such a carbonyl function is versatile and involves oxidations, reductions and chain altering reaction, directly at the anomeric centre[52].

Early applications - as reductant – reducing sugar

As mentioned above (*A.3.1.1*), sugars can be categorised into reducing- and non-reducing sugars depending on their ability to act as reductant. Generally reducing sugars bear a hemiacetal function, that easily get oxidised to a lactone.
The nomenclature was derived from the *Fehling Test*[53], an important analytical method for sugar identification in the 19th century. The test is based on the addition of copper(II)tartrate – a dark blue coloured complex – to a solution of the carbohydrate to analyse. Reducing sugars reduce the Cu(II) to Cu(I), eliminating the blue colour, while being oxidised to the corresponding aldonic acid (see *Figure 18*). Non-reducing sugars. Even ketoses are reducing sugars, as the α-hydroxy-ketone can tautomerise to form an aldose (*vide infra*). Only if no hemiacetal is present, the Fehling test gives a

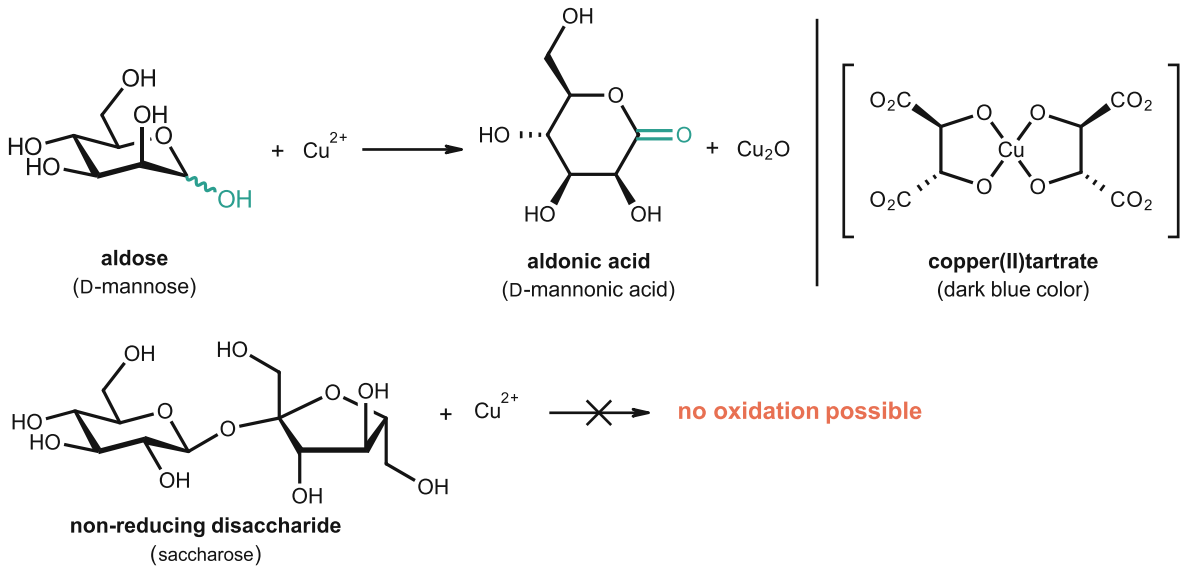


Figure 18. Fehling Test for reducing sugars

negative result. For example, saccharose as a disaccharide of glucose and fructose linked between their anomeric carbons is a non-reducing sugar, as no hemiacetal is present in the molecule.
Other tests that resemble the Fehling test exist, for example: In the *Tollens Test*[54] silver ions are reduced to form an elementary silver coating glass-plate.

Reduction to Alditols

The aldehyde moiety of aldoses can also be reduced to an alcohol function. The resulting compounds are substituted with a hydroxy group on every carbon of the chain and are called sugar alcohols or alditiols. These transformations were of great importance, as they reduce the innate complexity of carbohydrate structures[55]. In the early days of sugar chemistry, identifying the standard set of monosaccharides was only possible *via* such reductions. Sugar alcohols are less common in nature, but their accessibility has drawn some attention for further research[56,57].
Reductions are commonly performed with standard reducing agents like $NaBH_4$ or Raney-Ni are used.

Ketose-Aldose Isomerisation

A characteristic reaction of aldoses is the isomerisation into ketoses, also called *Lobry-de-Bruyn-Alberda-van-Ekenstein-Rearrangement*[38]. This reaction is base catalysed and mechanistically an endiol forms upon tautomerisation of the aldose. The endiol can then either form the corresponding ketose or undergo re-formation of the aldose. In the latter case, the stereo information of the former C2-position is lost, therefore giving a mixture of 2-epimeres. This endiol-derived transformation has to be considered in all cases, where sugars are in contact with strong bases like KOH or NaOH.

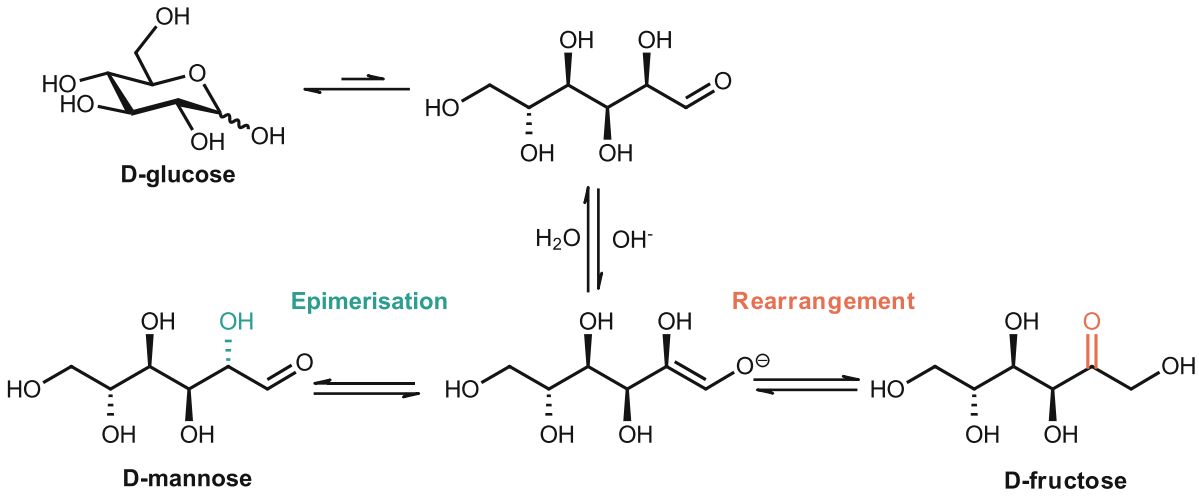


Figure 19. Ketose-aldose isomerisation exemplified on the isomerisation of D-glucose to D-fructose. The innate epimerisation to D-mannose is also drawn.

Industrially this isomerisation plays a role in the synthesis of non-natural ketoses, the resulting complex mixtures of sugars, however, renders this transformation generally unpopular and rather a possible side reaction to be considered. (see *Figure 19*)

Chain-length altering reactions

Next to the already described reactions that directly change the aldehyde function into a different functional group, a wide array of reactions can occur on the aldehyde moiety and lead to elongation or shortening of the carbon-backbone of the sugar.

The set of possible reactions features radical (e.g. *Ruff degradation*[58], *Barton decarboxylation*), oxidative (e.g. *Periodate cleavage*) or organometallic (e.g. *Rhodium-catalysed decarbonylation*) methods for dehomologation (= chain shortening). Also, addition reactions for chain elongation[59] are available (e.g. *Kiliani ascension, Aldol reaction*[60]).

Development of such methods for shortening and extending carbon-chains of unprotected reducing sugars has been the subject of carbohydrate research for over a century, as carbohydrates serve as excellent enantiopure starting materials for various total synthesises of natural products[61,62]. The interconversion of sugars, by altering the chain lengths is a powerful tool, as only a handful of carbohydrates is readily available from natural sources.

Common to all these methods, that act on the carbonyl moiety of carbohydrates, is that they suffer from low availability of the aldehyde. As already described in *A.3.1.2,* sugars can undergo intramolecular hemi-acetalisation, masking the aldehyde and making it initially unavailable for transformations mentioned above. Only the minute amounts (for hexoses <1%) of sugar in open-chain form can react as aldehydes. By constant withdrawal from the equilibrium of the reaction products, the starting material constantly reequilibrates. Therefore, full conversion is achievable for such transformations, but the kinetics are generally slow.

A.3.3.1. Dehomologation of Aldoses

Radical Dehomologation – Ruff Degradation

In the Ruff degradation, salts of aldonic acids are used under oxidative conditions in an alkaline solution of hydrogen peroxide and transition metal salts (often Cu(II) or Fe(III) salts). The aldonic acids are generated beforehand by oxidation with Br_2 in an aqueous solution. The reaction was shown to proceed *via* two different single-electron-transfer steps and trapping of the forming carbocation by the solvent. First, an acyloxy radical gets generated *via* a SET mechanism, which readily decarboxylates, thus causing shortening of the carbohydrate by one carbon[63] (see *Figure 20*).

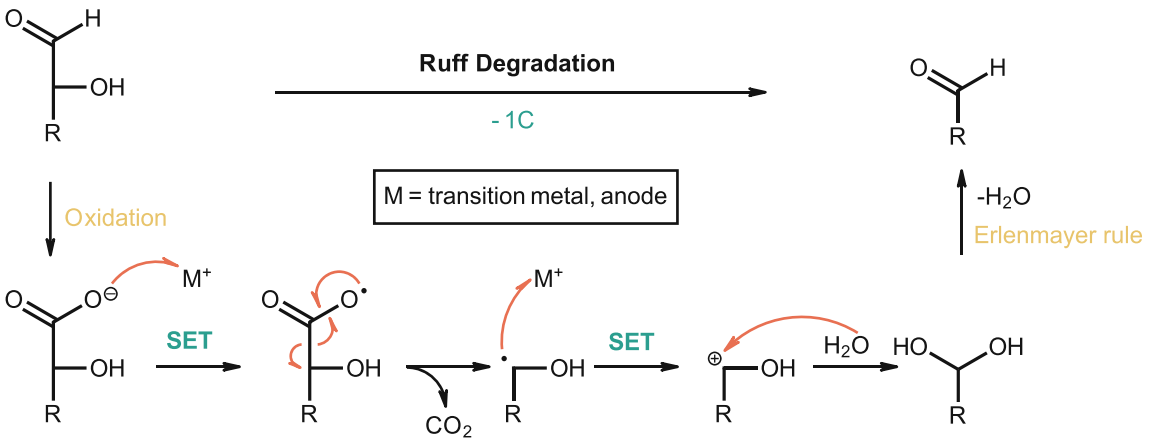


Figure 20. Ruff degradation

Modern developments of the reaction, which originates from 1898, are applying electrochemical methods instead of transition metal solutions. Also, zeolites have proven to be beneficial for the reaction under classical conditions, as it encloses the reaction partners in close proximity [64].

The Ruff degradation has only little significance in modern carbohydrate-chemistry, mostly because of mediocre yields. However, it receives some attention, as it works relatively efficient for the

dehomologation of hexoses to pentoses.

Dehomologation *via* Elimination – Wohl Degradation

In the Wohl degradation, an unprotected reducing sugar gets converted into an oxime, by treatment with hydroxylamine. Subsequent addition of acetic anhydride can dehydrate the oxime to give a peracetylated nitrile species. This nitrile can then be eliminated in two ways. In the original method, silver oxide and ammonia are used to give a peracetylated dehomologated sugar. In the Zémplen variant, sodium methoxide is used to eliminate the nitrile, while the acyl groups undergo transesterification with methanol to form back the unprotected aldose.

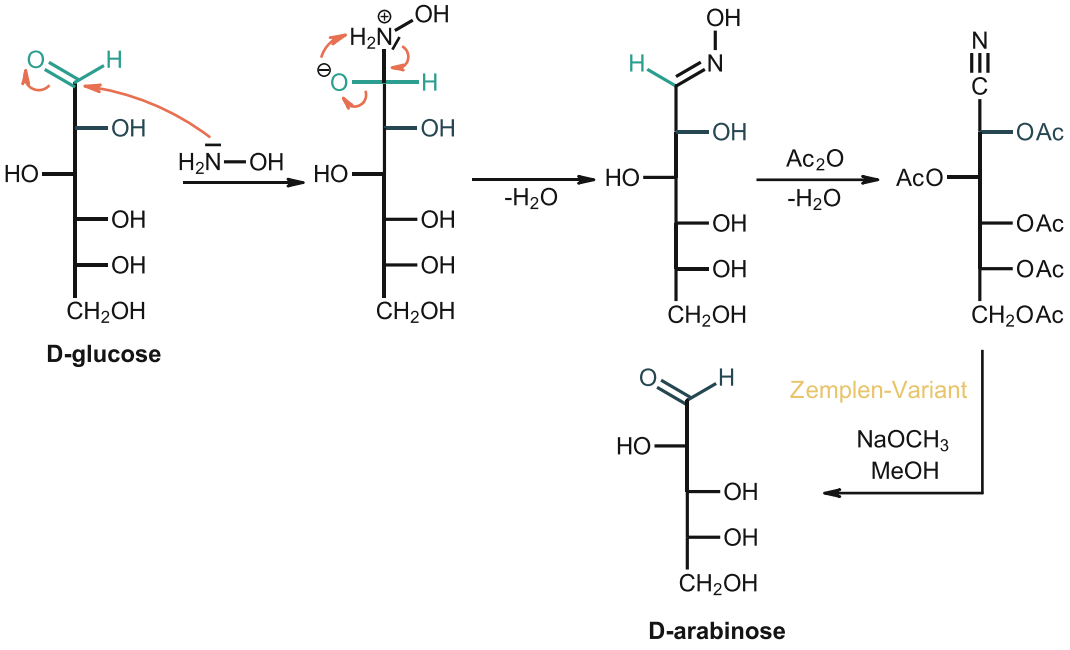


Figure 21. Wohl degradation of D-glucose to D-arabinose.

Despite the first report of the Wohl degradation well over 100 years ago[65] (1893), the reaction still sees substantial use in laboratory scale applications. The simplicity of the used reagents and the higher yields compared to the Ruff degradation are a significant factor for its popularity.

Oxidative Dehomologation – Periodate Cleavage

One of the most widely used methods for carbohydrate shortening is the periodate cleavage. With periodate or lead-tetraacetate,1,2 diols or α-hydroxy carbonyl compounds can be cleaved into the corresponding aldehydes[59]. The method generally needs partial protection of the sugar, as the reaction is itself only little selective for specific bonds[66].

The reaction has some characteristics that make it attractive. First, the reagents are non-toxic, and the yield is excellent for some specific cases. *Storz et al.*[66] achieved 92 % yield for the dehomologation of a 3*O*-protected glucose derivate to the corresponding arabinose. The protection grouped ensured selective attack at the 1,2-diol of the glucose hemiacetal. The periodate cleavage comes with a significant advantage compared to other methods that it can cleave the cyclic carbohydrate. Thus, it is not limited by the mutarotation equilibrium. However, the necessity of protection groups causes requires higher synthetic effort than other dehomologation reactions. Mechanistically, periodate forms a cyclic intermediate with a 1,2-diol, that then undergoes reverse cycloaddition (comparable to an ozonide

breakdown), to form two aldehydes. The former periodate (oxidation state VII) gets reduced to iodate (oxidation state V) in the processes. Performing this reaction on a 1,2-diol of carbohydrates leaves behind a formyl ester, which acts as a temporary protection group, that can easily be cleaved upon mild alkalic workup (see *Figure 22*).

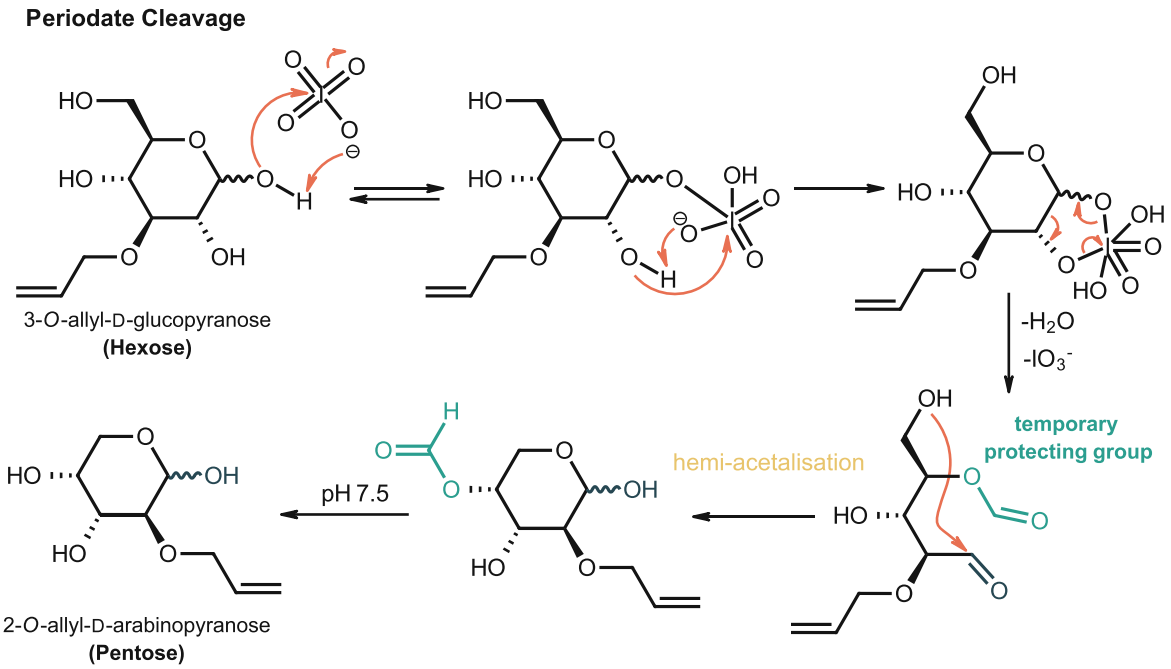


Figure 22. Periodate cleavage of 3-*O*-allyl-D-glucopyranose with sodium periodate. *Storz et al.*[66] achieved 92 % yield for this specific transformation.

Organocatalytic reductive Dehomologation – Rhodium-catalysed decarbonylation

This method allows for catalytic dehomologation of unprotected aldoses to alditols by heating to around 160 °C, using $Rh(dppp)_2Cl$ as a catalyst[67]. Again, the reaction can only take place on the free aldehyde moiety. Thus mutarotation enhancing additives (e.g. acetic acid, pyridone or pyridine) proved beneficial. The reaction yields up to 75 % of the corresponding alditols[59]. Substantial amounts of 1,4-anhydroalditols have been identified as major side-product, which comes from rhodium-mediated dehydration. This decarbonylation is not only used to shorten carbohydrates but also to provide CO. For example, *Morimoto*[68] used the carbohydrates as a feedstock for CO in the *Pauson-Khand* reaction. Mechanistically, the reaction is well studied and understood and consists of 4 main steps.

First, the aldehyde of an aldose gets added to the catalytical active moiety. Carbon monoxide gets expelled in this process. Next oxidative addition of the Rh(I) species into the C-H bond of its aldehyde-ligand occurs, resulting in a Rh(III) species. Following is the rate-determining-step (r.d.s.): a migratory extrusion of carbon monoxide to form a Rh(III)-complex with another CO-ligand. Finally, the alditol gets reductively eliminated, thus restoring the original catalytically active Rh(I) species. (see *Figure 23*)

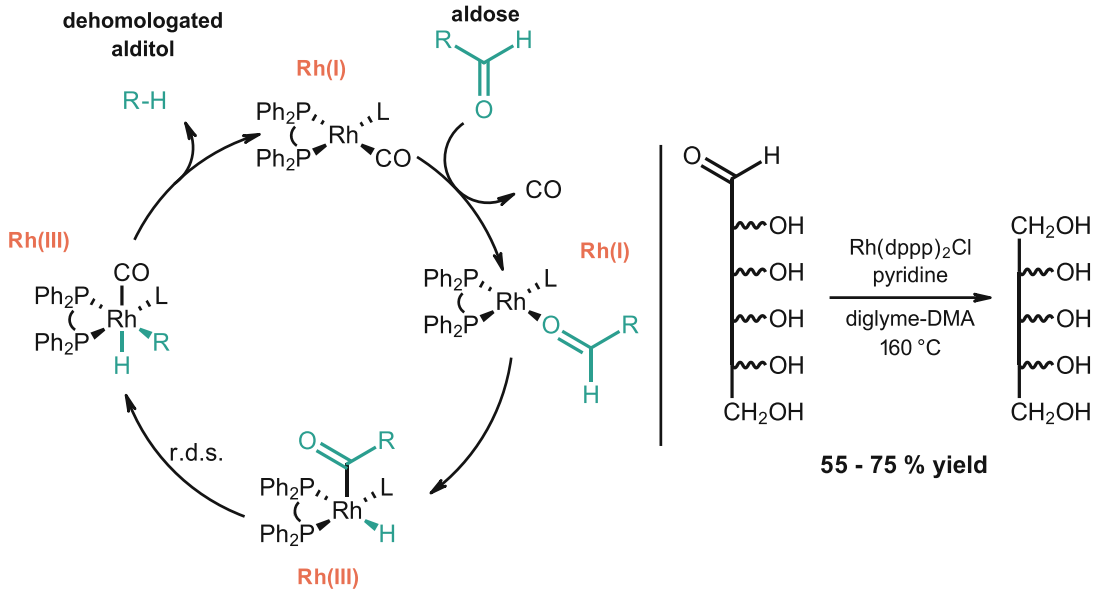


Figure 23. Organocatalytic dehomologation of aldoses *via* rhodium catalysis. The proposed mechanism is depicted on the left; on the right, a general conversion of hexoses to hexitols is shown.

A.3.3.2. Chain Elongation of Carbohydrates

Addition of Carbanions – Kiliani Ascension

In 1886 *Heinrich Kiliani*[69] reported a one-carbon elongation of aldoses upon addition of cyanide. The so-called Kiliani ascension is one of the oldest known reaction in carbohydrate chemistry and was the first example of nucleophilic addition to the carbonyl moiety of sugars.

The already described Wohl degradation is the reverse reaction of the Kiliani ascension. Mechanistically, a cyanide anion directly undergoes nucleophilic attack at the aldehyde moiety, forming a cyanohydrin species. Hydrolysis of the nitrile function gives the corresponding acid, which directly

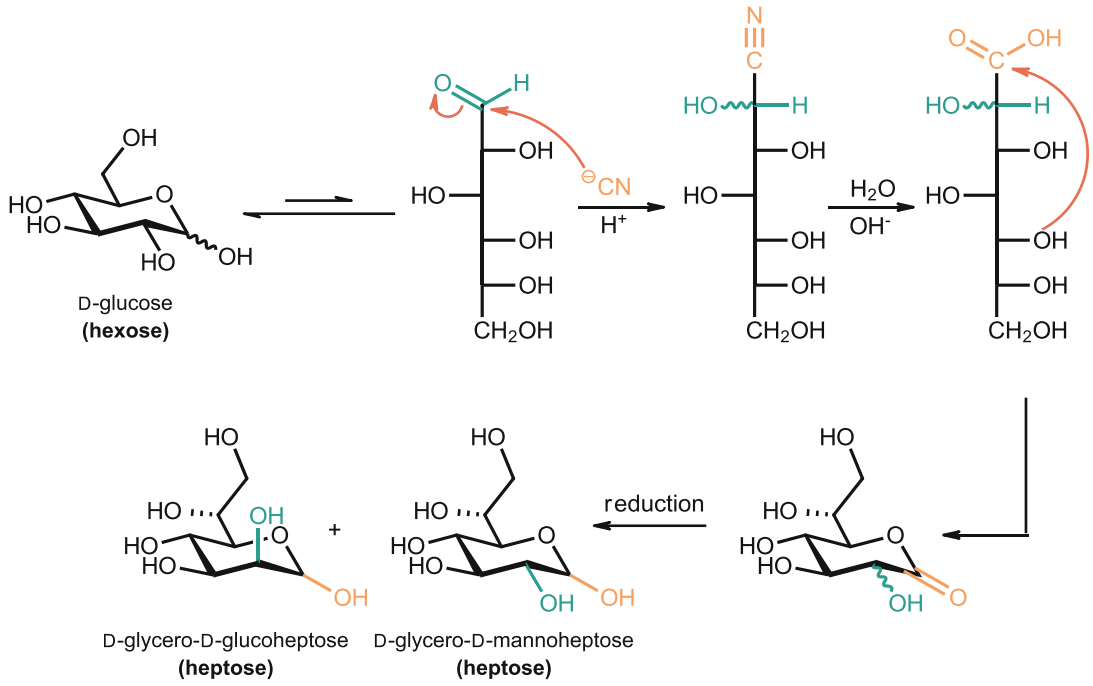


Figure 24. Kiliani ascension of D-glucose to heptose.

cyclises into a lactone moiety. This lactone can be reduced, to give a hemiacetal of the elongated sugar. This method cannot influence the formed products' stereochemistry, as the attacking nucleophile (CN^-) cannot be altered chemically. A new stereocenter at the former carbonyl position is formed, leading to 2-epimeres in a purely substrate controlled ratio (most often around 1:1). Subjecting D-glucose to the ascension, unavoidably yields a mixture of *manno*-heptose, and *gluco*-heptose in a ~1:1 ratio[70].
Separation of the formed epimeres can be difficult, its success heavily substrate-dependent and may need derivatisation for crystallisation[71].
This reaction is particularly of interest when performing isotope labelling (^{13}C) of sugars, as the needed reagents are cheap even in labelled form. In general, for elongation applications, other methods, that circumvent selectivity and reactivity drawbacks have emerged[52].

Organometallic Additions

It was shown, that the addition of classic organometallic compounds (like organolithium or magnesium) is possible, even on carbohydrates with low open-chain content[59]. However, for this reaction to happen, protic species need to be excluded. Therefore, non-protic solvents and (complete) protection of the sugar's hydroxyl groups is generally required. The benefit of such organometallic reactions is predictable diastereoselectivity. According to the Cram-chelate model, if the metal can chelate (e.g. with a free hydroxyl function), 1,2-syn-addition is observed. In the absence of a chelating partner 1,2-*anti*-addition, according to Felkin-Ahn model, is preferred (see *Figure 25* top)[52]. One of the

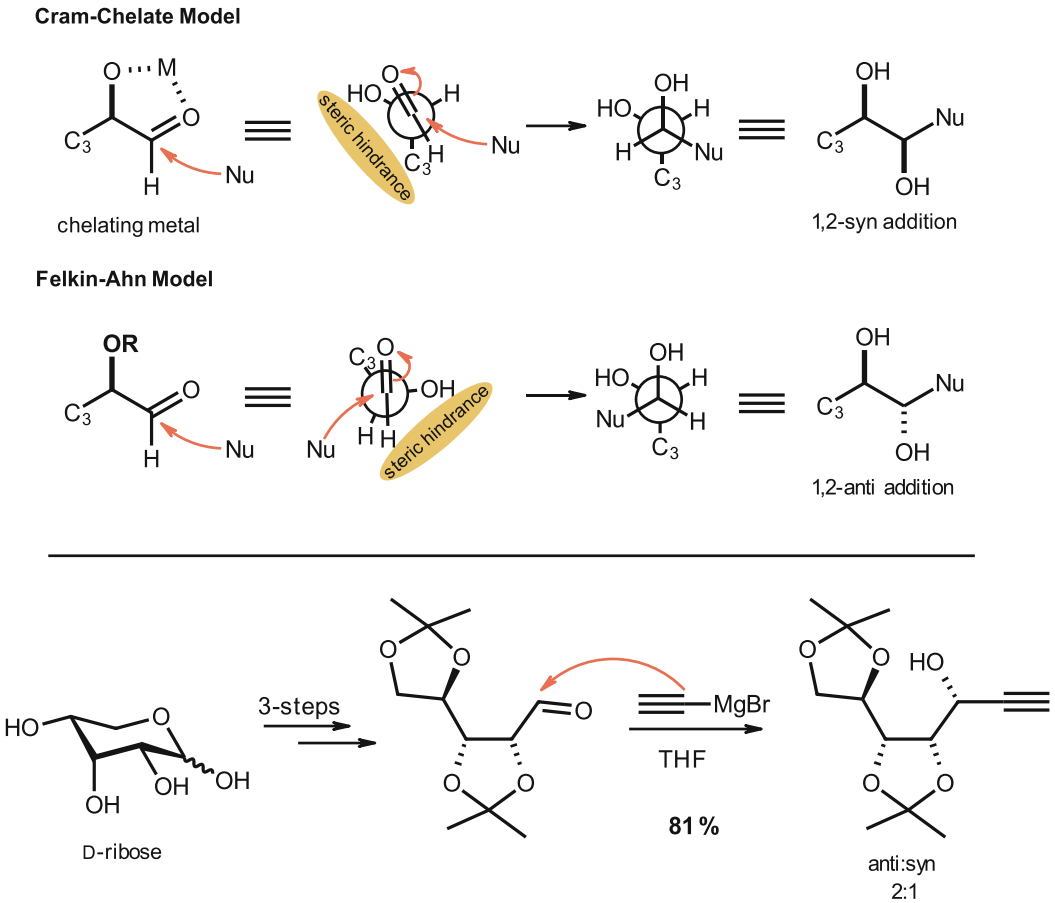


Figure 25. Top: Models to explain the facial selectivity of nucleophilic attack of an organometallic compound on an aldose's carbonyl centre. **Bottom**: Application of the method, Grignard reaction on a fully protected ribose with good yield and 2:1 dr.

first successful applications of this methodology came in 1985 by *Buchanan and Edgar*[72] who demonstrated nucleophilic addition of ethynyl magnesium onto 2,3;5,6-di-*O*-isopropylidene-D-ribose in good yield but only a diastereotopic ratio of 2:1 anti/syn (see *Figure 25* bottom). The stereocontrol within an elongation reaction is a significant benefit of using this method, compared to the 'classical' variants like the Kiliani ascension.

The higher synthetic effort needed to protect the sugars beforehand; however, is a drawback. More recent research focused on circumventing this problem, and other metals were explored. Soon zinc and

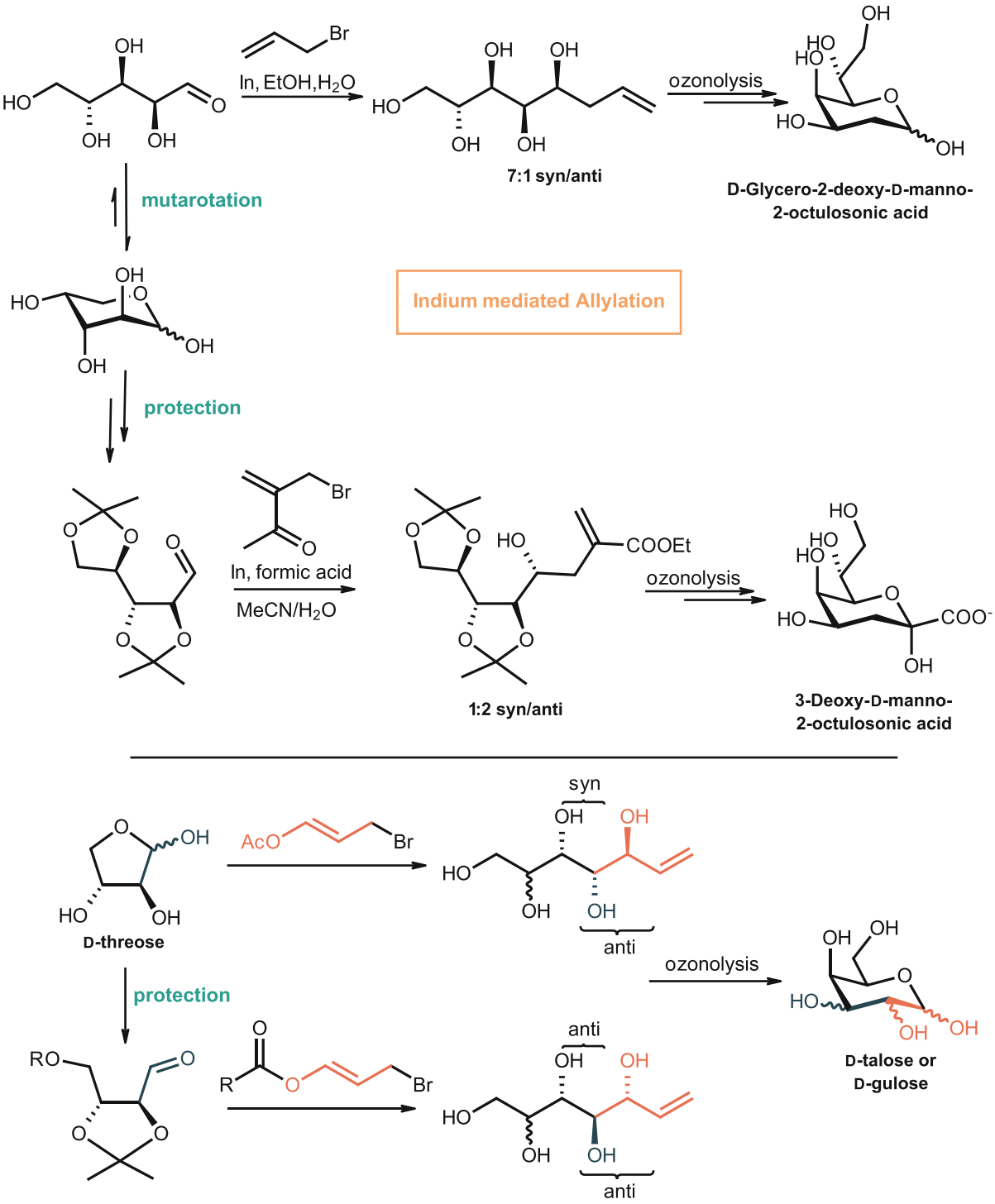


Figure 26. Indium mediated allylation and diastereoselective divergence by substrate control (Top). Indium mediated acyloxyallylation in diastereoselective divergence by substrate control[73] (Bottom)

indium were found to have much higher stability in protic conditions, accepting unprotected carbohydrates and even alcohols as the solvent[74,75]. Using indium, already first reports showed remarkable stereoselectivity, based on the indium's high tendency to coordinate to neighbouring hydroxyl-functions. From that finding, two elongation protocols were developed. The indium mediated allylation procedure gives elongated 2-deoxy sugars upon nucleophilic addition of an allyl-halide with indium and subsequent ozonolysis in good diastereotopic selectivity (see *Figure 26* top). This method is a 2-carbon elongation.

For the synthesis of standard carbohydrates, another nucleophile has to be used – 1-acyl allyl halides. In 2005 *Madsen*[76] showed the applicability of this indium mediated acyloxyallylation in a proof of concept study, to elongate hexoses to heptoses and octoses in remarkable diastereoselectivity. A target-oriented application was delivered by *Stanetty and Baxendale*[77] who showed a large scale synthesis of L-glycero-D-mannoheptose (100 mmol scale) in 2015. An in-depth investigation into the method was performed by *Draskovits and Stanetty*[73] in 2018, pinpointing the influences for diastereoselectivity. (see *Figure 26* bottom).

A.4. NHC and Carbohydrates

As already discussed in previous chapters (*A.1.2*), NHC catalysis is selective for aldehyde functions, undergoing Umpolung reactions. Reducing sugars can be chemically addressed as aldehydes, thus providing a potential field of application for NHC catalysis. Despite the matching reactivity of NHCs and reducing sugars, literature precedence featuring both fields is sparse. Especially, examples where the aldehyde moiety of a reducing sugar gets addressed are hard to find.

A.4.1. Non-Umpolung Chemistry in the Crossover of NHCs and Sugars.

Often NHCs and sugars are used together as ligands of gold(I) complexes[78-80]. Such complexes were found to act as potential inhibitors for thioredoxin reductase (TrxR), an enzyme involved in apoptosis suppression. Such complexes, therefore, are hopeful candidates for cancer treatment. As previously described (see *A.1.2.2*), NHCs helps to stabilise transition metal complexes, a property used to increase the lifetime of such complexes under physiological conditions (see *Figure 27* top).

Studer[81] reported another combined application in 2016. In this study, NHCs were used to regioselectivity acylate endocyclic positions of monosaccharides *via* a transesterification mechanism described previously (see *A.1.2.4*). While only demonstrated with aromatic aldehydes, the shown regioselectivity for acylation at the 2*O*-position of the carbohydrate is outstanding. However, a protection group for the primary hydroxy function is required (see *Figure 27* bottom).

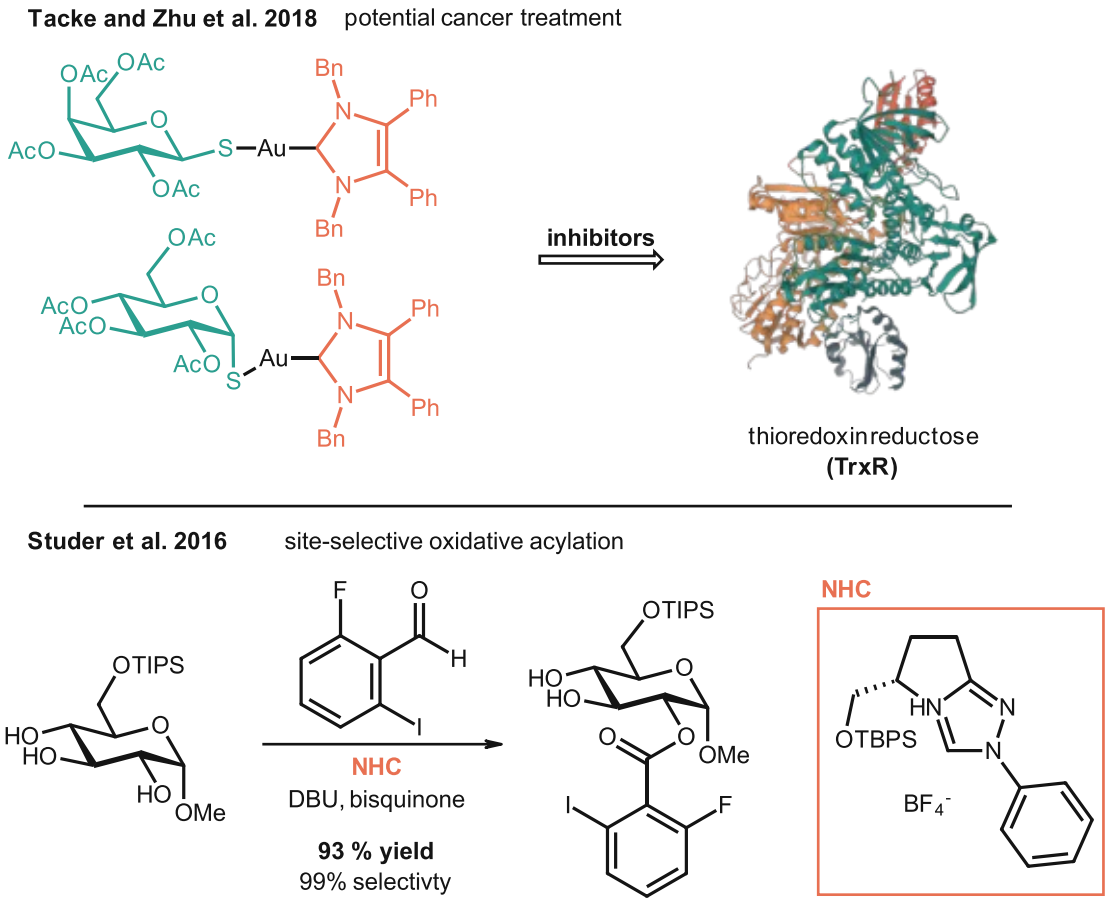


Figure 27. Application of NHC together with carbohydrates where the aldehyde function does not get addressed. **Top**: Au(I) complexes with sugars and NHCs as potential anticancer drug[78]. **Bottom:** Regioselective oxidative acylation of carbohydrates using NHC catalysis[81] (best example is shown).

A.4.2. Umpolung at the Anomeric Position of Reducing Sugars

The precedence of reactions targeting the aldehyde moiety of reducing sugars with NHCs is scarce. The field of research is best exemplified by three examples.

A.4.2.1. Stereoselective NHC mediated Inositol Formation from Carbohydrate Derived Dialdehydes

Greatrex[82] reported an example where an NHC targets the aldehyde function of a carbohydrate derived 1,6-dialdehyde to catalyse stereoselective benzoin condensation. The formed carbocycle could then be reduced to form inositols. The downside of this method is that the dialdehydes require a lengthy synthesis, starting from the corresponding aldose. Protection is mandatory throughout the NHC catalysis step, as increased stereoselectivity for the cyclisation was observed with bulky protecting groups on the molecule. (see *Figure 28*).

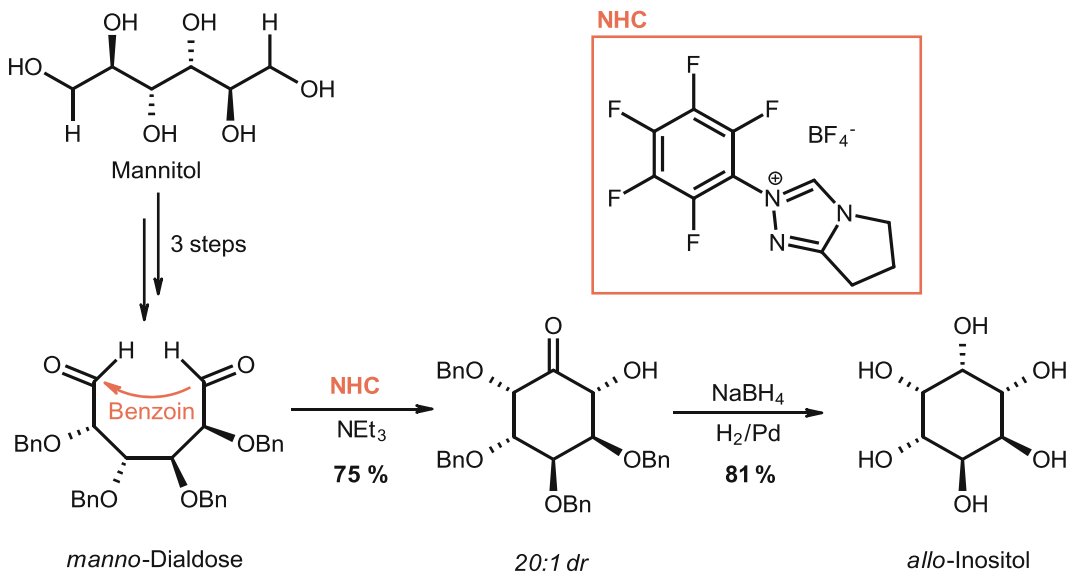


Figure 28. Aldose derived 1,6-Dialdehyde undergoing stereoselective NHC catalysed benzoin condensation form inositols upon reduction.

A.4.2.2. NHC Catalysed Redoxlactonisation of Carbohydrates

In 2011 *Wendeborn* published a study where he directly addressed the carbonyl function of reducing sugars *via* NHC-Umpolung[83]. The initial idea was to enable the anomeric carbon of protected aldoses to undergo direct Stetter functionalisation with α,β-unsaturated carbonyls. Instead, α-elimination of an

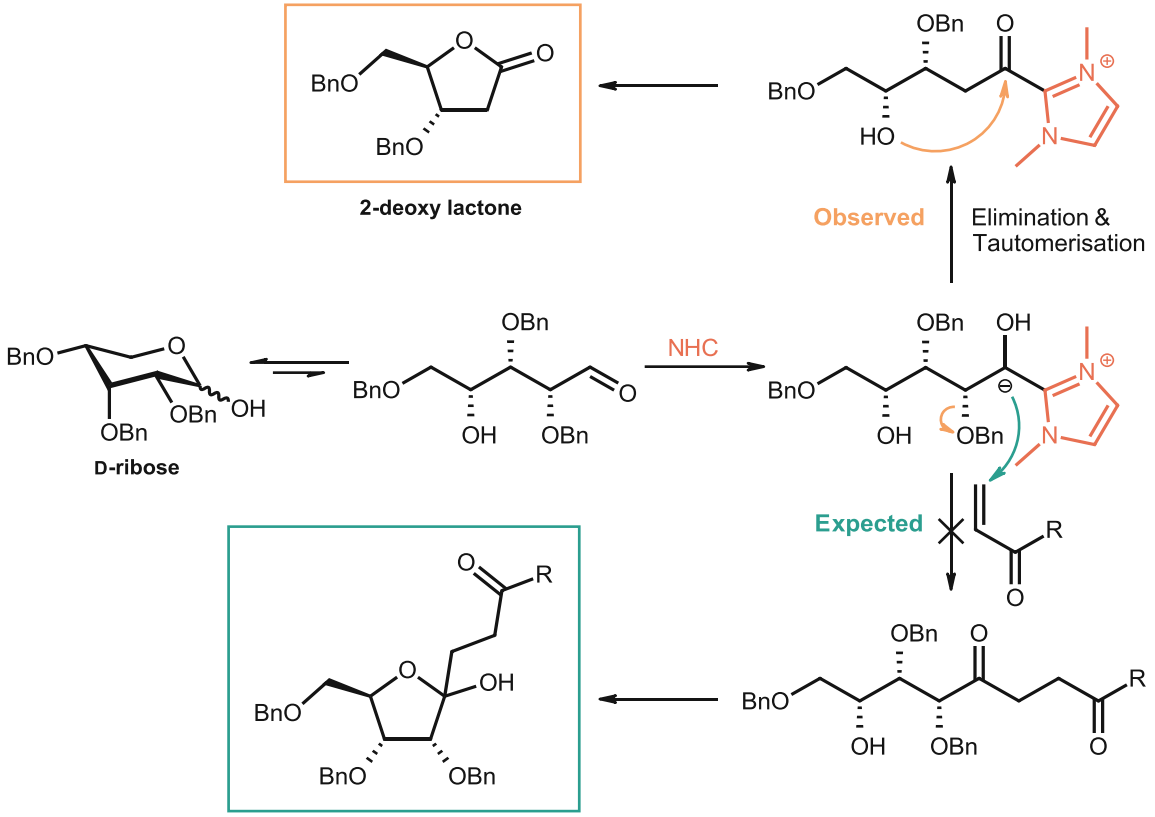


Figure 29. NHC Umpolung of the aldehyde moiety of reducing sugars by *Wendeborn*. The pathway they expected to find is marked in turquoise, while the actually observed α-elimination is drawn in orange.

oxygen leaving-group was observed, resulting in a redox transfer. Such reaction pathways were found by *Rovis*[84] and *Bode*[85] independently on non-carbohydrate based aldehydes bearing a leaving group in α-position.

Such a reaction can result in an internal nucleophilic attack of the 4OH function on a pentose scaffold, forming a 2-deoxy-lactone (see *Figure 29*).

Although such α-eliminations were already reported before[84,85], it was a new type of reactivity within the realm of carbohydrate chemistry.

A.4.2.3. NHC-Mediated Degradation of Carbohydrates as Formaldehyde Source for Stetter Reactions

Shortly after *Wendeborn*, the group of *Chi* also published a study about NHCs and carbohydrates as aldehyde starting materials in 2013[86]. They realised that aldoses are α-hydroxy carbonyl moieties that could undergo a retro-benzoin reaction to form a shorter aldose and delivering a formaldehyde equivalent with a reversed polarity available to undergo a Stetter reaction on enone species. Therefore, they reported a synthetic application where formaldehyde derived from sugars could be utilized as a nucleophilic C1 building block.

Why is this necessary: Usually, formaldehyde undergoes selective self-benzoin condensation reaction under Umpolung conditions, rendering it an unusable substrate for general NHC catalysis. This self-condensation of formaldehyde is called formose reaction [87]. The high electrophilicity of formaldehyde makes it the preferred target for nucleophilic attack of an acyl anion. Such Formose reactions can be completed within 5 minutes[86,88], providing superior reaction kinetics compared to other possible benzoin as well as intended Stetter reactions, as in this particular work.

The mechanism proposed involved a catalytic cycle, where first an NHC catalyst would catalyse a retrobenzoin reaction, liberating a Breslow intermediate of formaldehyde and a shortened aldose. The Breslow intermediate would then undergo Stetter reaction with a Michael acceptor (chalcone), liberating the NHC catalyst for another catalytic cycle. They suspected that the shortened sugar could undergo an analogous cycle again (see *Figure 30*). In addition to GC-MS detection of dehomologated sugars in various lengths, the ultimate proof for their proposed mechanism was delivered when they demonstrated that one equivalent of glucose could formylate 5 equivalents of Michael acceptor giving moderate yields of the formylated product (55 %), which can only be explained by multiple catalytic cycles proceeding.

They investigated various NHC catalysts and different reducing sugars for the formylation of chalcone, finding the best reaction with D-arabinose together with a trimethyl thiazolium salt. Overall they achieved 81 % isolated yield of formylchalcone. They also showed that the formed formylchalcone could be used to undergo cyclisation to various 5-membered heterocycles.

It is remarkable for this transformation that the C1-formyl building blocks can be generated, while self-benzoin (formose) reactions are suppressed. It is even more noteworthy, that free carbenes react selectively with the aldehyde moiety avoiding quenching by the protic components in the reaction mixture (hydroxy functions of the aldose).

Together with the *Wendeborn* method, two methods for the direct transformation of the anomeric centre of reducing sugars are available. The selection of a specific pathway is substrate controlled, with 2OH carbohydrates undergoing retrobenzoin reaction, while carbohydrates with a potential oxygen leaving-group undergo α-elimination followed by redoxlactonisation.

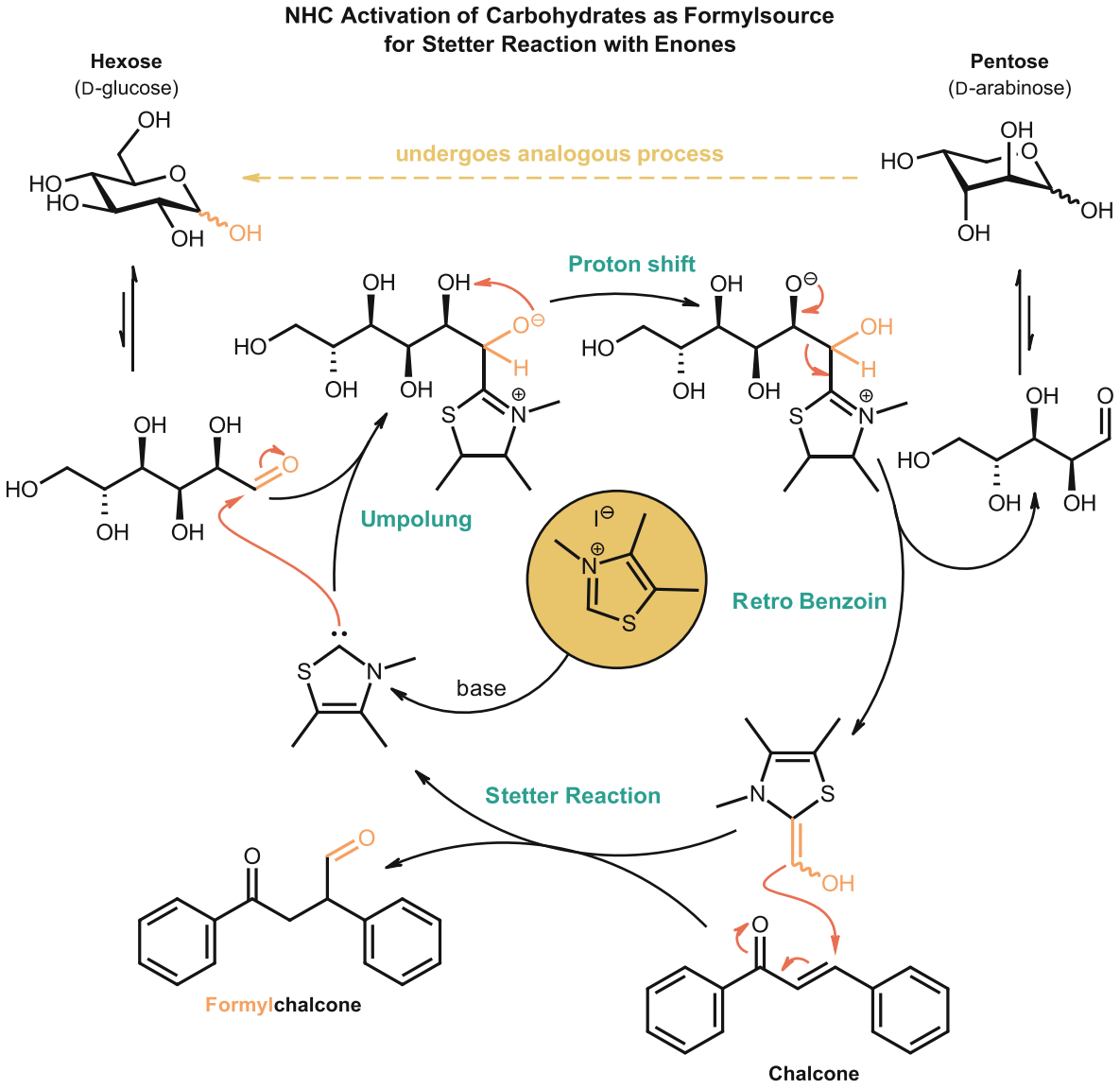


Figure 30. Proposed mechanism of the NHC activated use of carbohydrates as formaldehyde equivalent for Stetter reaction with chalcones.

A.5. Change of Perspective – The NHC Controlled Dehomologation of Aldoses

While the work of *Chi* (see *A.4.2*) was entirely focused on generating formaldehyde equivalents for the nucleophilic attack utilizing sugars as sacrificial feedstock, the presented reaction can also be viewed from the perspective of the carbohydrate. In that case, it is an NHC catalysed dehomologation reaction, with a Stetter reaction catalyst recycling system.
This change of perspective is the main focus of the research project, which this thesis is a part of.

A.5.1. Main Idea – Stopping the Dehomologation Cycle

Chi could not isolate specific dehomologated sugars in his work, as the dehomologation process gave multiple sugar fragments with various chain lengths. Stopping this dehomologation at specific chain-lengths would be a novel transformation for reducing sugars. As the dehomologation process occurs *via* retro-benzoin reaction, which requires an α-hydroxy carbonyl function, a protection group at the

α-position should intercept and terminate this dehomologation. In line with their functionality, such protecting groups are inhere referred to as *intercepting groups*. Mechanistically, the reducing sugar would undergo dehomologation cycles until such an intercepting group blocked the 2O position rendering a retro-benzoin reaction impossible.

However, as *Wendeborn* already showed with fully protected reducing sugars, Redoxlactonisation can occur upon NHC activation with *O*-protection groups at the α-position. Therefore, this alternative reaction pathway was an expected follow-up upon interception of the retro-benzoin-cycle (see *Figure 31*).

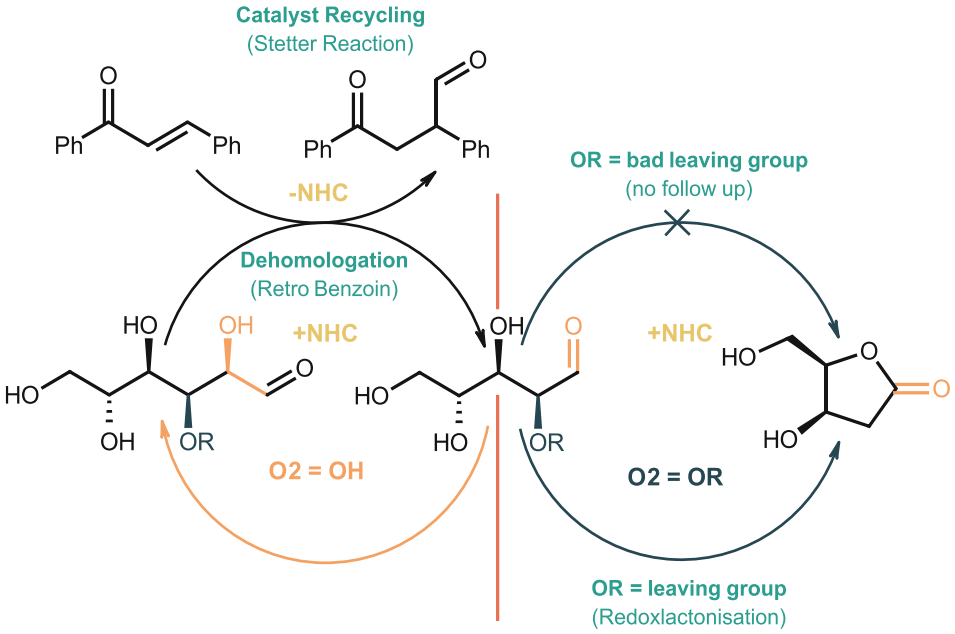


Figure 31. NHC activated intercepted dehomologation of carbohydrates and the expected follow-up reaction with substrate controlled divergence

The redoxlactonisation is likely dependent on the leaving group quality of the protected α-hydroxyl moiety. Ideally, substrate control can be achieved by a suitable choice of the protection group.

A.5.2. Proof of Concept for the intercepted dehomologation

The first step in investigating this potential new transformation was to deliver a proof of concept study, demonstrating that the dehomologation can be intercepted with suitable intercepting groups. For this study, two extreme cases were investigated: L-arabinose acetonide [**1**] was used as a substrate capable of undergoing one dehomologation cycle and was found not to undergo further redoxlactonisation. Tentatively the formed dehomologation product (L-erythrose acetonide) is capable of forming two fused five-membered rings upon hemiacetal formation, resulting in high inherent stability. The other case was 4,6-*O*-benzylidene glucose, a substrate that smoothly underwent two dehomologation cycles and a follow-up redoxlactonisation. The reaction-intermediate does not undergo hemiacetal formation, as it would lead to the formation of an energetically unfavored fused trans-6,4 ring system. Therefore the aldehyde would stay available for additional NHC activation and lactonisation. Both products were isolated as the corresponding acetates (see *Figure 32*).

3,4,5-Trimethyl thiazolium iodide [**2**] was used as pre-catalyst salt, which had been identified as the most efficient one in the original publication by *Chi*. Chalcone [**3**] was used as Michael acceptor for the

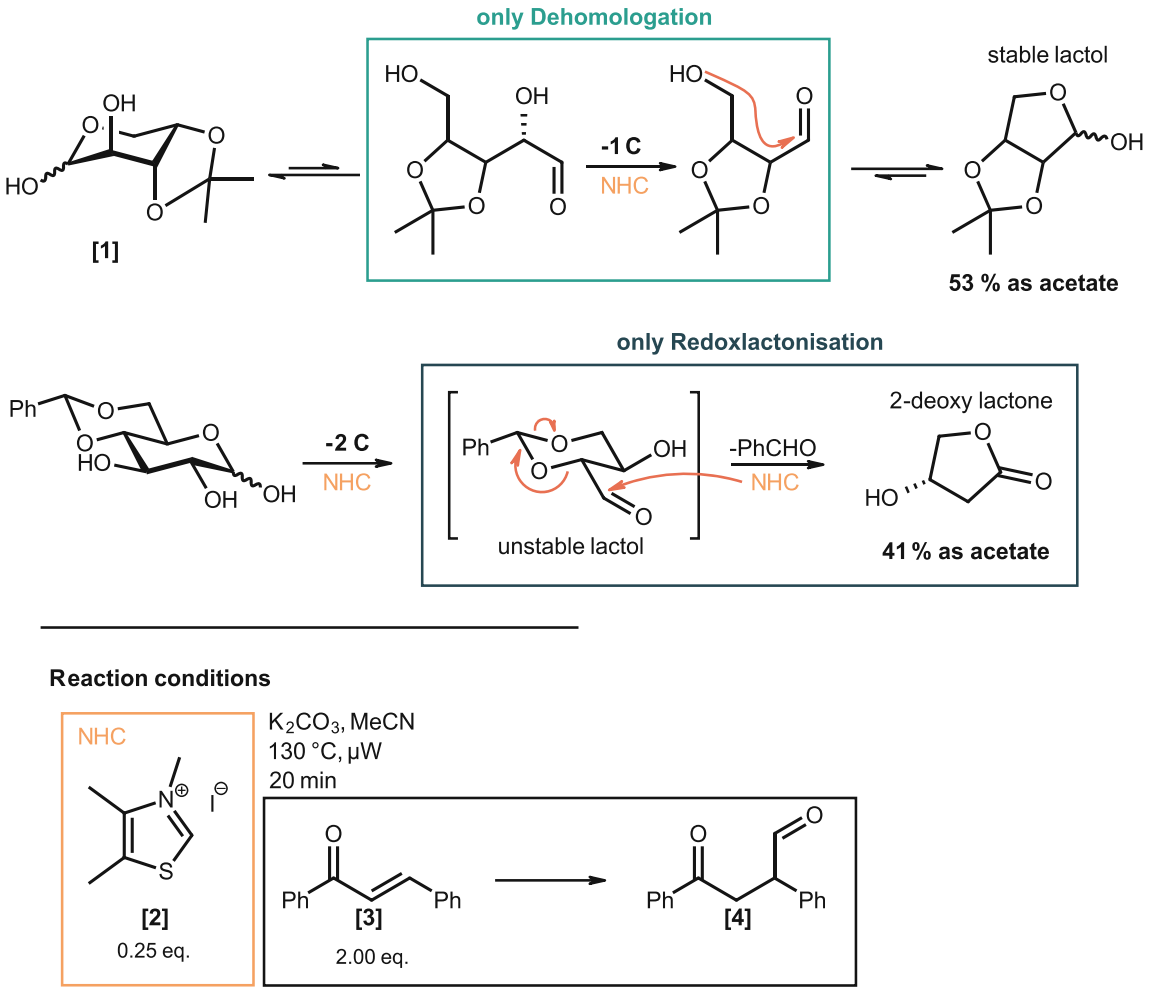


Figure 32. Successful proof of concept study for substrate controlled divergence.

Stetter reaction, ultimately recycling the catalyst (forming formyl chalcone [**4**] in the process).

A.5.3. Development into a Catalyst Driven Selectivity

After this successful demonstration of substrate controlled divergence, the goal was to aim at catalyst driven control over the reaction outcome. Therefore, a relatively unbiased substrate was required as a benchmark for the catalyst design process. Such a substrate was found with 3-*O*Bn-D-mannose [**5**], as the observed reaction outcome was about 1:1 between dehomologated sugar (2-*O*Bn-D-arabinose [**6**]) and redoxlactonisation product deoxy ribonolactone [**7**]. 3-OBn-D-glucose [**8**] was also analysed as another substrate; however, an increased preference for the lactone product was observed. This shift in selectivity between glucose and mannose is interesting, as those sugars are 2-epimers, and give the same dehomologated product [**6**] upon retro-benzoin reaction. Therefore, the same lactone [**7**] is formed in the follow-up reaction (see *Figure 33*).

A robust and fast screening procedure was required for the efficient design of catalysts to generate data about the reaction with high throughput and an efficient way to synthesise the non-commercial 3-OBn sugars [**5**] and [**8**].

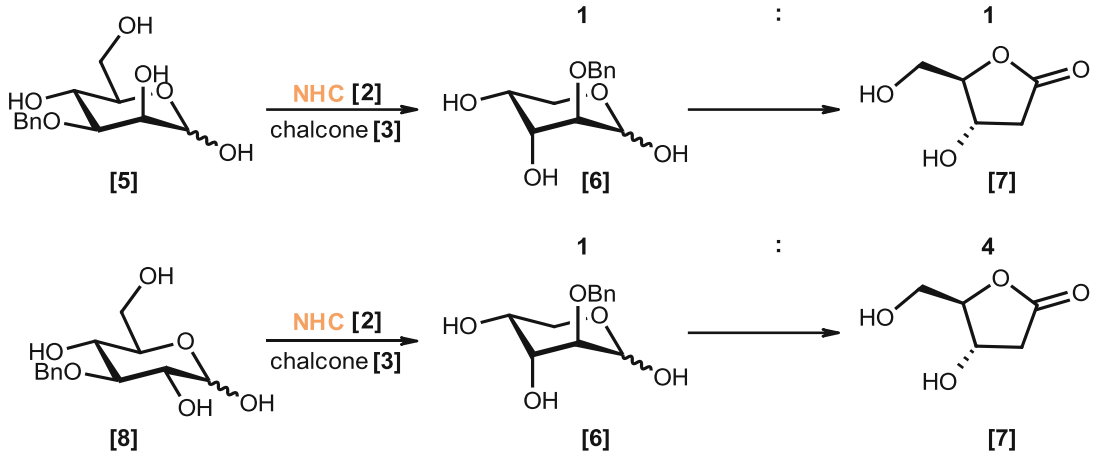


Figure 33. Dehomologation of 3-OBn-mannose and 3-OBn-glucose and observed selectivity for the two 2-epimeres.

A.5.3.1. Synthesis of Sugar Probes

The two starting materials relevant for this in-depth investigation are 3-*O*Bn -mannose [**5**] and -glucose [**8**].

The synthesis of [**8**] was straight forward by benzyl protection of commercially available glucose-

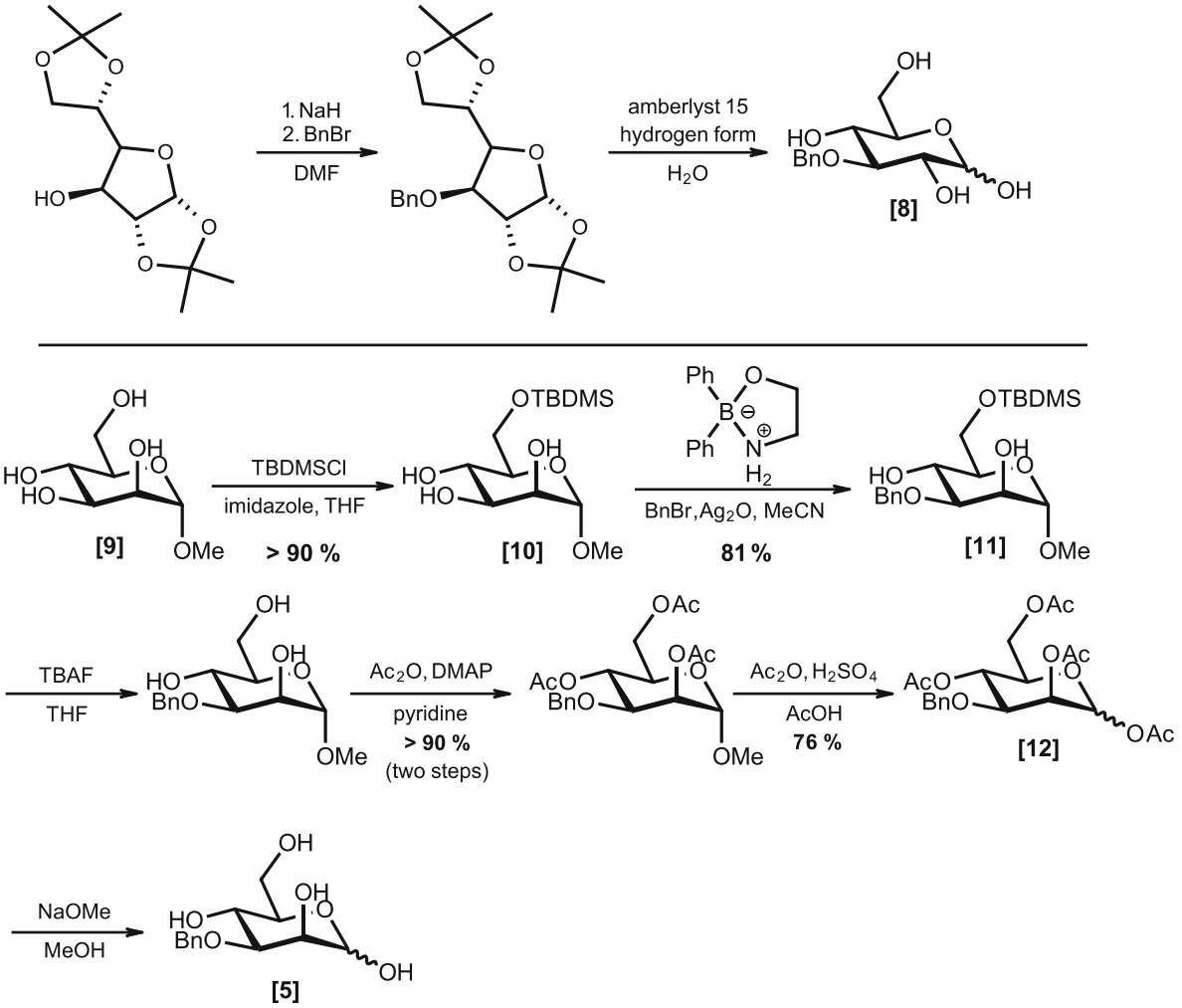


Figure 34. Synthesis of sugar starting materials for the investigation of the NHC Controlled Dehomologation.

diacetonide, followed by acidic removal of the acetonide groups. This route afforded the target material fast and efficient at larger scale (>30 mmol) as an anomeric mixture. (see *Figure 34* top).

The synthesis of 3-*O*Bn-mannose [**5**] was not that straight forward but worked reliably well in its "state of the art"-form, as developed by *H. Kalaus* in his Master thesis[89]

The route started with the commercially available α-methyl mannoside [**9**]**.** The key step is the regioselective alkylation of the 3*O* position based on borinic acid catalysis using 2-aminoethyl diphenylborinate as catalyst and benzyl bromide as the alkylating agent, originated by the *Taylor group*[47] (see *A.3.2.2*). *Taylors* method is selective for the equatorial position of a *cis*-diol.

Within the synthesis, a silyl protection group (TBDMS) was first introduced at the primary position to give [**10**]. Afterwards, alkylation was carried out to give [**11**]**.** The TBDMS group was removed directly after the alkylation *via* standard TBAF cleavage. Acetylation was followed by an acidolysis procedure to convert methyl 3-*O*Bn-mannoside into the tetra-acetylated product [**12**] (see *Figure 34* bottom). The steps starting with the TBAF cleavage until the end of acidolysis were performed without purification. However, one intermediary workup was required after acetylation to remove unwanted TBAF salts. The final deacetylation gives the target compound [**5**] in quantitative yield as an anomeric mixture. It is best practice to store the tetra-acetylated compound [**12**] to increase shelf lifetime and to deprotect immediately prior to utilisation.

A.5.3.2. Analysis of Complex Reaction Mixtures

For the development of catalysts, a fast screening method was required to quickly monitor the

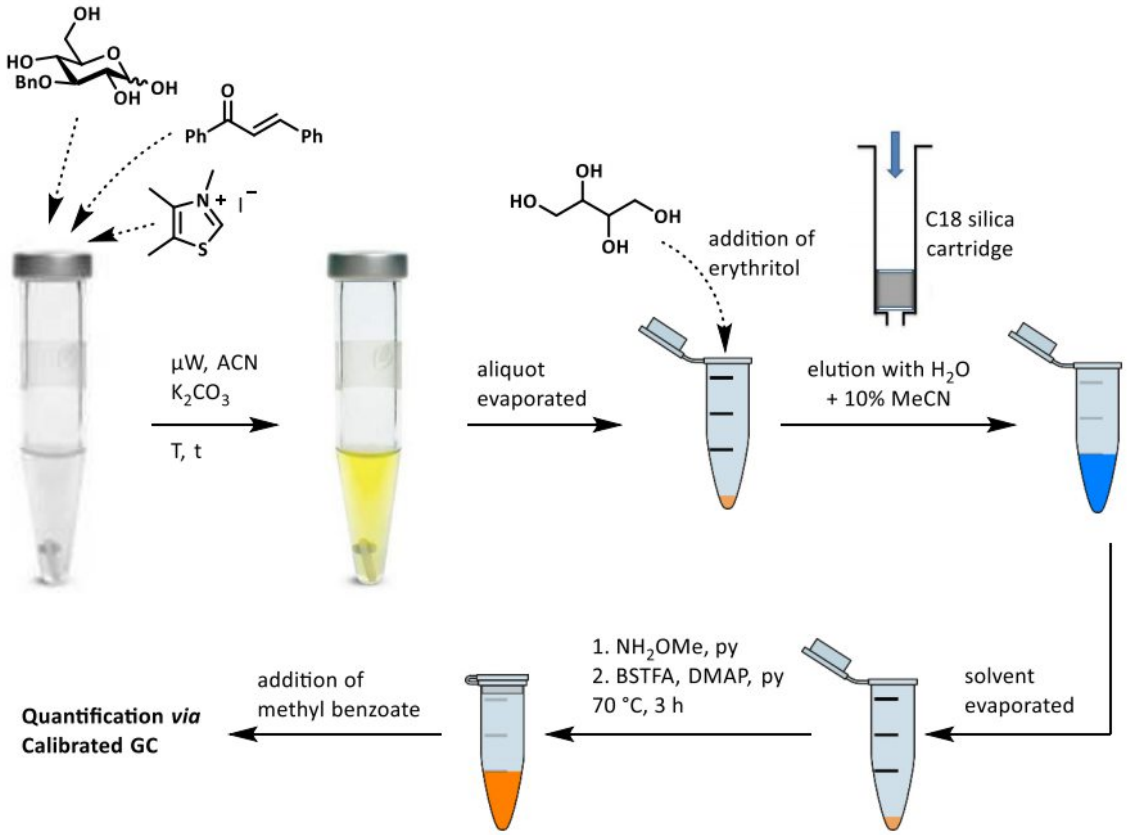


Figure 35. Flow chart for quantifying reducing sugars and sugar-derived compounds from crude reaction mixtures after the NHC-catalysed dehomologation of aldoses[52].

concentration of relevant compounds in the crude reaction mixture. The procedure should allow for easy parallelisation to achieve high throughput. Direct chromatographic analysis is challenging, as the reaction mixture is very complex, containing substances with a wide range of polarity.
A screening procedure based on calibrated GC was developed, which allowed for monitoring the mixture's main sugar-derived compounds. The lipophilic compounds are removed *via* solid-phase-extraction, and the remaining carbohydrate species are then derivatised into TMS-protected oximes. Additionally, a reactive standard (erythritol) accounts for potential incomplete derivatisation[52].
This screening technique allows for time-resolved analysis of up to 12 reaction mixtures with 8 time-points each (total of 96 samples) within 8 working hours.

A.5.3.3. The Standard Conditions for Dehomologation Reactions

The (so far) best practice protocol was developed by several condition optimisation experiments. For the efficient dehomologation of sugars, a catalyst loading of 25 mol%, 20 % K_2CO_3 to liberate the carbene and 2 eq. of chalcone **[3]** at 130 °C gave the best results in DMSO. As reported previously by *Chi,* MeCN was identified as the solvent that achieves the highest yields; however, to achieve temperatures needed for the transformation, microwave heating is required, making time-resolved screening impractical, as no samples can be taken out of the reaction. Using DMSO and conventional heating was a willing trade-off between yields and gathering time-resolved datapoints.

A.5.3.4. Catalyst Derived Divergence on Selected Catalyst/Sugar Pairs

Aiming at optimised catalysts for both reaction outcomes, two NHC scaffolds were thoroughly investigated. Based on the work of *Chi*[86], the thiazolidine was first investigated, and the structure was iteratively changed. An increase of the steric bulk prevented secondary activation, presumably due to steric clash with the intercepting group. In the end, NHC catalyst **[13]** bearing a fused cycloheptane ring and an *N*-2,6-diisopropylphenyl substituent was identified as the best working catalyst. With this catalyst, benzyl mannose **[5]** was dehomologated to benzyl arabinose **[6]** with about 80 % GC yield with only little deoxy lactone **[7]** formation. Interestingly, the selectivity was lost entirely when the starting carbohydrate was changed to benzyl glucose **[8]**. This observation followed the pattern that was already present with the original trimethyl catalyst **[2]** that glucose gave higher conversion to deoxy lactone than mannose although proceeding *via* the same intermediate (see *A.5.2*).
On the other hand, the already observed selectivity for the deoxy lactone shown by glucose as the starting substrate was a good start point for catalyst development towards selective lactone formation. *Wendeborn*[83] had the best results using a triazolium catalyst, while also reporting disadvantages in reactivity for thiazolium scaffolds. Therefore triazolium type catalysts were explored for the task. Among several catalysts screened, a triphenyl triazolium catalyst **[14]** gave the best results towards lactone formation with 70 % GC yield. Using this catalyst with benzyl mannose **[5]** also gave the lactone selectively but with an overall lower conversion (see *Figure 36*).
Overall, two examples of a good match between catalyst and substrate were identified. However, many open questions about the reason for the observed selectivities and different reactivities remained still to be answered. Several of those were addressed within this theses (see A.6).

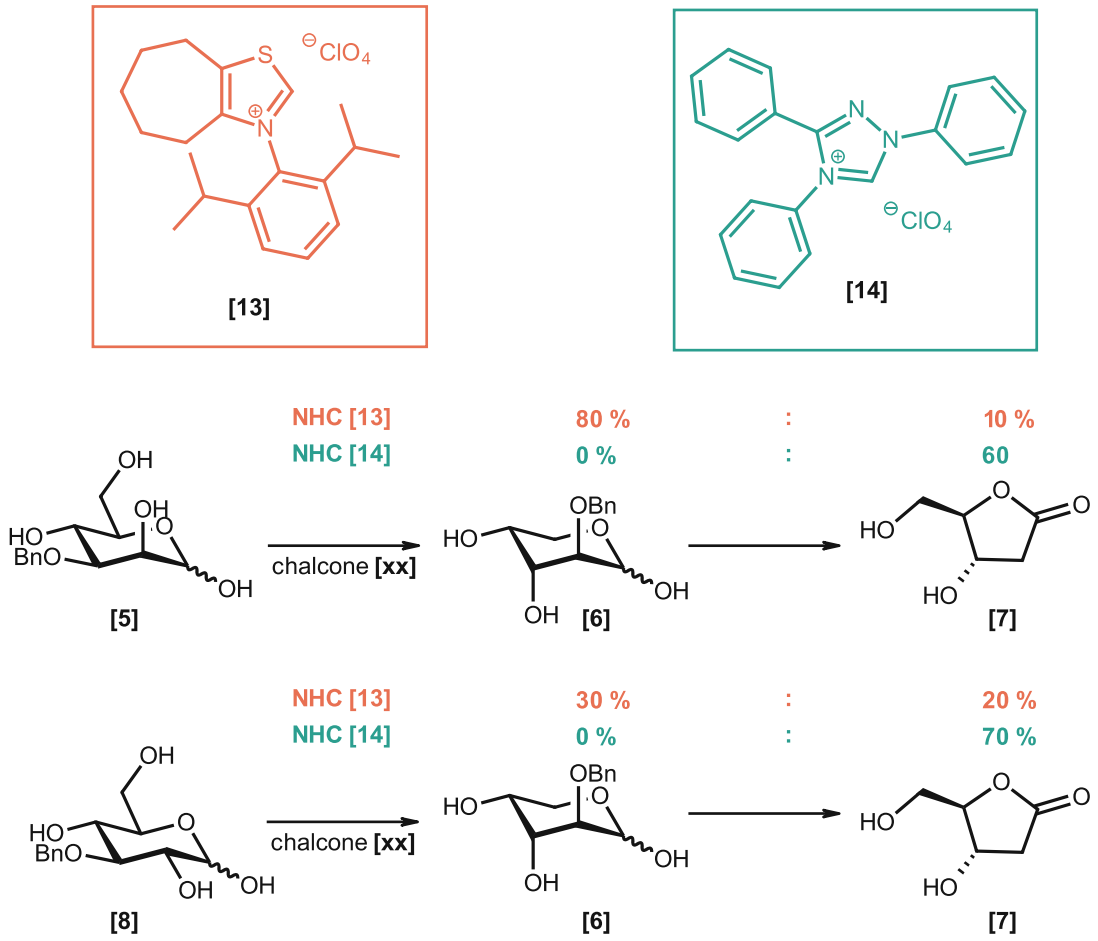


Figure 36. Results of rational catalyst design towards catalyst driven divergence of the two possible reaction products

A.6. Aim of the Thesis – Untangeling Mysteries behind the observed Selectivities

The above-described results (see *A.5 Change of Perspective – The NHC Controlled Dehomologation of Aldoses*) were published in a communication[90] in 2019 and are the starting point of this thesis. The main focus of this previous study was to understand the reasons for the observed selectivities based on the chosen pair of carbohydrate and sugar. The difference in selectivity when using the same catalyst with 3-*O*Bn-glucose **[8]** or -mannose **[5]**, which are 2-epimeres and should proceed *via* the same intermediate, was puzzling and required thorough investigation.

As *Chi* had mostly investigated the reaction from a chalcone perspective and our previous work was heavily focused on the sugar side, we believed that a unified view about the processes in the reaction vessel looking at the two sides of the reaction simultaneously was required to obtain a better understanding of the origin of selectivity.

The following important questions were addressed:

The Influence of the Open Chain Content on the Overall Reaction Rate (see *B.1*)

The investigated dehomologation reactions of benzyl-glucose **[8]** and -mannose **[5]** showed that

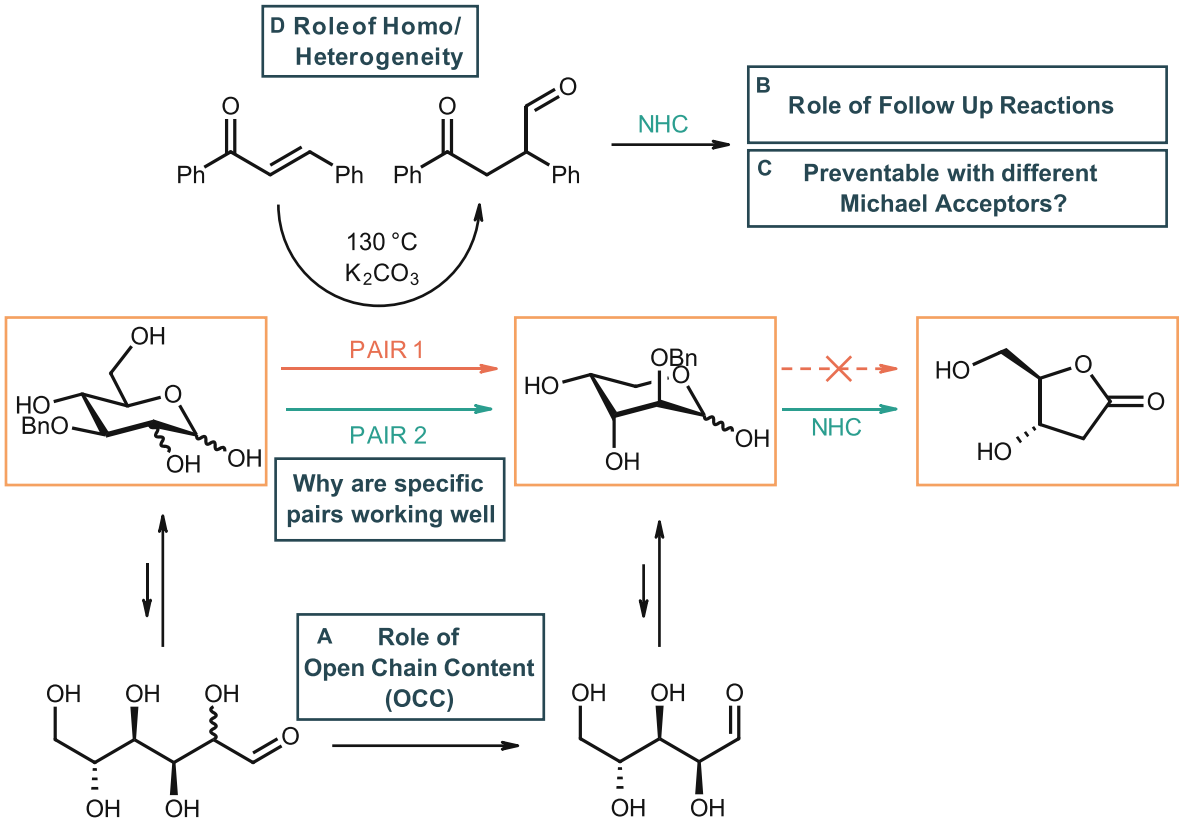


Figure 37. Overview of the reaction and derived influences on the reaction outcome and general factors to investigate.

generally, very forcing conditions (130 °C) were required to achieve the conversion into the desired products. We believed that low open-chain-content (OCC) of the used carbohydrates are the primary reason for this requirement. Those harsh conditions were also reported by *Chi*, who primarily investigated affordable and commonly available carbohydrates, which generally show low OCC values. We, therefore, wanted to test if more uncommon sugars with high OCC numbers increase the reactivity at lower temperatures. (see *Figure 37* **A)**

Identification of side reactions tentatively competing with the targeted reaction paths (see *B.2*)

The overall reaction has the potential for several side-reactions. In the course of the reaction, multiple potential targets for the NHC catalyst are present. For example, formylchalcone [**4**] – the product formed upon catalyst recycling – is an aldehyde. Therefore, formylchalcone is eligible for an NHC attack, leading to a wide array of possible side products. Identification and, ultimately, prevention of generation of such side products is critical for a better understanding of the reaction and an overall cleaner transformation. (see *Figure 37* **B)**

Influence of different Michael Acceptors *(see B.2.3)*

The effect of the Michael acceptors on the reaction outcome was not part of the investigations, so far; however, it might play an essential role, as more efficient catalyst recycling, or recycling products not prone to further reactions, might increase catalyst availability/longlivability. Mostly, Michael acceptors that do not allow further NHC activation were of high interest and should be investigated within this thesis. (see *Figure 37* **C)**

Achieving homogeneous reaction conditions (see *B.3*)

The standard reaction conditions had the drawback of heterogeneity, as insoluble K_2CO_3 was used. Particle size of the solid base affected the reaction outcome substantially, hampering the reproducibility of the method. Therefore, it was a goal to achieve homogeneous conditions by altering the base and thereby allow to investigate the effect of the based on reactivity and selectivity in a more controlled fashion. (see *Figure 37* **D)**

B. Results and Discussion

B.1. Investigating the Influence of the Open Chain Content

The open-chain content (OCC) states the amount of available aldehyde moiety of carbohydrates in equilibrium. As common carbohydrates generally show very small OCC numbers, the mutarotation step is often rate-determining for reactions targeting the aldehyde moiety. We wanted to see if the initial de-cyclisation of the carbohydrate is also rate-determining within our particular transformation. In any other case, we wanted to attempt the identification of any other elementary reaction step that can be pinpointed as the r.d.s.

B.1.1. Experiment Design

We decided that multiple carbohydrates with varying OCC should be tested and evaluated for their reaction speed under standard reaction conditions and temperature (130 °C). Additionally, if the OCC plays a role for the reactivity, temperature screens to potentially lower the temperature were planned, to see if the reaction can also proceed at temperatures below 130 °C. Compared to the original conditions reported by *Chi* (MeCN, microwave), we chose DMSO as the solvent and decided to perform the reaction with conventional heating, as time-resolved screenings can be done more efficiently.

We assumed that the kinetics of the Stetter reaction and the retro-benzoin step are unaffected by the carbohydrate used. Thus, the formation rate of formylchalcone [**4**] is directly proportional to the amount of available aldehyde (OCC). Therefore, an analytical method to analyse the formation of formylchalcone is sufficient to compare different reducing sugars.

The sugars we chose were L-arabinose [**15**] (ca. 0.1 % OCC), D-idose [**16**] (ca. 1 % OCC), D-threose [**17**] (ca. 10 % OCC) and D-erythrose [**18**] (ca. 12 % OCC). The OCC values were measured *via* the ABAO-assay[91] developed within our group by *A. Reichetseders* during his Master thesis[92] for applications in carbohydrate chemistry (see *Figure 38*).

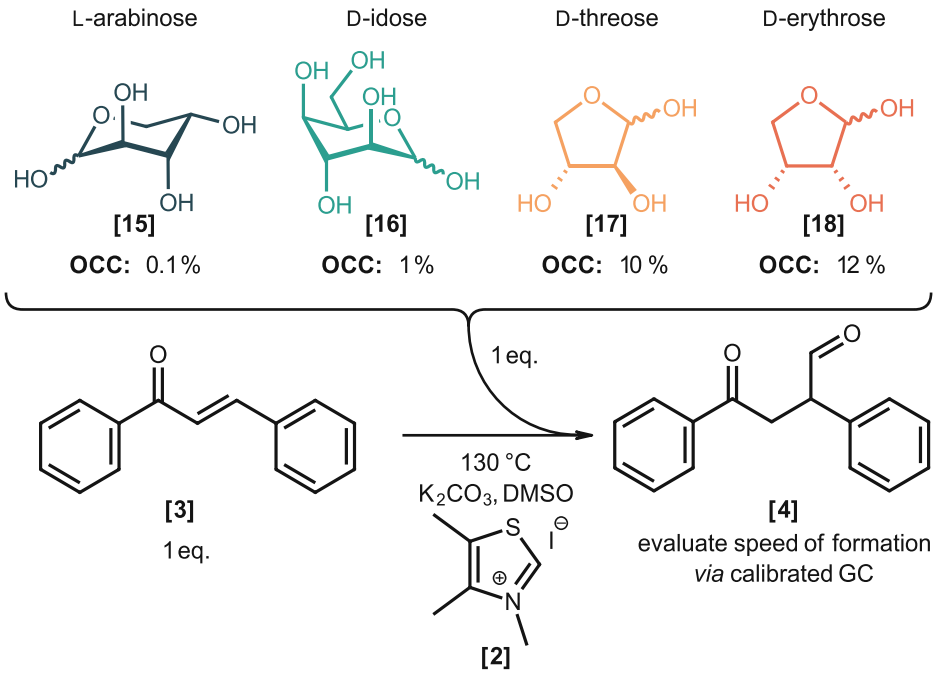


Figure 38. Planned experiment to investigate the influence of the OCC of the sugar starting material used.

B.1.2. GC-Monitoring of Chalcone-Reaction

As the first step, formyl chalcone reference material was synthesised in one synthetic step, using the optimal procedure by *Chi*[86]. Therefore L-arabinose [**15**] was submitted to NHC catalysed dehomologation with the original trimethyl thiazolium catalyst [**2**] and chalcone [**3**] to form formylchalcone in preparative scale. This reaction was performed in DMSO with conventional heating and also in MeCN in the microwave, to have a direct comparison of the two conditions.

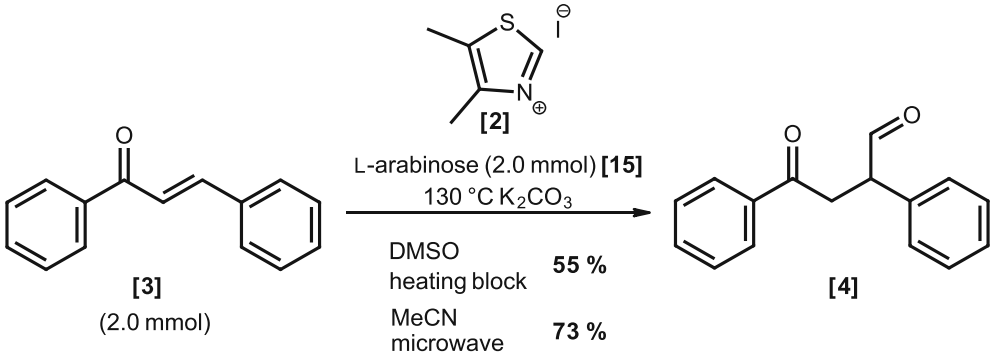


Figure 39. Formation of formylchalcone [**4**] on a preparative scale to obtain it as reference material.

The formylchalcone was obtained in pure form *via* column chromatography. Immediately it became clear, that the reaction in the microwave and MeCN is superior from a yield-perspective.

Both chalcone species were used to calibrate the GC with methyl benzoate as an internal reference. A small sample of the crude material from the reaction in DMSO was used to evaluate the sample preparation for GC analysis.

Small aliquots of the crude mixture were evaporated from DMSO *via* vacuum concentrator and were distributed between water and EtOAc. TLC analysis showed that both chalcone [**3**] and formyl chalcone [**4**] were cleanly and comprehensively extracted from the aqueous solution with two extractions with equal volumes of EtOAc compared to the aqueous layer. Formylchalcone [**4**] can be easily identified, as it gives a bright pink colouration upon staining with anisaldehyde on TLC, while chalcone [**3**] stains with yellow colour.

B.1.3. Time-resolved chalcone formylation utilising sugars with varying OCC

The reactions were performed in closed vials and were probed at different time points. Each sample was evaporated from DMSO and then dissolved in water and extracted twice with EtOAc containing methyl benzoate as GC standard. This extraction with a solution containing the reference standard is critical to obtain reproducible results, as potential pipetting mistakes while performing small-scale extraction can be accounted for.

B.1.3.1. Comparison of Sugars

The performance of different sugars was evaluated by measuring the decrease of chalcone concentration [**3**] and, simultaneously, the increase of formylchalcone concentration [**4**] at multiple timepoints. Considering both aspects, concomitantly is essential, as potential follow-up reactions of the formyl chalcone could lead to misinterpretations of the observed rate of formation.

For both cases, the conversion of chalcone and the formation of formylchalcone, the sugars with high OCC react faster than those with lower OCC (see *Chart 1* and *Chart 2*).

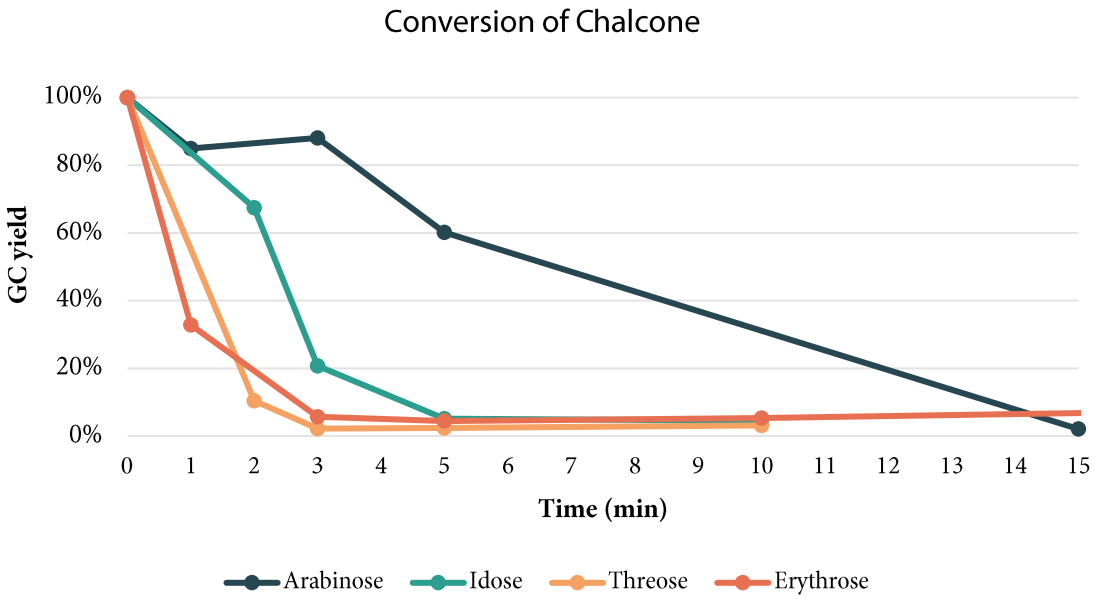


Chart 1. Screening results in the investigation of the OCC's influence for different sugars at 130 °C (Standard reaction conditions. The ratio of carbohydrate to chalcone was 1:1 mol/mol. The loss of chalcone **[3]** over time is drawn

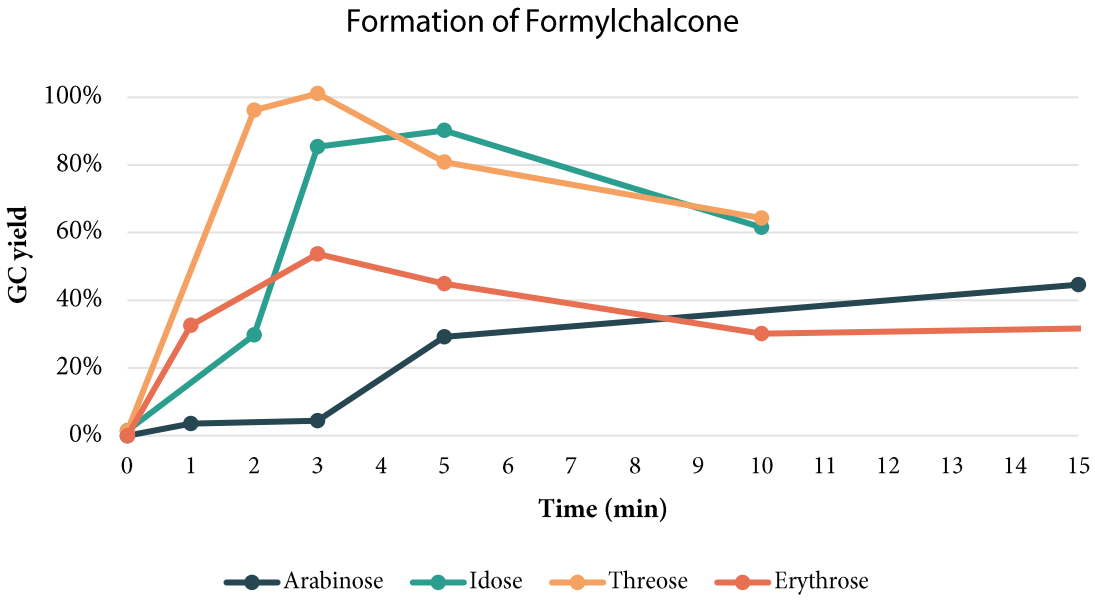


Chart 2. Screening results in investigating the OCC's influence for different sugars at 130 °C (Standard reaction conditions). The ratio of carbohydrate to chalcone was 1:1 mol/mol. The formation of formylchalcone **[4]** over time is drawn.

The slowest conversion is observed with arabinose **[15]**. It nearly took 15 minutes to achieve the full conversion of the starting material. The comparison of formylchalcone **[4]** yields from this experiment to the yields of the preparative experiments (2.00 mmol chalcone) reveals a significant difference, as the screening experiment only gave a 43 % yield after 15 minutes, which might be caused by the small scale (0.08 mmol) as the heterogeneity of K_2CO_3 plays a more significant role.

Idose **[16]** (1% OCC) showed mich higher reactivity, with a maximum yield of formylchalcone of 90 %

after 5 minutes. The two sugars with the highest OCC erythrose [**18**] and threose [**17**], which are 2-epimeres with comparable OCC (~10%), also show a very comparable conversion rate of chalcone, with full consumption after already 3 minutes. However, those sugars differ significantly in the amount of formed formylchalcone. While D-threose gave a quantitative yield of formylchalcone in 3 minutes, erythrose only reached 55 %. While this difference in formylation is not understood at this point, the quantitative yield of formylated product [**4**] in the threose reaction is remarkable and an improvement compared to *Chi*, who had the best results with arabinose (83 % NMR yield).

Overall the results show an evident influence of the open chain-content on the reaction speed. The conversion-speeds directly correlate with the OCC value, while the formation of formylchalcone [**4**] seems to be only one of multiple reaction paths possible. Additionally, the presence of follow-up reactions seems evident, as the concentration of formylchalcone is decreasing over time.

B.1.3.2. Temperature Screening with D-Threose as Formyl Source

Earlier studies with 3-OBn mannose [**5**] and –glucose [**8**] showed a dropoff in yield and conversion of starting material when lowering the temperature even slightly[52,89,90]. The hypothesis for this effect was that the low OCC is the reason for the required 130 °C. Based on D-threose [**17**] showing a quantitative yield of formylchalcone [**4**] within the first 3 minutes of the reaction, this sugar was chosen for a time/temperature screening. The goal was to investigate whether or not lower reaction temperatures are feasible with sugars with high-OCC, probing if the retro-benzoin step is in principle possible at such milder conditions. We planned on performing screening reactions at different internal temperatures (130 °C – 50 °C) while monitoring the formyl-chalcone formation in a time-resolved fashion (as described in *B.1.3.1.*).

Additionally, temperature curves of the reaction mixture were recorded by measuring the internal temperature of a reference vial to correct for the heating process to the set temperature in the reaction vial.

The observed results indicate that a decrease of temperature down to about 90 °C is feasible while a

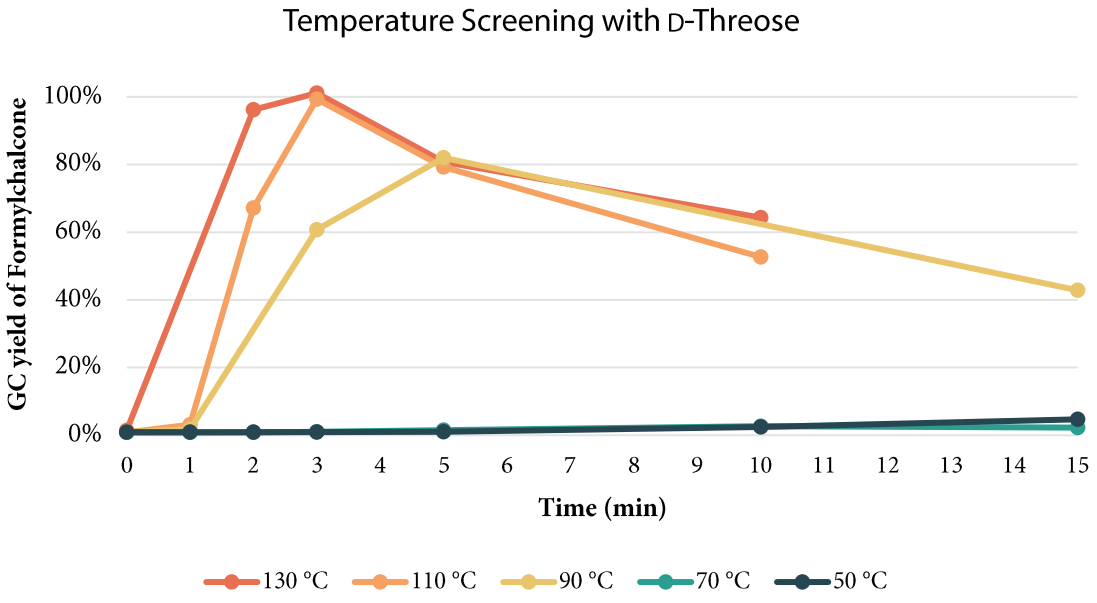


Chart 3. Temperature screening results with D-threose.

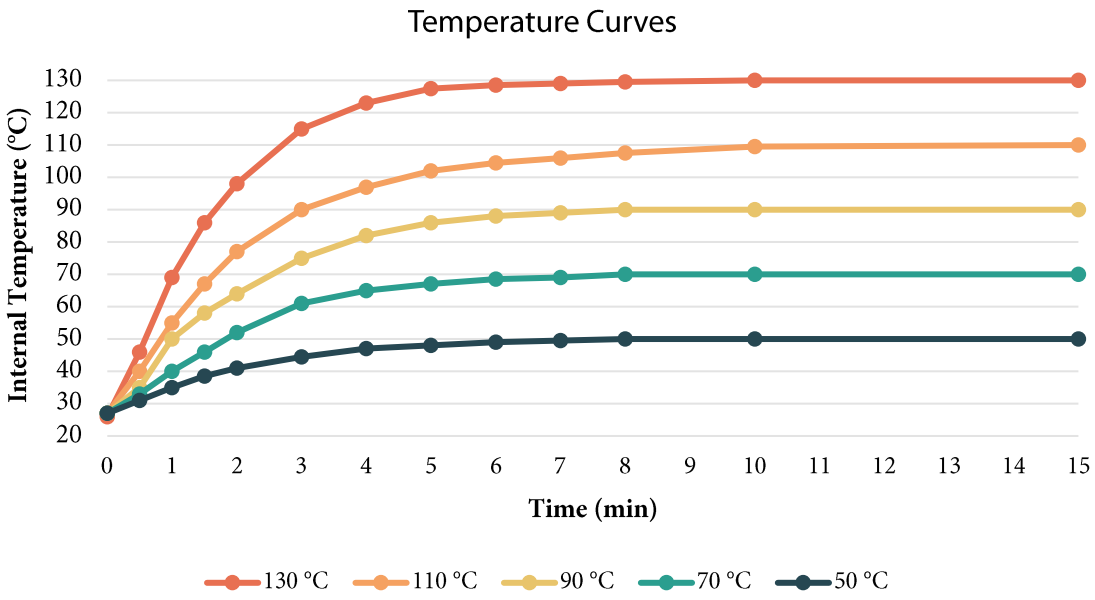


Chart 4. Internal reaction temperature over time, measured *via* reference vials on an analogue thermometer.

drastic dropoff in reactivity below that threshold temperature (see *Chart 3*) was observed. Above the threshold temperature, normal reaction kinetics are observed with a steady increase of formation speed with increased temperature. While the reaction reaches quantitative yield for temperatures at 130 and 110 °C, at 90 °C already only 82 % are achieved. Again all reactions that initially showed product formation also show that the concentration of formylchalcone [**4**] decreases over time, thus indicating that follow-up reactions can occur.

At 70 and 50°C, close to no formylchalcone formation is observed.

When putting the observed GC yields of formylchalcone [**4**] in perspective with the internal reaction temperature measured during the reaction, another interesting effect becomes apparent (see *Chart 4*). The 0 min timepoints were recorded as soon as the vessel was put into the heating block (at room temperature); it takes approximately 5 minutes to reach the target internal temperature. Therefore it is interesting that reactions where formylchalcone was formed, show conversions at timepoints where the internal temperature was lower than the observed threshold temperature. For example, in the screening reaction at 110 °C, the GC yield of formylchalcone [**4**] was already 67 % after 2 minutes. However, at this point, the internal temperature was only at 77 °C. This can most likely be explained by a temperature gradient from the vessel-wall towards the middle of the vial.

B.1.4. Conclusion

Clear evidence for a strong influence of the OCC on the overall reaction rate was found. We have strong indications for the mutarotation step being rate-determining (r.d.s.) by limiting the substrate for the retro-Benzoin reaction, as the formation of formylchalcone generally increased with higher OCC values. Therefore, the Stetter reaction was not the limiting factor. The exact OCC values for which the Stetter reaction remains faster than the retro-benzoin reaction is unclear but for standard carbohydrates a change of the r.d.s. can be excluded, as with erythrose [**18**] and threose [**17**], two of the sugars with highest aldehyde availability were investigated.

The found quantitative GC yield of formylchalcone [**4**] when using threose [**17**] is superior to previous

literature data by *Chi*[86] and shows again that the use of carbohydrates with high OCC is beneficial for the overall reaction outcome.

Additionally, the data supports follow-up reactions of formylchalcone [**4**] to others not yet identified side products, as all observed conversion/time curves showed a clear maximum in GC yield.

B.2. Investigation and Prevention of Potential Sidereactions

As described above, we observed decreasing formylchalcone [**4**] concentrations after initial formation over the timecourse of the Stetter reaction. This observation indicated follow-up reactions, potentially caused by NHC activation. We aimed at first identifying and then preventing those.

B.2.1. Overview of Potential Side Products

Throughout the course of the reaction, multiple different aldehyde moieties exist, that can in principle be activated by an NHC attack. Therefore, the number of potential side reactions leading to yet unidentified side-products is large.

Besides side-reactions derived from the NHC-Umpolung, base catalysed ketose-aldose isomerisation (see *A.3.3*), or unidentified degradation of starting material at the required harsh reaction conditions might be observed. In this investigation, the focus was set at the NHC derived side reactions aiming first to understand and then prevent them.

We envisioned that most side reactions would occur with or directly at the formed formylchalcone [**4**].

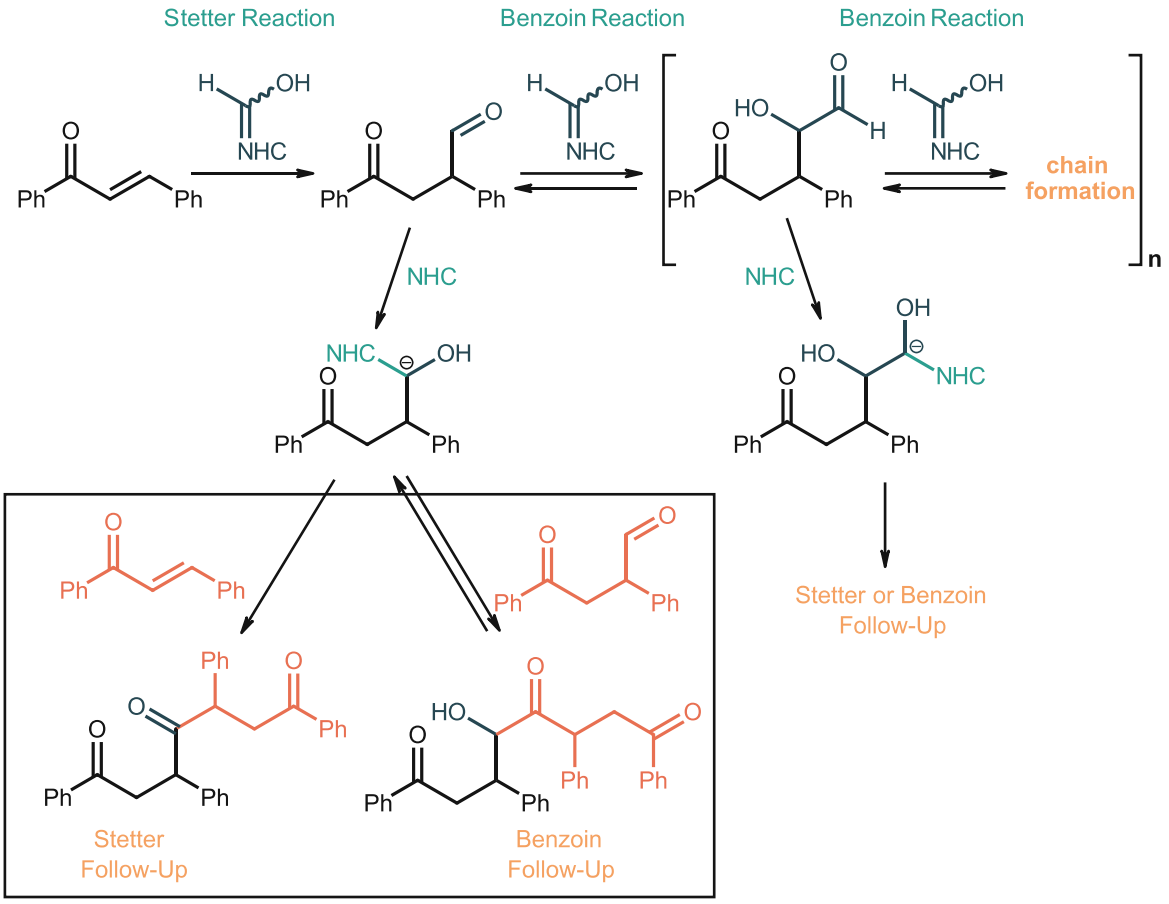


Figure 40. Overview of thinkable side-reaction upon NHC controlled carbohydrate dehomologation.

As this molecule has an aldehyde moiety, an NHC can attack and utilise it as a carbon nucleophile to undergo a Stetter reaction with another chalcone molecule [**3**] or undergo a homo-benzoin formation with another formylchalcone molecule. Further, formylchalcone [**4**] could act as an electrophile for a benzoin condensation with a formaldehyde equivalent generated from the carbohydrate dehomologation. This would allow for repetitive addition of additional formaldehyde equivalents, leading to the formation of polyhydroxy chains – resembling carbohydrates formed by the Formose reaction. Each step would itself be eligible for NHC attack undergoing a Stetter, retro-benzoin or benzoin reaction. (*Figure 40* is an attempt to visualise potential side reactions).
In the timecourse of the reaction, more and more aldehyde containing species get formed, thus giving the catalyst more targets instead of the targeted conversion of the initial carbohydrate species. In this light, it is already an impressive performance of targeted transformation, at least with the best matches between substrate and catalyst. Nonetheless, we believe that the prevention of those side reactions would ultimately lead to cleaner and more complete dehomologation reactions.

B.2.2. Identification of Side-Reactions of the Formylchalcone

Two previous observations in chalcone to formylchalcone reactions indicated the existence of such secondary reactions. First, TLC analysis of dehomologation reactions with triazolium catalyst [**14**], delivering predominantly the deoxy lactone [**7**], never showed the expected concomitant formylchalcone [**4**] formation. A possible interpretation was a follow-up reaction of [**4**] proceeding faster than the original Stetter transformation required for catalyst recycling.
The second observation was already described during our investigation on the influence of the OCC the (see *B.1.3.1* and *B.1.3.2*), we observed the degradation of formylchalcone over time, thus indicating that secondary NHC reactions occur.
We set out to study the interaction of formylchalcone [**4**] with the NHC catalyst. We set up a reaction containing formylchalcone, base and triazolium catalyst [**14**], but no carbohydrate. Therefore, the reaction's overall complexity was decreased to only allow for NHC activation of the formylchalcone and allowing for more straightforward analysis of the reaction mixture in light of not yet identified compounds.
The reaction was carried out like a normal dehomologation reaction and was closely followed *via* TLC. We observed the formation of a new species, less polar than formylchalcone [**4**]. We were able to isolate and identify this compound as 2,4-diphenyl furan [**19**]**,** which accounted for about 10 % (see *Figure 41*).

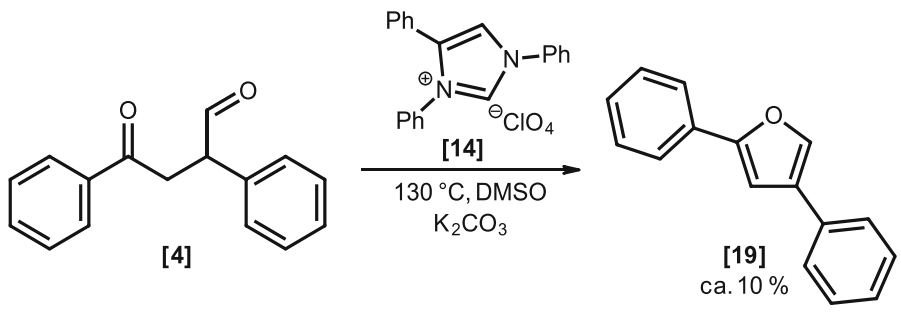


Figure 41. Results of sugar exclusion experiment to identify unwanted side products

However, even after a thorough analysis of the reaction mixture, mostly starting material, but no

additional species, especially no homo-benzoin products, were found.

While not showing any expected side products, the furan species can easily be formed without NHC catalysis as a simple condensation reaction. The group of *Chi* used the formylchalcone [**4**] to synthesize [**19**] upon the addition of acid to the crude reaction mixture in moderate yield (63 %)[86] in an additional step, showing that no NHC species was needed.

Next, we treated a 1:1 mixture of chalcone [**3**] and formylchalcone [**4**] with identical conditions to allow potential Stetter side-reactions to occur. However, also in that experiment, the furan [**19**] was the only observed species. No product derived from NHC catalysed Umpolung was identified.

Conclusions

We were able to identify 10 % formation of furane as a side reaction that is occurring within the time-frame of a standard dehomologation experiment. However, this was not the full picture to explain the lack of formylchalcone in the dehomologation process with triphenyl catalyst [**14**]. We observed over 60 % yield of lactone [**7**] with a loading of 20 mol% of triphenyl triazolium catalyst [**14**] while the formylchalcone [**4**] was not formed. Certain that, other not yet understood reactions must be taking place, we decided that the best way of moving forward in our investigation was to prevent any follow-up NHC-activations by altering the Michael acceptor.

B.2.3. Preventing Side-Reactions of Formylchalcone

We wanted to reduce the formation of follow-up products forming from formylchalcone [**4**], to increase the availability of catalytically active species for the desired dehomologation reaction and maybe get a cleaner or even faster transformation.

B.2.3.1. Mechanistic ideas and design of alternative chalcones

The main idea was to design a Michael acceptor that forms a product of low reactivity or deactivates itself upon the initial formylation reaction. We followed two strategies based on the original chalcone structure.

The first idea was to introduce an additional substituent at the double bond of the chalcone [**3**];

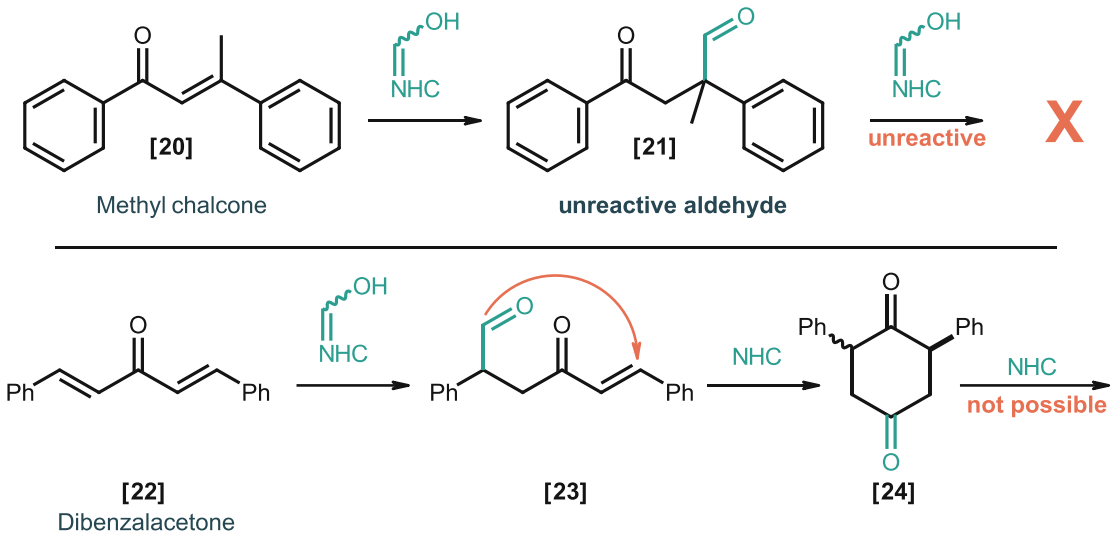


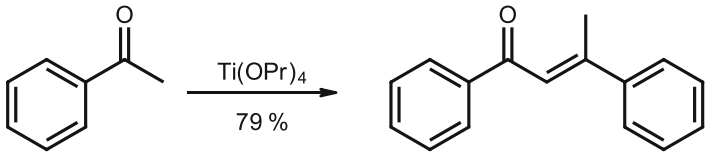
Figure 42. The idea to prevent follow-up NHC activation by creating an unreactive aldehyde upon first Stetter reaction.

therefore, the structure we wanted to investigate was the methyl chalcone **[20]**. Upon the first (wanted) Stetter reaction, the aldehyde **[21]** would form, bearing a quaternary α-carbon atom, with increased steric congestion to at least slow down subsequent NHC activation. (see *Figure 42* top)
The second approach was installing a second Micheal acceptor to direct reactivity upon a secondary NHC activation towards intramolecular Stetter reaction, to form a cyclic diketone. Such a diketone is no longer able to react with any NHC. Alteration of the standard chalcone structure revealed dibenzalacetone (DBA) **[22]** as the ideal substrate for that task. After the first Stetter formylation, DBA would form intermediate **[23]**, which could undergo a secondary Stetter reaction to form the cyclic diketone **[24]**. (see *Figure 42* bottom)
As in this approach, the chalcone removes itself from the array of possible side-reactivities, we called it the "Suicide chalcone".

B.2.3.2. Synthesis of Alternative Michael Acceptors

Synthesis of Methyl Chalcone

For methyl chalcone **[20]** retrosynthetic analysis revealed a simple aldol condensation of acetophenone **[25]**. Interestingly a standard aldol condensation does not work for this specific substrate as low yields (<30 %) were reported previously[93]. Within our group, trimerisation was observed, which is likely the problem[94]. The literature revealed a Lewis-acid mediated milder variant using tetrapropyl orthotitanate, to form methyl chalcone **[20]** selectively[93,95]. During the reaction, propanol forms, which is removed *via* Dean-Stark trap filled with conc. H_2SO_4.

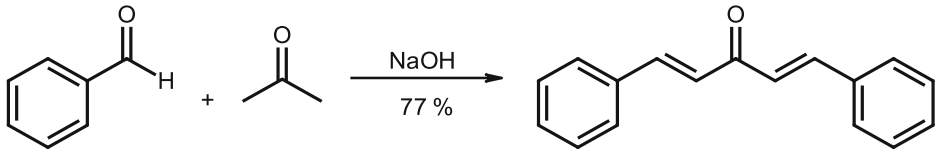


[25] **[20]**

Figure 43. Synthesis of methyl chalcone **[20]** from acetophenone **[25]**

Synthesis of DBA

Dibenzalacetone could be synthesised in one step *via* condensation of acetone with benzaldehyde **[26]** under basic conditions. The product was obtained upon recrystallisation from EtOH/water (4:1) as yellow crystals.



[26] **[22]**

Figure 44. Synthesis of DBA **[22]** from benzaldehyde **[26]** and acetone

B.2.3.3. Investigation on the Formylation of the Alternative Michael Acceptors

A chalcone-screening was set up as previously described (see *B.1.2*), to evaluate whether the alternative Michael acceptors also undergo the formylation reaction.We used erythrose **[18]** as a carbohydrate and

the two NHCs with the highest respective selectivity ([**13**] and [**14**]) as well as the unselective trimethyl thiazolium compound [**2**] as catalysts. Time-resolved screenings (time-points 0, 1, 3, 5, 10, 20 and 30 min) were conducted with all three possible Michael acceptors: methyl chalcone [**20**], DBA [**22**] and standard chalcone [**3**] as a reference experiment.

Screening Results of Methyl Chalcone [20]

Upon time-resolved screening of methyl chalcone [**20**] with three catalysts, GC analysis showed no conversion to the expected product [**21**], as well as nearly full recovery of the starting material (>90%) over multiple timepoints within 30 minutes. Although Stetter transformations on double bonds with similar substitution patterns are reported[96,97], we did not observe conversion as expected in our investigation. In the literature, such transformations require unique catalyst designs and often an intramolecular reaction to run reliably. Therefore we concluded that the approach to prevent side-reactions by forming an unreactive aldehyde is not feasible with our catalysts and conditions, as the additional methyl group at the chalcone double bond prevents already the required initial reaction (see *Table 1*).

Screening Results for DBA [22]

On the contrary, the time-resolved screening with DBA [**22**] and the three catalysts showed conversion to several species upon GC analysis with catalysts [**2**] and [**13**]. The reaction with DBA and triphenyl triazolium catalyst [**14**] showed no conversion and a recovery of DBA of about 60 %.

With trimethyl catalyst [**2**] we observed a fast conversion to the monoformylated but not cyclised intermediate product [**23**] already after 1 min, that got converted into two different species over time. In a follow-up experiment, one of the formed products was isolated and identified as the desired cyclised material [**24**]. The second product was not isolated but tentatively assigned as di-formylated species [**27**] (see *Figure 45*), based on the observed mass spectrum. Based on the GC calibration of the starting material, an estimated 35 % of formylated species were observed.

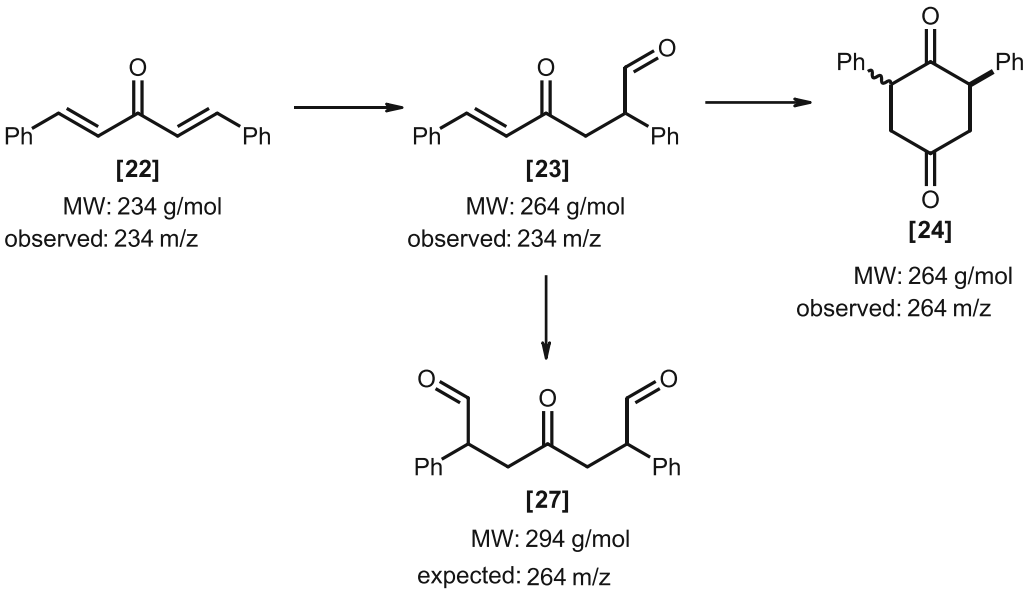
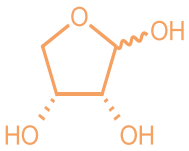
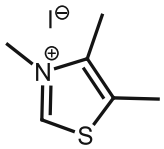
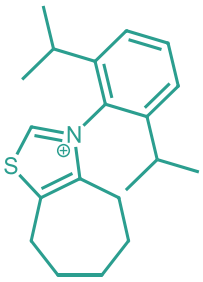
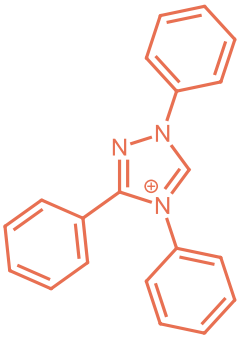
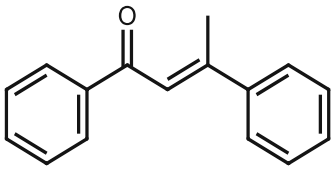
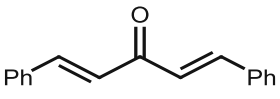
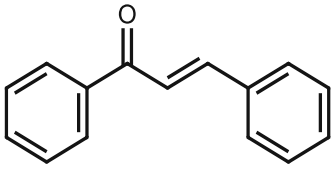


Figure 45. Products of the DBA cyclisation reaction, and the observed masses in the GC-MS spectrum.

Table 1. Summary of the screening with different Michael accepters to potentially prevent side-reactions.

Sugar:  **[18]**	 **[2]**	 **[13]**	 **[14]**
 **[20]**	**No reaction** >90% recovery of s.m.	**No reaction** >90% recovery of s.m.	**No reaction** >90% recovery of s.m.
 **[22]**	**35 % Formylation** **[24]:[27]≈1:1** Full consumption of s.m.	**50% Formylation** **[24]:[27]≈1:2** 20 % recovery of s.m.	**No reaction** 60 % recovery of s.m.
 **[3]**	**50 % Formylation** **[4]**	**20% Formylation** **[4]**	**No reaction** >80% recovery of s.m.

With the thiazolium catalyst **[13]**, overall slower consumption of starting material was observed. Interestingly, no intermediate product **[23]**, but conversion into the presumed di-formylated product **[27]**, and formation to the cyclic DBA **[24]** was seen. Overall we saw about 50 % yield of the formylated products in a ratio of 2:1 for the diformyl-species **[27]**; however, 20 % of starting material were still present after 30 min of reaction time. (see *Table 1*).

It is noteworthy, that the correct assignment of GC peaks is tricky without reference material, as in the GC-MS DBA derviates containing aldehyde groups give only very small intensities for the molecule-peak. Therefore, a di-formylated DBA-species appears to have the mass of the monoformylated **[23]**.

We assumed that the high OCC of erythrose might cause the double-formylation, as a lot of formyl-equivalents get generated in the reaction mixture.

The observed results for the triphenyl-catalyst were puzzling and put the primary explanation for the missing formylchalcone **[4]** upon reaction with the catalyst **[14]** (see *B.2.2*) in doubt. For all chalcones, no formylation but also no consumption of starting material was observed. These results suggested either a different mechanism to form the lactone **[7]** or an alternative catalyst recycling mechanism, not requiring chalcone.

Identification of Reaction Products

We wanted to identify the reaction products. Theoretically, there was a variety of different species that could form during the reaction. After the initial Stetter formylation, the reaction could stop to form the monoformylated but not cyclised material [**23**]. Next to the expected follow-up Stetter reaction, directly forming the cyclised material [**24**], we were also aware of an additional formylation that could occur to form the di-formylated species [**27**] which could then undergo an internal benzoin condensation to form [**28**] (see *Figure 46*).

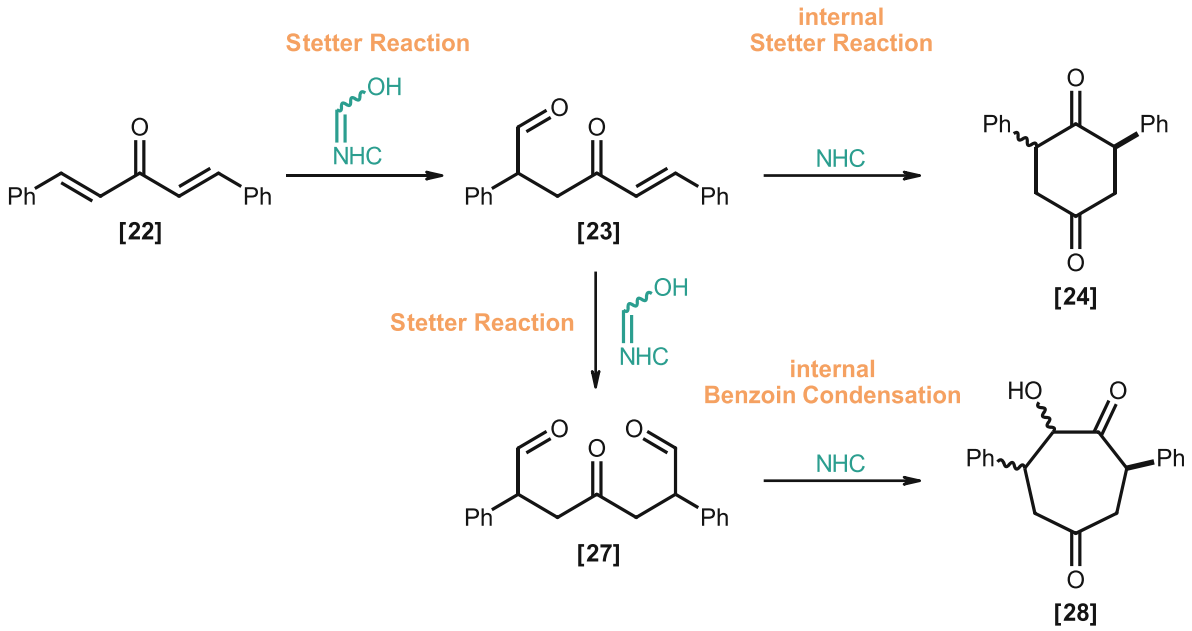


Figure 46. Potential products of the DBA cyclisation reaction

Therefore, we probed the reaction on a preparative scale with carbohydrates with different OCCs to see potential selectivity differences in die reaction outcome. We decided to start the investigation using arabinose acetonide [1], which undergoes exactly one dehomologation step and then forms a very stable lactole as shown in our initial proof of concept study (see *A.5.2*). Additionally, the reaction mixture would be more comfortable to analyse if the carbohydrate-derived products were chemically well defined. We decided on using the trimethyl catalyst [**2**] for this reaction, as the unselective reaction behaviour.

Following the reaction conditions used in that study of *Chi et al.*, we treated the material at 130 °C in the microwave using MeCN as the solvent. Upon GC-MS analysis, after extracting the crude reaction mixture with EtOAc, we observed the clean formation of exactly one chalcone derived product while the starting material was entirely consumed. Upon addition of Et_2O, a powder started crashing out. The material was filtered and recrystallized from EtOAc. Analysis *via* NMR confirmed it to be an isomeric mixture of the expected cyclised material [**24**] (see *Figure 47*).

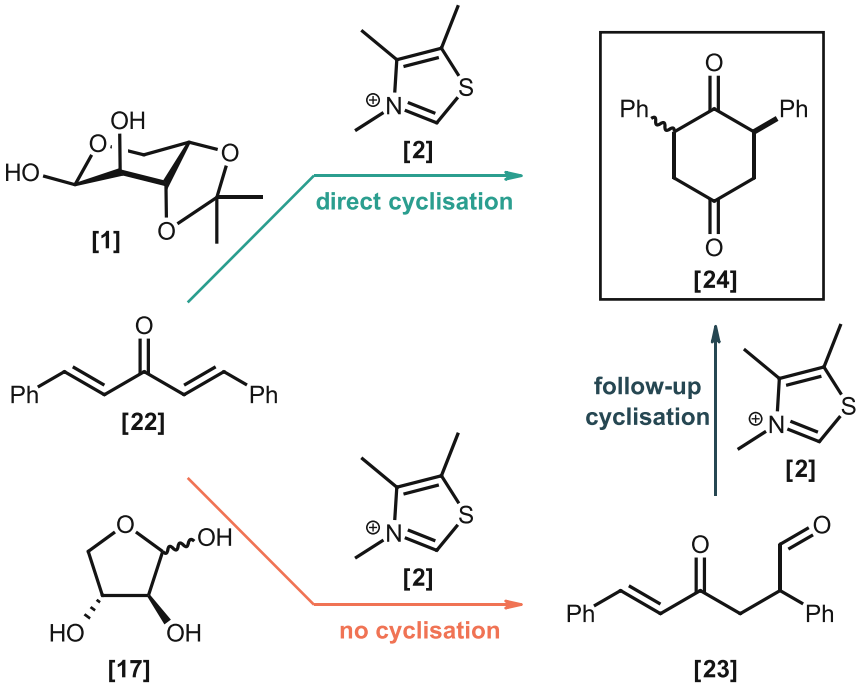
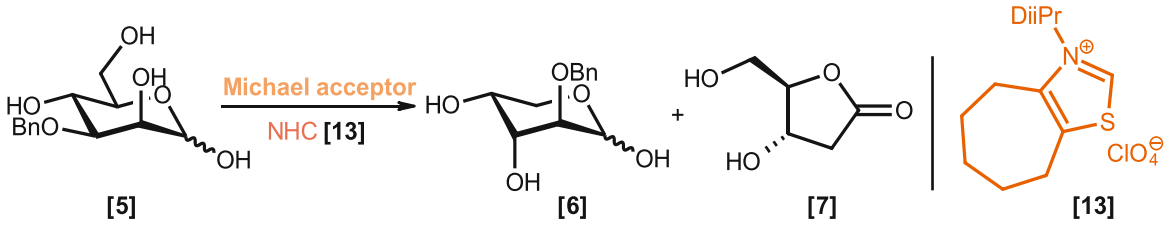


Figure 47. Observed selectivity based on the chosen carbohydrate as formyl source. In the process with D-threose [**17**], the monoformylated material [**23**] could be cyclised in a follow-up reaction.

Upon further analysis of the material, a few interesting observations were made. First, the material is hard to visualize on TLC, anisaldehyde and $KMnO_4$ staining do only lead to very faint spots. Also, the material is surprisingly insoluble in apolar organic solvents like Et_2O, LP and even acetone. When extracting the material, this proves troublesome as a substantial amount is extracted into the aqueous layer. When using arabinose acetonide [**1**] as carbohydrate substrate, the carbohydrate residues are carried over into the organic layer, rendering extractive separation insufficient. We observed a yield of 26 % as a diastereomeric mixture of about 2:1, but we believe that further investigation into the downstream processing would drastically increase the yield, as the GC-MS chromatogram showed no other material formation. The class of compounds arising, is interesting for example, as anti-oxidants.
We then changed the carbohydrate to D-threose [**17**], the fastest and cleanest reacting carbohydrate we used when investigating the formylation reaction of chalcone [**3**]. Interestingly the reaction afforded only monoformylated uncyclized material [**23**] and showed incomplete conversion after 10 minutes under microwave conditions – as confirmed *via* NMR after column chromatography. We believed that the high OCC of D-threose caused masking of the catalyst for the secondary Stetter reaction. In a proof of concept experiment, a small amount of the monoformylated species [**23**] was successfully converted into the desired cyclic di-ketone [**24**] by addition of trimethyl catalyst [**2**] (see *Figure 47*), however also the reverse reaction back to DBA [**22**] was observed. To this point, it remains unclear why the reaction was not reacting to completeness, as we were also able to observe full conversion with other carbohydrates, but the observed reverse reaction might play a role.
Interestingly, the monoformylated material gives no molecule peak on GC-MS. Instead, the exact mass of starting material is observed (234 m/z). For that reason, we figured, that a potential over-formylation into [**27**] would show either the mass of the mono-formylated (264 m/z) product or of the starting material.

B.2.3.4. Application in the Controlled Dehomologation of 3-O-Benzyl mannose with Suicide Chalcone DBA



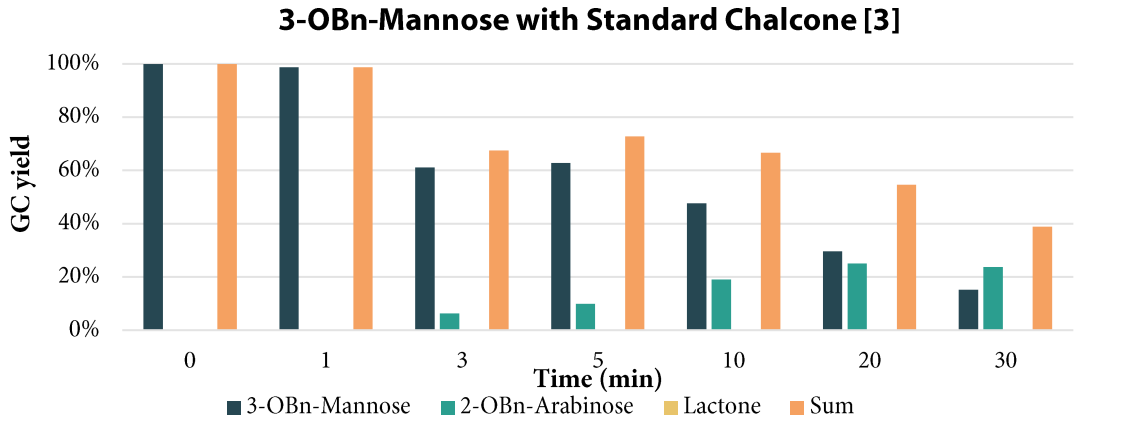


Chart 5. Reference experiment of the catalyst **[13]** (0.25 eq.) with standard chalcone **[3]** (2.00 eq), K_2CO_3 (0.20 eq.) and benzyl mannose **[5]** (1.00 eq).

Based on the successful cyclisation we observed with DBA **[22]** and DiiPr-catalyst **[13]** with erythrose as ready formyl source, we wanted to put the concept to the test in a controlled dehomologation reaction. We chose benzyl mannose **[5]** as the carbohydrate as it already gave the best results with that specific catalyst. The expectation was, that in that setting, using a sugar with lower OCC and an intercepting group, the observed overformylation (see above) would be less of an issue and "neutralization by intramolecular Stetter reaction" might prevent other side reactions. Therefore we set up two time-resolved screening reactions, one with DBA **[22]** as Michael acceptor and one with the standard chalcone **[3]**, as a reference experiment (see *Chart 5* and *Chart 6*).

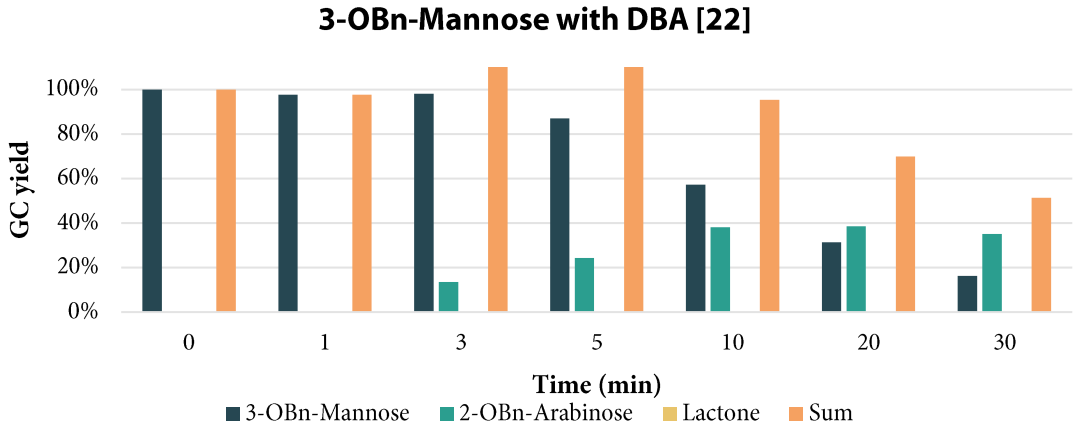


Chart 6. Experiment of the catalyst **[13]** (0.25 eq.) with DBA **[22]** (2.00 eq), K_2CO_3 (0.20 eq.) and benzyl mannose **[5]** (1.00 eq). To investigate a potential benefit in using DBA

Next, we re-visited the phenomenon of the lactone-selective triphenyl catalyst [**14**], without concomitant formylation reactions. To prove the validity of the assumption that either a different reaction pathway towards the lactone or an alternative catalyst recycling mechanism exists, we first needed to confirm, that the lactone gets formed, without simultaneous chalcone formylation. Therefore we set up a screening using DBA and the catalyst [**14**], with a catalyst loading of 20 % (standard conditions) and followed both the sugar and the chalcone side.

We observed 51 % yield of the lactone and simultaneously 74 % of recovered DBA after 30 minutes, while no formylated products were detected *via* GC. The amount of lactone-formation can not be explained without alternative catalyst recycling, further supporting alternative chemistry taking place. The results for this experiment are summarised in *Chart 7*.

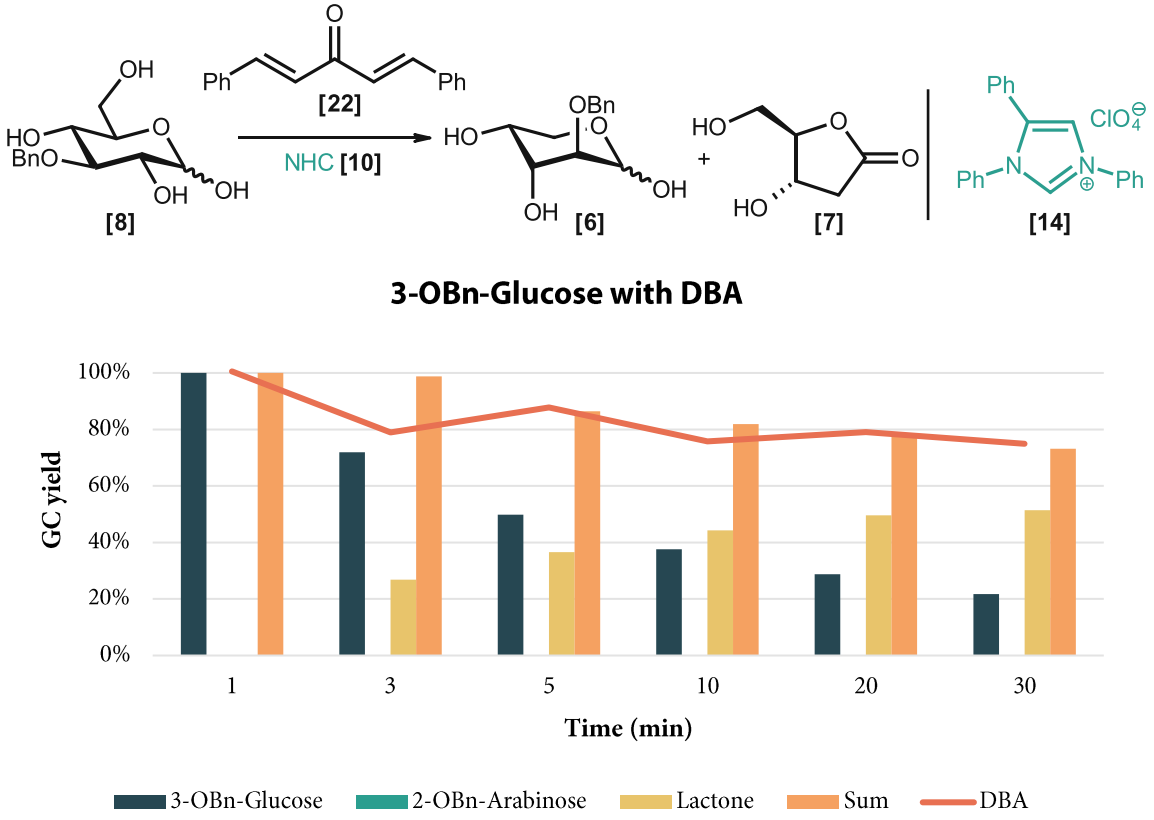


Chart 7. Experiment of the catalyst [**14**] (0.25 eq.) with alternative Michael acceptor DBA [**22**] (1.00 eq), K_2CO_3 (0.20 eq.) and benzyl glucose [**8**] (1.00 eq.). For this experiment also the concentration of DBA was followed *via* GC

B.2.3.5. Conclusion

Upon inspection of the chalcone/formylchalcone interaction with the triphenyl catalyst [**14**], we observed intramolecular condensation of formylchalcone [**4**] to 2,4-diphenyl furan [**19**] in minor amounts. Unfortunately, we could not identify any reaction from the immense pool of potential NHC activated side-reactions.

When trying to prevent uncontrolled secondary NHC activation, we investigated DBA [**22**] as an alternative Michael acceptor for catalyst recycling. The concept was that mono formylated intermediate [**23**] would form a cyclic diketone upon intramolecular Stetter reaction instead of entering a multitude of different possible follow-up reactions. This approach was successful because we observed cyclisation of DBA to form [**24**], which was direct proof that a secondary NHC activation is indeed

possible, but overall the use of DBA did not prove beneficial for the transformation. We observed a substrate mediated selectivity for the cyclised product **[24]** or the monoformylated but uncyclised material **[23]**. Moreover, it was shown that **[23]** can be converted into the target material **[24]**.
Surprisingly, in the experiments, we also observed that the lactone selective triphenyl catalyst **[14]** was not undergoing the reaction mechanism that we envisioned, a behaviour that requires further investigation. Another way of catalyst recycling must exist, or there is a direct reaction path to reach the *ribo*-lactone **[7]** without prior dehomologation.
The literature revealed that the observed cyclisation type is a novel transformation and is therefore of interest for further exploration. While preliminary results indicate that stereocontrol is hard to achieve for this reaction, as constant racemistation seems to occur *via* enolate formation. The oxidation into the corresponding hydroquinone structure, erasing the stereochemistry, would also give access to an interesting class of compounds (e.g. anti-oxidants) on a novel path

B.3. Revisiting Optimal Reaction Conditions

B.3.1. The Problem: Heterogeneity of the Base

Earlier base screenings showed an incompatibility of the dehomologation reaction with organic bases[52,98] and also in the initial report of *Chi*[86] bases like DBU, DIEA and Et_3N were shown to deliver inferior results compared to K_2CO_3, which was found to be the best working example in MeCN and DMSO.
However, K_2CO_3 is an inorganic base insoluble in DMSO. Therefore, we had to deal with the innate issues a heterogeneous reaction brings upon, most significantly we observed an influence of the particle size of K_2CO_3. Using two different qualities of K_2CO_3 with unequal particle size, changed the reaction outcome drastically: With a fine powder, we saw a benefit in the redoxlactonisation process especially for the benzyl-glucose/triazolium pair, while grainier K_2CO_3 was beneficial for the selectivity of

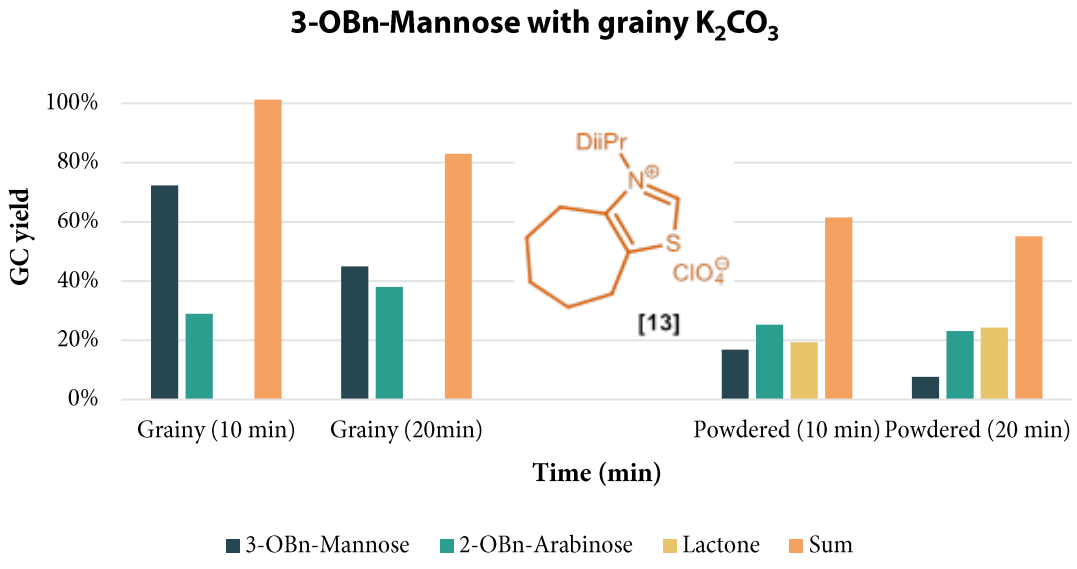


Chart 8. Experiment with catalyst **[13]** (0.25 eq.), standard chalcone **[3]** (2.00 eq.), benzyl mannose **[5]** (1.00 eq.) and grainy K_2CO_3 (0.20eq.)

dehomologation with mannose and DiiPr catalyst. The drastic effect of particle size is visualised on two deterministic timepoints in *Chart 8*.

We believed that the relative surface area difference would result in different amounts of the dissolved base during the reaction, causing the reaction-outcome to change. We circumvented the problem of particle size by strictly using the same batch of K_2CO_3 (*Alfa Aesar*, product number A16625) for the screening reactions. However, this dependency on dissolved base became even more problematic, as the needed amount of base on an analytical scale was less than 5 mg and reliant and reproducible weighing was experimentally tricky to guarantee.

Therefore, we wanted to investigate different inorganic bases, with higher solubility in DMSO to achieve homogeneous reaction conditions.

B.3.2. Base Screening of Inorganic Carbonate Bases – Towards homogeneous Reaction Conditions

Literature research showed that alkali metals' carbonate salts become more soluble in organic solvents like DMF or DMSO with increasing atom number[99,100]. Therefore, of the commercially available alkali carbonates, Li_2CO_3 shows the lowest solubility, while Cs_2CO_3 and Rb_2CO_3 are relatively well soluble in DMSO. As earlier reports of *Chi*[86] already suggested that inorganic carbonates are generally well-performing bases in this transformation, we set out to investigate if homogeneous conditions can be achieved and how this effects reaction outcomes compared to the standard conditions using K_2CO_3.

We particularly were interested to see if lactone formation was promoted by higher base loadings – a fact that was of high interest as we started speculating over a competing additional alternative mechanism to form lactone [**7**]. On the other hand, we wanted to know if homogeneous conditions were achievable using Cs_2CO_3 and if the yield was comparable to the standard conditions using K_2CO_3.

First, we set up time-resolved screening reactions using four different inorganic carbonate bases: Li_2CO_3, K_2CO_3, Rb_2CO_3 and Cs_2CO_3 for the lactone selective reaction couple of benzyl glucose [**8**] with triazolium catalyst [**14**] as well as for the pentose selective pair benzyl mannose [**5**] with DiiPr-catalyst [**13**]. Equal molar amounts of each base were used throughout the screening.

Base-Screening with 3-*O*Bn-mannose *[5]* and DiiPr thiazolium catalyst [13]

The time-resolved screening reactions of 3-OBn mannose [**5**] with the equal amounts (0.2 eq.) of four inorganic bases, showed that for the least soluble base – Li_2CO_3 – perfect selectivity for the dehomologated arabinose [**6**] was achieved, with a GC yield of 41 %. Overall the reaction showed very good mass-recovery (92 %) as also more than 50 % of starting material were recovered. The reaction with the standard K_2CO_3 gave the highest yield of dehomologation product after 20 minutes (46 %), but also a slight drop in selectivity, as 10 % of lactone was observed. The examples with even better solubility, Rb_2CO_3 and Cs_2CO_3, both show a complete loss of selectivity towards the dehomologation product, as equal amounts of lactone get formed. However, combined yields for lactone and arabinose are within the same range as the other bases (see *Chart 9*). Noteworthy, Cs_2CO_3 lead to a completely homogeneous reaction mixture at 130 °C.

These results show that increasing amounts of dissolved base promote the lactone formation. Additionally, an increase of available base is also causing lower mass-recovery, presumably caused by

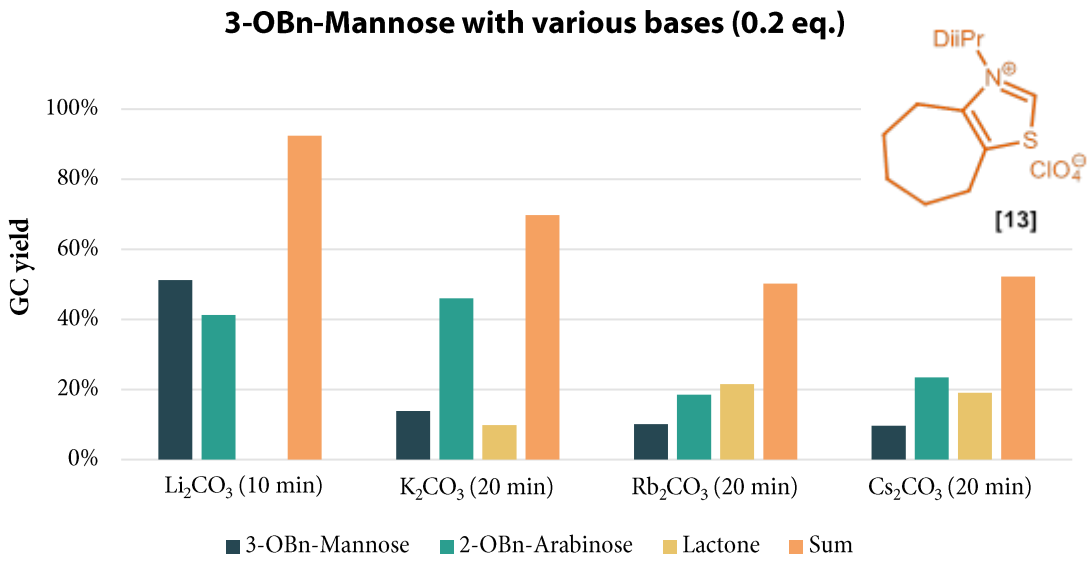


Chart 9. Base screening of benzyl mannose **[5]** (1.00 eq.) and the catalyst **[13]** (0.25 eq.) using 0.2 eq. of all bases and chalcone **[3]**. The time-point with the best-combined yield of lactone **[7]** and benzyl arabinose **[6]** is shown. The full time-resolved analysis can be found in the experimental section C.6.3.1).

the degradation of the starting material.

Base screening with 3-OBn Glucose [8] **and Triphenyl triazolium catalyst (Lactone pair)**

The time-resolved screenings of benzyl glucose **[8]** with the lactone selective triphenyl catalyst **[14]** showed that with the least soluble Li_2CO_3 only little conversion towards lactone or dehomologation product after 30 minutes was observed, while the highest combined yield was observed after 20 minutes (28 %). Additionally, full mass recovery was detected *via* GC. (see *Chart 10*)

The more soluble K_2CO_3 achieved the known high conversion towards lactone, and the highest combined yield of 2-*O*Bn-arabinose and lactone after 30 minutes (70 %). The amount of formed arabinose **[6]** was equal to the reaction using Li_2CO_3. The two examples with the highest base-solubility in DMSO (Rb_2CO_3 and Cs_2CO_3) showed very comparable results, as only lactone was observed in the timecourse of the reactions with a similar yield of around 50 %. For both bases, the starting material was consumed after 20 minutes; therefore, both reached their maximum lactone-yield at that time-point.

The results again suggest an increased lactone formation with higher concentrations of the dissolved base, and also a faster degrading of starting material was observed with more available base. Those results are in accordance with the trends that we had observed in the screening with the other pair, catalyst **[13]** and benzyl mannose **[5]**.

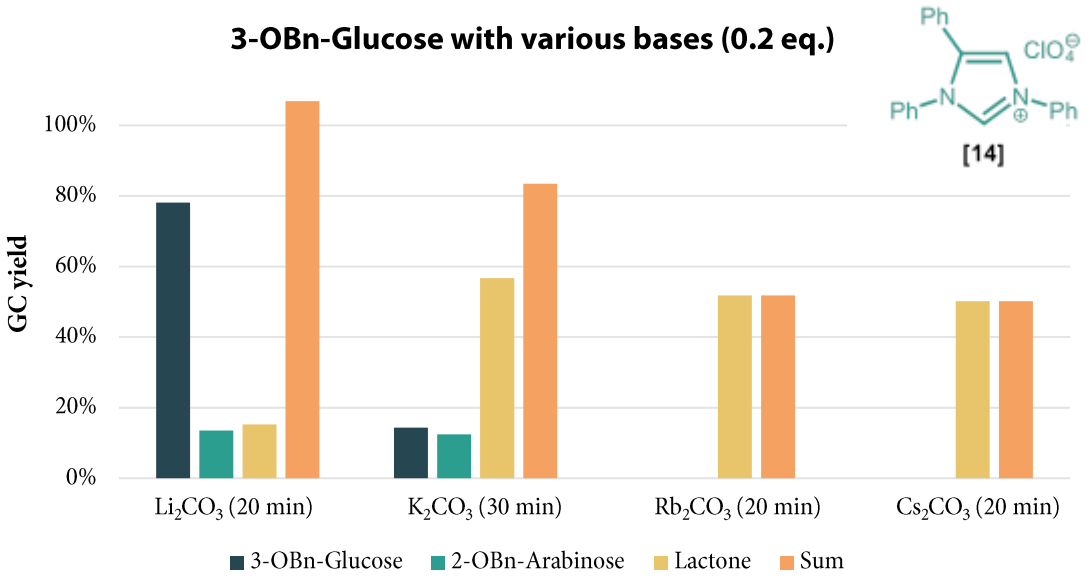


Chart 10. Base screening of benzyl glucose **[8]** and the catalyst **[14]** using 0.2 eq. of all bases and chalcone **[3]**. The time-point with the best-combined yield of lactone **[7]** and benzyl arabinose **[6]** is shown. The full time-resolved analysis can be found in the experimental section C.6.3.1).

B.3.3. Selectivity Derived from Base Concentration

In the investigation where we used different inorganic carbonate bases, we achieved homogeneous reaction conditions with Cs_2CO_3 but observed a drop-off of selectivity for 3-*O*Bn-mannose and a general increase of lactone formation. Based on those observations, we wanted to investigate the influence of different Cs_2CO_3 concentration on the reaction. We believed that lower concentrations of Cs_2CO_3 could restore the selectivity of the dehomologation, but also the effects of even higher base concentrations were interesting.

Therefore we set up time-resolved screenings with five different base concentrations (no base, 0.05 eq., 0.1 eq., 0.2 eq. and 0.3 eq.) for benzyl glucose **[8]** and benzyl mannose **[5]**.

Varying Cs_2CO_3 amount with of 3-*O*Bn-Mannose and DiiPrCatalyst

The time-resolved screening reaction with 3-*O*Bn-mannose as starting material was again analysed *via* GC. In the screening-reaction using no base at all, we observed the formation of 10 % 2Bn-arabinose **[6]** after 20 min while showing nearly complete mass-recovery. The formation of dehomologation product without base is surprising; however, can most likely be explained by auto-deprotonation of precatalyst salt at 130 °C.

The reaction using 0.05 eq. of Cs_2CO_3 already showed relevant amounts of dehomologation product (35 %), but overall slow and incomplete conversion, as 37 % of starting material was still left after

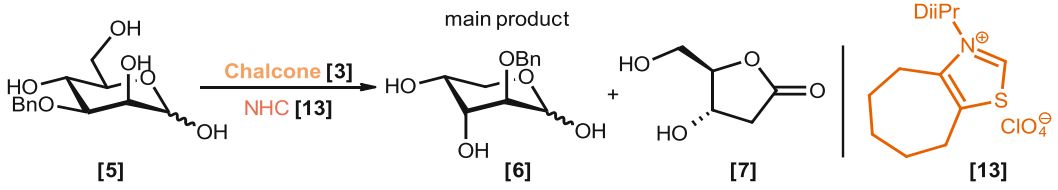


Figure 48. The reaction of 3-OBn-mannose **[5]** and the catalyst **[13]** with selectivity for the dehomologation product

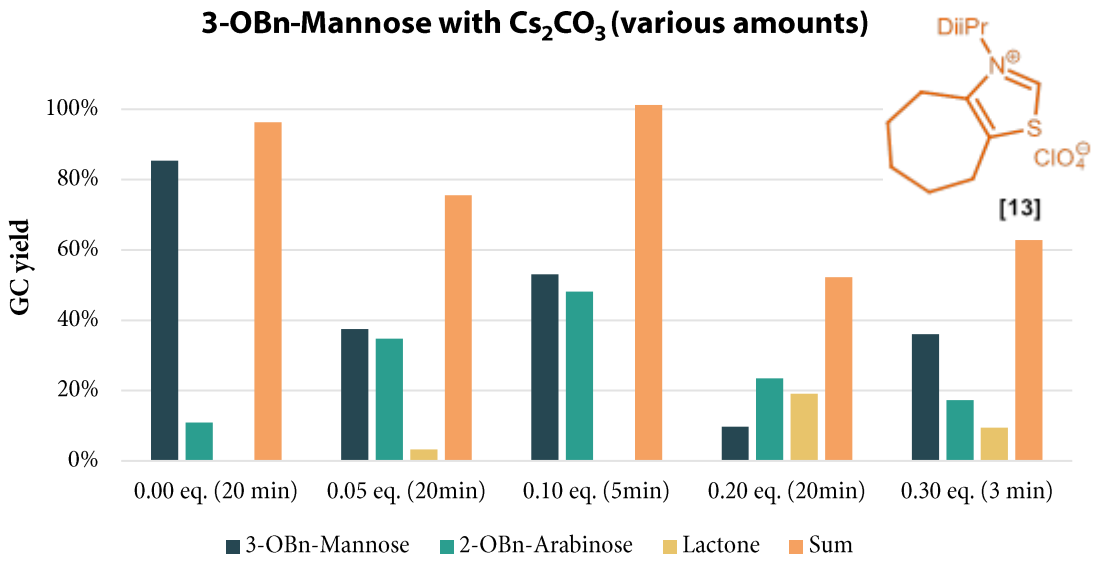


Chart 11. Screening of benzyl mannose **[5]** (1.00 eq.), catalyst **[13]** (0.25 eq.) and chalcone **[3]** using various amounts of Cs_2CO_3 as the base. The time-point with the best-combined yield of 2-*O*Bn-arabinose **[6]** lactone **[7]** is shown for each base-concentration. The full time-resolved analysis can be found in the experimental section (see C.6.3.2)

20 minutes.

Interestingly, the conversion-speed can be drastically increased by using 0.10 eq. of Cs_2CO_3, showing the best yield of 2-*O*Bn-arabinose already after 5 minutes (48 %), with complete selectivity towards the dehomologation product and no detectable lactone **[7]**. Noteworthy at the point where the highest yield of arabinose is observed, also full mass-recovery was achieved, with the remainder being unreacted starting material. The reactions with more added base (0.20 eq. and 0.30 eq.) again showed the drop-off in selectivity and degradation of starting material, already observed previously (see above), especially in the reaction using 0.30 eq. of Cs_2CO_3 the degradation became noticeable, as already after 3 minutes only 60 % of mass-recovery was detected based of GC analysis. The over-equivalent addition of base (0.30 eq) compared to pre-catalyst salt (0.25 eq.) very likely causes this extreme tendency towards degradation. (see *Chart 11*) and is in line with earlier base-catalyst-amount screening with standard catalyst and K_2CO_3.

Overall we observed a sweet spot for yield and selectivity when using 0.10 eq. of Cs_2CO_3, giving comparable results to the "standard conditions" but additionally benefit from achieving homogeneous reactions and a very clean conversion. Also, an overall increase in conversion rate can be deducted from an increase of base concentration caused by the innate increase of liberated catalyst concentration. This could be a key finding in the development of a generally applicable method.

Results of 3-*O*Bn-Glucose

The time-resolved screenings with alternating concentrations of Cs_2CO_3 for the lactone selective reaction-pair with benzyl glucose **[8]** and triazolium catalyst **[14]** were performed with the standard screening protocol. The reaction without base showed only small loss of starting material (ca. 10 %) but no conversion into identifiable products after 30 min of reaction time.

However, the addition of minimal amounts of Cs_2CO_3 (0.05 eq.), showed significant amounts of lactone formation, with relatively clean but incomplete conversion (40 % s.m. left). Increasing the base loading further, improved the GC yield of lactone even more, as 60 % were achieved with 0.10 eq. of Cs_2CO_3,

after 20 minutes. This base-concentration marks the highpoint in yield and cleanness. Further increase of base loading led to faster conversion, but a steady drop-off in lactone-yield and mass-recovery was observed. In the extreme case, using more base than catalyst **[14]**, the maximum yield of lactone of 39 % was observed after 3 minutes, at a time, where 95 % of starting material were already converted (see *Chart 12*).

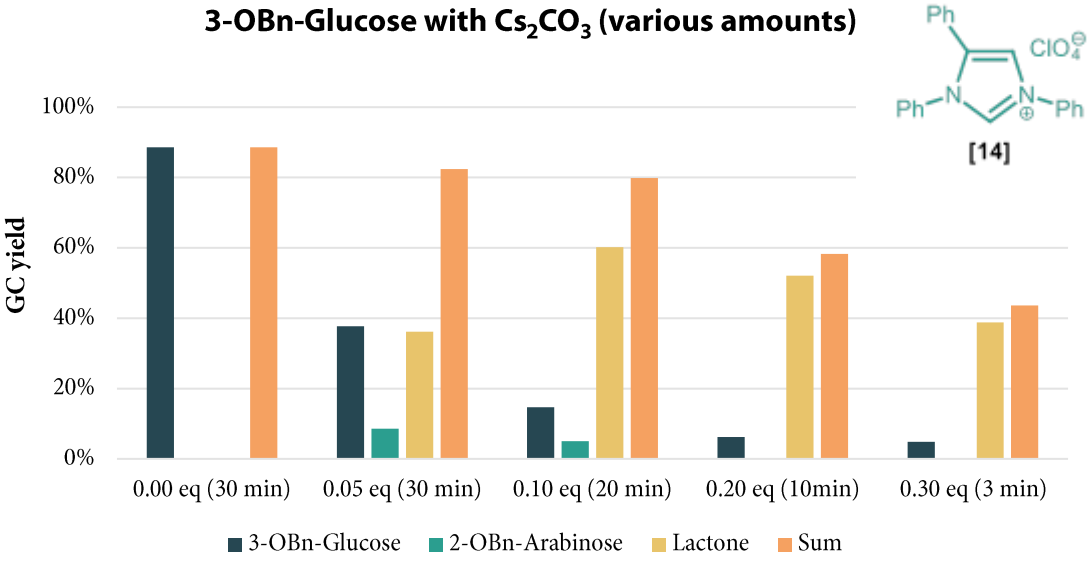


Chart 12. Screening of benzyl glucose **[8]** and the catalyst **[14]** (0.25 eq.) and chalcone **[3]** using various amounts of Cs_2CO_3 as the base. The time-point with the best-combined yield of 2-OBn-arabinose **[6]** lactone **[7]** is shown for each base-concentration. The full time-resolved analysis can be found in the experimental section (see C.6.3.2)

B.3.4. Conclusion

Based on the conducted experiments, we were able to find for the first time in the overall study reaction conditions in a fully homogenous regime by using the soluble base – Cs_2CO_3. Investigations to follow after this thesis can utilize these homogeneous reaction conditions to achieve more reproducible and overall better and cleaner results. Further, the use of stock solutions further facilitates rapid screening of conditions.

We observed that lactone formation is directly dependent on the amount of base dissolved in the reaction mixture. Further, the initially assumed reaction mechanism of the reaction of 2-OBn-arabinose to lactone is partly in doubt, with this base dependency as a critical feature that a potential new additional mechanism also needs to be able to explain.

B.4. Pinning Down an Alternative Mechanism from 3-OBn-Hexoses Directly to the Lactone

B.4.1. Indications for a Different Mechanism

We started to doubt that our initially proposed reaction pathway to form 2-deoxy lactones is the full picture (see *Figure 49* top). First of all, we noticed that we were unable to detect formylchalcone **[4]** when the lactone selective triphenyl triazolium catalyst was used. At first, we believed that a fast follow up reaction could disguise the formation of formylchalcone. Herein, we could show that the chalcone

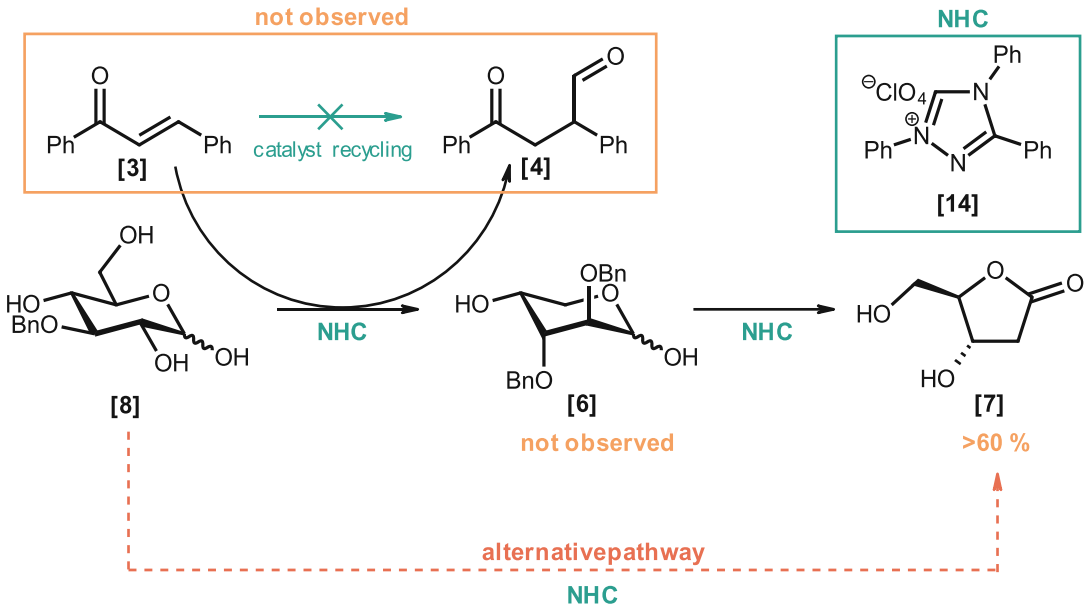


Figure 49. Reasons indicating a direct pathway from hexose [**8**] towards lactone [7]

starting material is not consumed during the reaction, while simultaneously the carbohydrate [**8**] gets converted into lactone [**7**] with about 60 % yield (see chapter *B.2.2*).

Therefore, we concluded that either an alternative catalyst recycling occurs without the participation of chalcone or a direct mechanism from the starting material towards the lactone exists. The first case seemed very unlikely as we could not observe any additional reaction products while investigating potential side-reactions. Therefore, our focus was on unambiguously proofing such an alternative pathway and deducting a working hypothesis how such a reaction can occur mechanistically.

B.4.2. Proving the Existence of an Alternative Mechanism

Two different experiments were designed to investigate our assumption, directly proceeding to the lactone stage without Stetter reaction to recycle the catalyst.

First, we wanted to see if the lactone formation is possible without any Michael acceptor in the reaction mixture. Then we wanted to see if the triphenyl catalyst [**14**] can convert the dehomologation intermediate (2-*O*Bn-arabinose [**6**]) into the lactone [**7**].

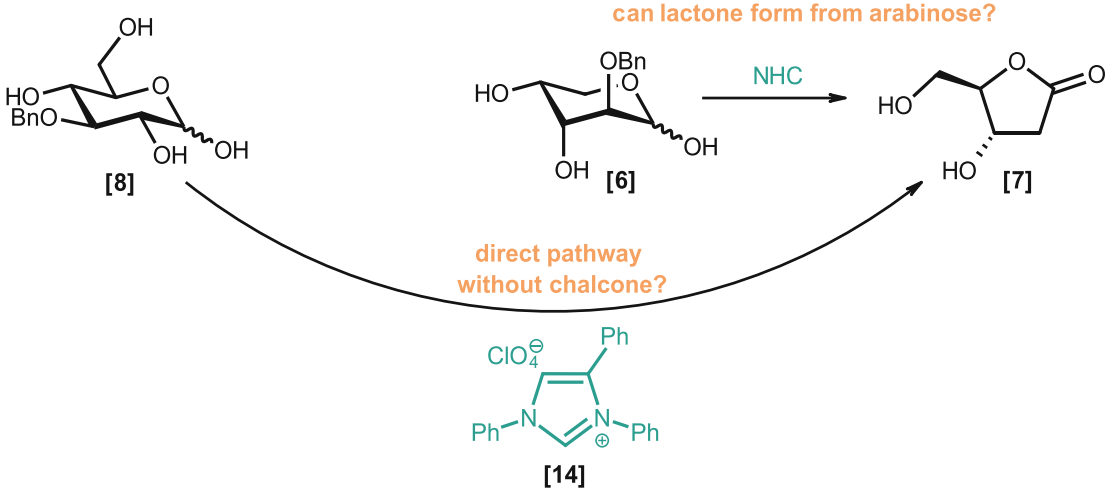


Figure 50. Planned experiments to test the hypothesis of a direct reaction pathway, to form lactone from 3-*O*Bn-glucose [**8**]

Additionally, we wanted to know if the old mechanism is also feasible with the original trimethyl catalyst [**2**] by *Chi.* Therefore we included catalyst [**2**] into the experiment with 2-*O*Bn-arabinose.

B.4.2.1. Lactone Formation without Catalyst Recycling

A time-resolved screening was set up, without the catalyst recycling chalcone [**3**]. In this reaction, triphenyl-triazolium salt [**14**] was used together with 3-*O*Bn-glucose [**8**]. GC analysis showed that 60 % yield of lactone was formed with a clean overall reaction profile after 10 minutes (> 80 % recovery). This was only explainable with a reaction that does not depend on a catalyst recycling system based on the Stetter reaction. Interestingly, small amounts of dehomologation product [**6**] were formed, which are explainable even without catalyst recycling, as the found 8 % are less than the catalyst loading of 0.25 eq. (see *Chart 13.*)

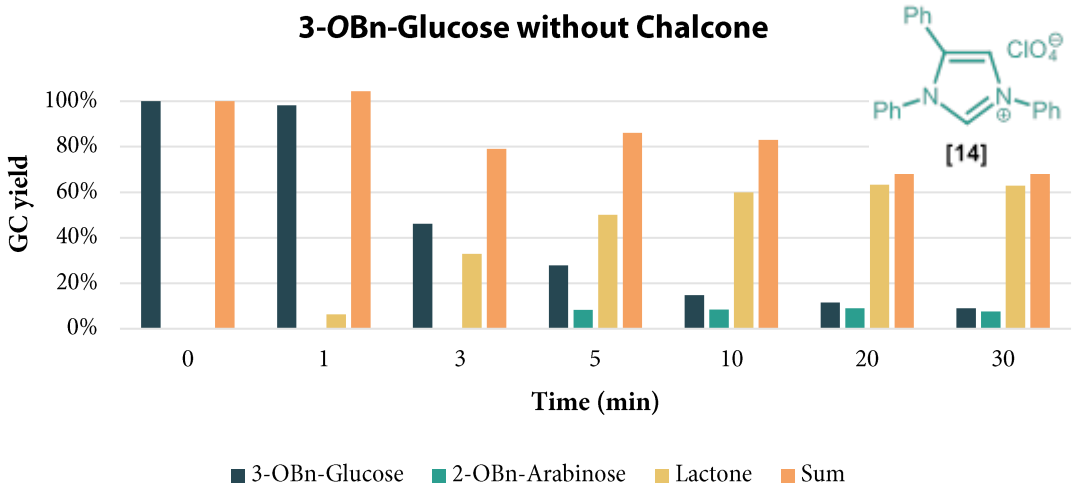


Chart 13. Experiment without the chalcone recycling system of the catalyst [**14**] (0.25 eq) with benzyl glucose [**8**] (1.00 eq.) and using K_2CO_3 (0.20 eq.)

In addition to this experiment, we also conducted a study without catalyst [**14**], to see if lactone formation depends on the presence of NHC. This experiment caused the complete degradation of starting material within 5 minutes, without any lactone formation (see *Chart 14*).

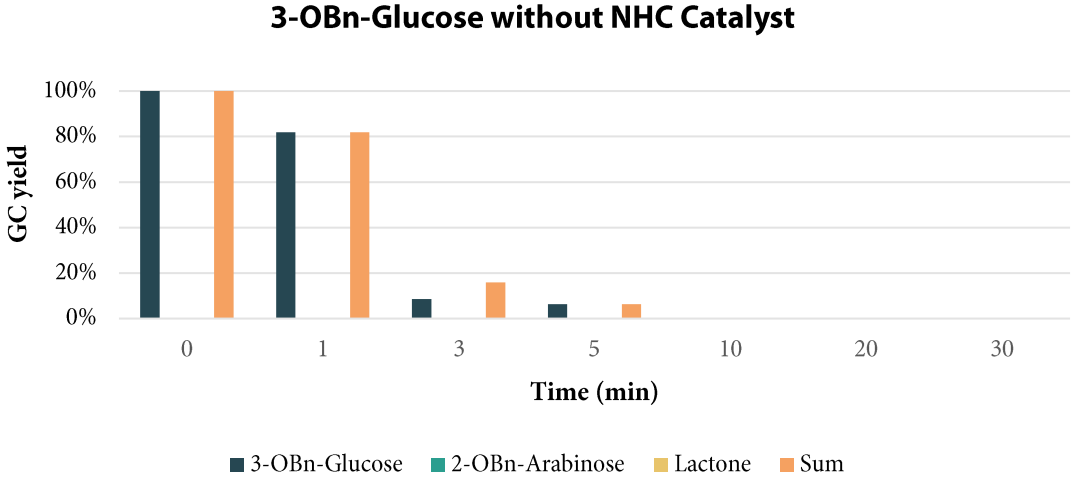


Chart 14. Reaction of 3-*O*Bn-glucose [**8**] (1.00 eq.), chalcone [**3**] (2.00 eq.) without a catalyst. 0.2 eq. of K_2CO_3 were used.

This observation can most likely be explained by the absence of NHC, as the base is not used to liberate the carbene but to facilitate competing reactions that degrade the starting material. Such base promoted loss of starting material was already observed previously (see *B.3.2*) and is likely the cause of lower recoveries with relatively higher amounts of base in relation to the catalyst which neutralizes the base.

B.4.2.2. Conflicting Reactivity of Intermediate 2-OBn-Arabinose [6]

In the second experiment, we tried to convert the dehomologated product **[6]** into the deoxy-lactone **[7]**. We wanted to utilize the previously observed dependency of the lactone formation on the base concentration, by running the reaction with an insoluble base (Li_2CO_3) as well as with a soluble base - Cs_2CO_3 (see *B.3.3)*, to investigate extreme cases on both ends of the spectrum. The time-resolved screenings showed no conversion of the dehomologated intermediate **[6]** into lactone **[7]** with triphenyl triazolium catalyst **[14]** for both bases.

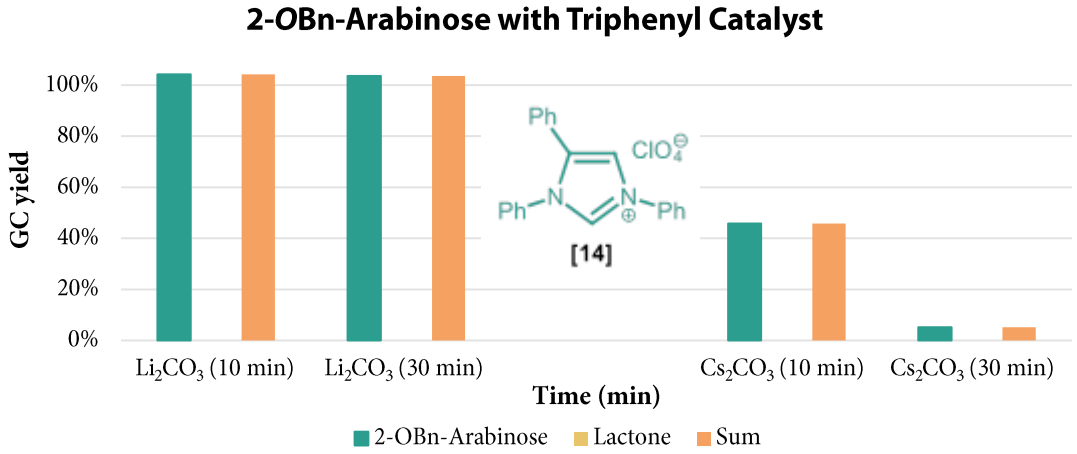


Chart 15. The reaction of arabinose **[6]** (1.00 eq.) with triphenyl triazolium catalyst **[14]** (0.25 eq.), chalcone **[3]** and two different bases shown at two different time points. 0.2 eq. were used for both bases. The full time-course of the reaction is shown in the experimental section (see C.6.3.3)

For Li_2CO_3 all of the starting material was recovered according to GC analysis, while Cs_2CO_3 showed steady degradation of 2-*O*Bn-arabinose. The same reaction conditions gave more than 50 % (15 % for Li_2CO_3 reaction) of lactone in the experiment where 3-OBn-glucose was used. We considered this hard evidence against the initially proposed mechanism (see *Chart 15*).

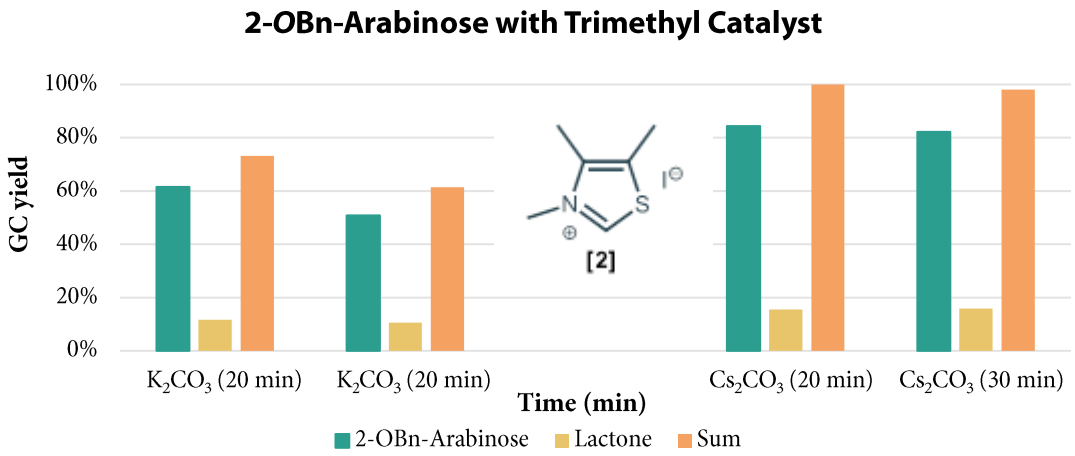


Chart 16. The reaction of arabinose [**6**] (1.00 eq.) with trimethyl thiazolium catalyst [**2**] (0.25 eq.), chalcone [**3**] (2.00 eq.) and two different bases shown at two different time points. For K_2CO_3 0.2 eq. were used (standard conditions), and for Cs_2CO_3 0.05 eq. were used. The full time-course of the reaction is shown in the experimental section (see C.6.3.3)

The experiment was repeated with trimethyl catalyst [**2**], but we decided to exchange the Li_2CO_3 by K_2CO_3 and lowered the base concentration for Cs_2CO_3, to prevent the fast degradation of arabinose observed in the first experiment. Using the trimethyl thiazolium catalyst [**2**], the lactone can be formed from the arabinose species [**6**], but the found amount of lactone was relatively little compared to reactions with the same catalyst started directly from the hexose [**8**]. Two factors can cause this difference in lactone formation. There could be a kinetic advantage in the reaction with preceding dehomologation, as the resulting 2-*O*Bn-arabinose [**6**] gets formed in acyclic form. Therefore, a secondary NHC attack would not rely on the mutarotation equilibrium or the two reaction-pathways coexist for the trimethyl catalyst, and we always observed the sum of both pathways (see *Chart 16*).

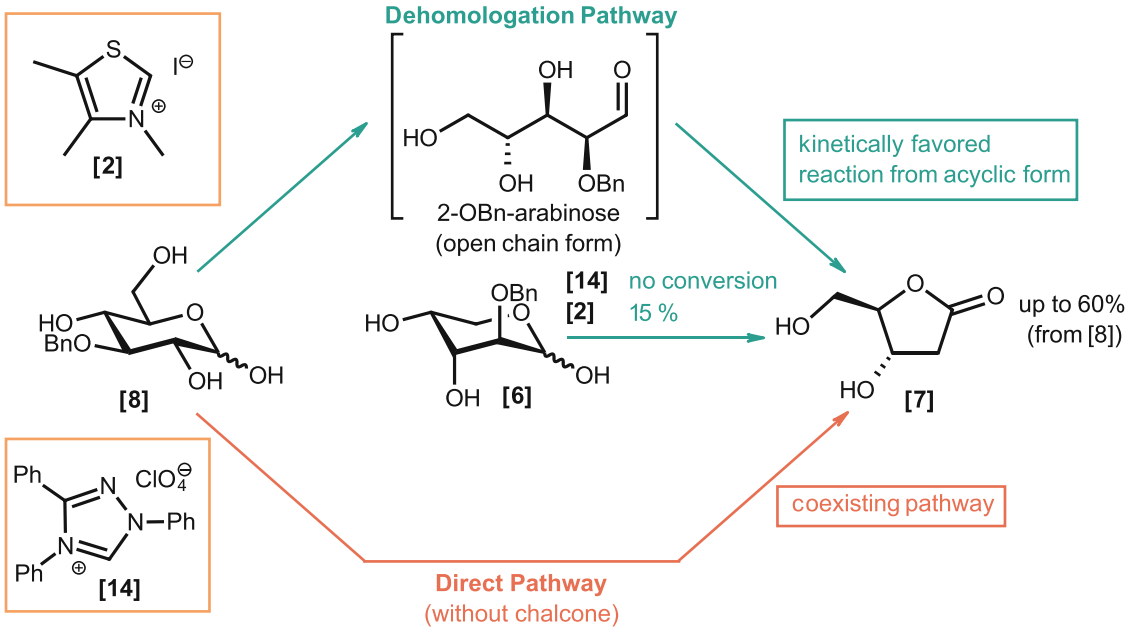


Figure 51. Observed reaction pathways of the transformation. As 2-OBn-arabinose [**6**] showed no conversion to lactone [**7**] with triazolium catalyst, but 3-*O*Bn-glucose [**8**] gave over 50% proved the existence of an alternative reaction pathway. As thiazolium catalyst [**2**] converted small amounts of benzyl arabinose, the dehomologation pathway was also viable.

B.4.3. Deducting a New Working Hypothesis for Direct Lactone Formation

An alternative mechanism needed to be in line with several observations that we identified so far. First, it needed to be a direct way, starting from 3-*O*Bn-glucose [**8**] to form the lactone [**7**]. Also, the NHC catalyst needs to be able to recycle internally without chalcone playing a role. Last, the mechanism should be able to explain a faster conversion with increased base concentration.

Many reports of direct carbohydrate oxidations to form deoxy-lactones can be found in the literature[101-104]. The common motive for these transformations is that they are not altering the chain-length of the carbohydrate in the process. However, our reaction pathway required such an oxidation combined with a C1-dehomologation.

We revisited the publication by *Wendeborn*[83] in which he reported an early experiment that showed β-elimination of an *O*3-benzyl group on a fully protected ribose scaffold as the only reaction product. The experiment was designed to form a ribo-lactone; however, the expected lactone product was not formed in that reaction (see *Figure 52*). *Wendeborn* claimed that the high basicity of the used NHC catalyst (pK_a 22.9 in DMSO[105]) could have induced such an elimination.

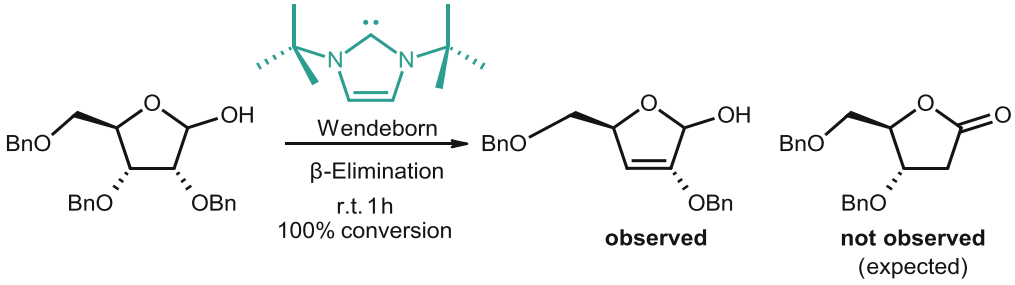


Figure 52. Observed β-Elimination of the *O*3 benzyl group of a fully protected ribose.

This report was intriguing, as such an *O*3 elimination could proceed while the carbohydrate stays in cyclic hemiacetal form. Therefore it is not reliant on the mutarotation and could be faster than processes that react with the aldehyde even if they are energetically unfavored.

Applying this reaction to our 3-*O*Bn-glucose scaffold, we would form a 3-deoxy-α-keto aldose, also known as deoxy-glucosone (see *Figure 53*).

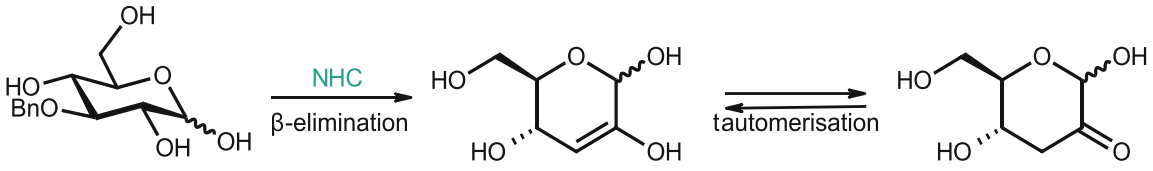


Figure 53. Formation of a 3-deoxy-glucosone upon *O*3-elimination

Such glucosone species are stable products that arise naturally from Maillard reactions of glucose[106]. Interestingly, our triphenyl triazolium catalyst has significantly lower basicity (calculated pK_a 12.9 in DMSO[105]) than *Wendeborns* catalyst, which makes such eliminations less likely. We believe that such a β-elimination is still possible on our sugar substrates, especially for 3-*O*Bn-glucose, which has an extremely low OCC. The steric bulk of the triphenyl catalyst, comparable to *Wendeborns* ^{t}Bu imidazolium catalyst[107], could hamper a reaction on the aldehyde moiety, providing a kinetic advantage

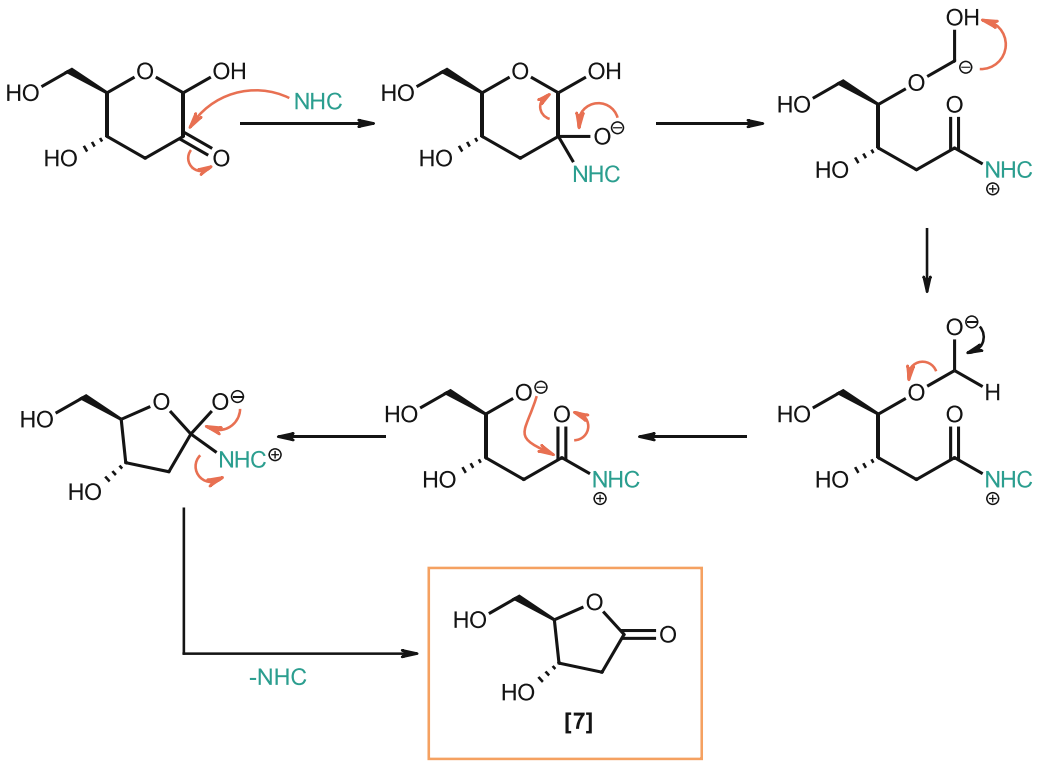


Figure 54. A hypothetical mechanism to form the 2-deoxy lactone [7] after β-elimination of 3-OBn glucose to a glucosone species.

for an elimination reaction.

Such a competing mechanism to the retro-benzoin pathway might also explain the base-dependency of such reactions. With high base loading, more catalyst is liberated at the same time. If very little sugar is available as an aldehyde, reaction kinetics might favour the elimination over the initial umpolung.

Assuming β-elimination to glucose is feasible, we believe that such species could then undergo a retro-benzoin reaction by NHC-attack at the ketone moiety liberating formaldehyde in the process. The NHC would then get liberated *via* S_N2T mechanism. (see *Figure 54*).

This proposed mechanism can facilitate the cyclic carbohydrate structure, and therefore avoids the mutarotation step, which was identified as rate-determining in the original dehomologation mechanism (see *B.1 Investigating the Influence of the Open Chain* Content).

How to probe the new tentative mechanism

The mechanism proposed above is purely speculative and can only be viewed as a working hypothesis as we advance in investigating this novel reaction. To prove or disprove this hypothesis, several experiments can be proposed.

First of all the fully protected ribose substrate used by *Wendeborn* should be reacted with our triphenyl catalyst at standard conditions (130 °C, 0.25 eq. catalyst, 30 min) to see whether or not such a β-elimination can occur even with the low pK_a of our triazolium species **[14]**. Further methyl glycosides could be used to exclude any involvement of the aldehyde moiety, assuming the *O*-methyl group is stable under these conditions.

If the initial β-elimination can be shown to be feasible, the commercial 3-deoxy-glucosone could be used as an intermediate to see if the lactone formation is possible with that proposed intermediate. Alternatively, the reaction mixture's analysis could be focused on identifying formaldehyde and/or its

formose reaction products.

B.4.4. Conclusions

We were able to unambiguously prove that a direct way to form lactone [**7**] from 3-OBn-glucose [8] exists. Simultaneously, our first proposed mechanism with redoxlacotnisation was also once more confirmed to be feasible but, therefore, we assume that both pathways co-exist and occur in different pronunciations depending on the catalyst. It remains unclear which factores facilitate either one of the reaction paths and why both are prevented with the DiiPr-thiazolium catalyst [**13**]. Also, the exact reaction mechanism for direct lactonization is unclear and purely speculative.
Based on findings by *Wendeborn*[83], we were able to deduct a working hypothesis to investigate further.

B.5. Summary & Conclusion

Within this thesis, an in-depth study on the NHC-controlled dehomologation of aldoses was conducted. We set the focus on understanding mechanistic characteristics, as well as dependencies for catalyst derived selectivity.
Mechanistically we were able to show that the OCC of carbohydrate plays a critical role in this transformation. We showed that the initial equilibrium between the carbohydrate's cyclic and acyclic form is rate-determining by investigating carbohydrates with different OCC.
While investigating the broad range of potential side-reactions, we were able to show that secondary NHC-activation is possible on a chalcone structure, as intramolecular Stetter-cyclisation of DBA [**22**] was observed. In the same investigation, we gathered evidence that in the reaction, the lactone gets formed on a different reaction-pathway that we were unaware of before. Further studies on that topic proved that an alternative direct mechanism for the lactone formation from the hexose exists. However, we also confirmed that the old mechanism co-exits with the direct pathway, at least for some catalysts.
Finally, we investigated various inorganic carbonate bases with different solubility in DMSO and were able to identify Cs_2CO_3 as a base that showed the same reaction outcome as K_2CO_3, but under homogeneous conditions. In that process, we also observed that the lactone formation gets promoted by increasing base concentration.
Overall a deeper understanding of the reaction was obtained. The identification of an alternative reaction pathway promoted by base-concentration is a key-finding that will help further improve the method in follow-up investigations. The possibility to perform such reactions under homogeneous conditions is a significant improvement that allows a more facile generation of reproducible and comparable results. Based on the obtained more in-depth understanding of the reaction, further method development in a rational way becomes possible. The observation that the OCC of the starting material plays a critical role in the reaction speed shows that the investigation of additives to stabilize the open-chain form of carbohydrates might be a fruitful road to go. Especially substances like pyridine or pyridone are well-known mutarotation catalysts that might enhance the overall reactivity in our reaction[59]. The observed base dependency of the lactone formation led us to conclude that base-free liberation of the catalytically active carbene might be an idea as we advance. In recently published works thermolabile NHCs were developed for base-sensitive processes[108]. Those special salts deprotonate upon heating to more than 100 °C without the addition of base. However, so far, no examples of such properties were reported on the triazolium or thiazolium scaffold, requiring first an in-depth look on

how to synthesize potential thermolabile catalyst salts.

Another interesting approach is to use prebuilt carbenes. It was shown for a few examples, that some free carbenes exhibit remarkable stability allowing isolation and preparative handling. *Enders*[109] showed that such carbene-prebuilding is feasible for our lactone-selective triphenyl catalyst [**14**] in multi-gram scale. Using solid-phase-bound bases like phosphazenes or basic clay could be an attractive option to pre-form carbenes to avoid additional (and locally excess) bases in the reaction mixture.

Elucidating the found alternative mechanism to form lactone represents a critical task for future studies, as it might hold the key to understand better the catalyst derived selectivity we observed allowing to tweak selectivity to both directions further. An interesting new facette of the project was found, when DBA [**22**] was successfully cyclised into [**24**], an in-depth investigation in this novel transformation is planned. Especially, the substrate scope and the influence of different catalysts (or even catalyst pairs) are of interest for this side-line topic.

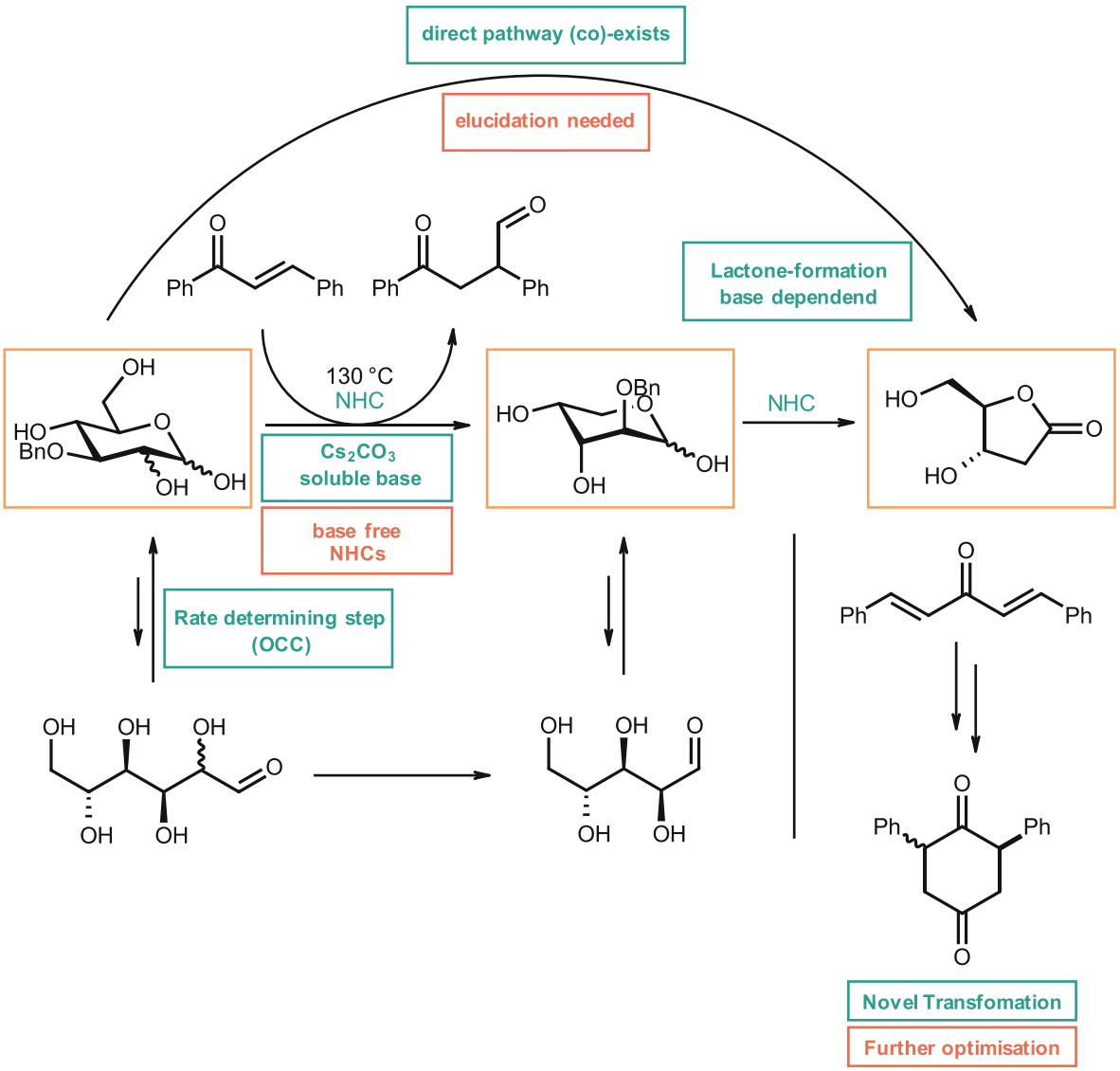


Figure 55. Summary of this thesis, all relevant findings are marked with turquoise boxes. The topics for future investigations are marked in orange.

C. Experimental Part

C.1. Materials & Methods

Reagents and solvents

All chemicals were obtained from commercial sources and used without further purification. Unless remarked differently, water-free solvents were used directly from the in-house solvent drying plant (PureSolv EN 1-4), or commercial sources with a water-free specification stored in bottles with a septum and over molecular sieve.

TLC

TLC analysis for reaction monitoring and analysis of chromatography fractions was performed on silica gel 60 F254-plates, with the eluent specified in the respective experimental section. Detection of compounds was done *via* UV light (254 nm), staining with an ethanolic anisaldehyde solution (180 mL EtOH, 10 mL anisaldehyde, 10 mL H_2SO_4 conc., 2 mL AcOH) or potassium permanganate solution (3.0 g $KMnO_4$, 20.0 g K_2CO_3, 250 mg KOH, 300 mL H_2O).

Microwave reactions

Microwave reactions were performed using a Biotage Initiator EXP EU Microwave Synthesizer.

Column Chromatography

Column chromatography was performed in self-packed glass columns using silica gel from Merck (40-63 µm) or on a Büchi Sephacore Flash (MPLC)-System consisting of two Büchi Pump Modules C-605, Büchi Pump Manager C-615, Büchi UV Photometer C-635 and a Büchi Fraction Collector C-660.
The use of the MPLC system is denoted by "MPLC" in the corresponding experimental sections.
LP, EtOAc and DCM were distilled before using them as eluent.

NMR

NMR spectra were recorded on a *Brucker Avance UltraShield 400* spectrometer (400 MHz machine) or a *Brucker Avance III HD 600* spectrometer (600 MHz machine). Spectra were calibrated to the solvent residue signal[110]. Coupling constants (*J*) are given in Hz and chemical shifts (δ) in ppm. Assignments are based on COSY, HSQC and HMBC spectra and follow IUPAC nomenclature.
According to phase-sensitive experiments, for 13C-NMRs virtual coupling patterns are given (s, d, t, q for CH_3, CH_2, CH, C) based upon phase-sensitive HSQC APT, DEPT or DEPTQ measurements.

GC

GC analysis of derivatised sugars and chalcone species was carried out on a Trace Dual GC, equipped with two TR-5MS columns (length 15m, inner diameter 0.25 mm, film thickness 1.0 µm) and FID Detectors. Carrier gas: Helium; Injector 230; °C; column flow: 1.5 ml/min; temperature gradient: 80 °C (1 min), 80-280 °C (60 °C/min), 280 °C (5 min). Injection volume: 1 µL. All chromatograms were referenced *via* internal standard: Methyl benzoate 1 mM in EtOAc.
This GC unit uses two parallel columns and detectors for parallel analysis (Front and Back-detector), therefore calibrations have to be calculated for both.

GC-MS

GC-MS spectra were measured on a Thermo Trace 1300 / ISQ LT (single quadrupole, EI) using a capillary column BGB 5 (30 m × 0.25 mm ID).

Melting points

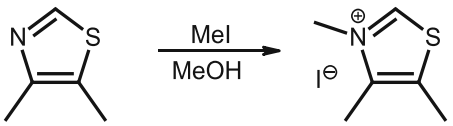
Melting points were measured on a BÜCHI Melting Point B-545 with 40%/90% threshold and a heating rate of 0.5 °C/min.

Parallel machine-assisted removal of solvents

Machine-assisted removal of solvents in a parallelised fashion was performed on a vacuum concentrator RVC 2-25 CDPLUS with an Alpha 2-4 LDplus freeze dryer. At 40 °C, 0.5 mbar and 1400 rpm.

C.2. Synthesis of Precatalyst salts

C.2.1. Synthesis of 3,4,5-trimethylthiazol-3-ium iodide **[2]**[52]



[29] **[2]**

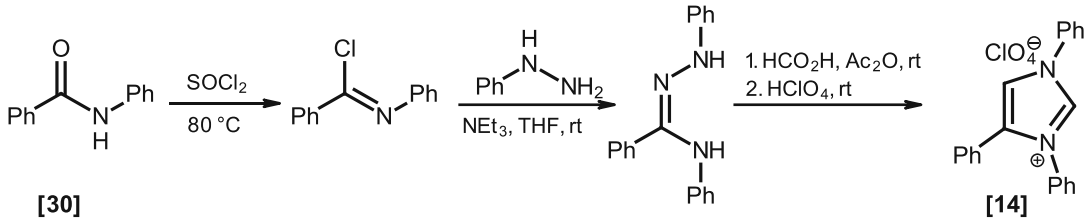
Procedure

4,5-Dimethylthiazole **[29]** (3.00 g, 26.5 mmol, 1.00 eq.) was dissolved in dry MeOH (15 mL), and methyl iodide was added in one portion. The mixture was stirred at rt for 6 days, after which it had turned brownish. Addition of EtOAc (50 mL) led to the immediate precipitation of a colorless solid. The solid was collected by filtration, was washed with cold EtOAc and dried in *vacuo* to give pure target compound **[2]** according to NMR.

Yield:	5.24 g (78 %)
Appearance:	colorless solid
Melting point:	227.5 – 228.3 °C (EtOAc), (lit.[52] 227.8 - 228.9 (EtOAc))
NMR:	^{1}H NMR (600 MHz, DMSO-d_6) δ 2.40 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 4.07 (s, 3H, N-CH_3), 9.93 (s, 1H, H2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 11.1, 12.0 (2×q, 2×CH_3), 40.4 (q, *N*-CH_3), 132.3 (s, C5), 142.1 (s, C4), 155.6 (d, C2)

Spectral data in accordance with the literature[52,98].

C.2.2. Synthesis of 1,3,4-triphenyl-1,2,4-triazol-1-ium perchlorate **[14]**[52]



Procedure

Benzanilide **[30]** (4.00 g, 20.3 mmol, 1.00 eq.) was dissolved in dry toluene (20 mL) in a 3-neck flask equipped with condenser and dry-tube ($CaCl_2$). Next, $SOCl_2$ (7.20 g, 60.8 mmol, 3.00 eq.) was added in one portion before the mixture was heated to 80 °C overnight.

The next day, the condenser was removed and exchanged for a suction valve, to remove the excess of $SOCl_2$ at reduced pressure (9 mbar, 60 °C). The distilled $SOCl_2$ was collected in a cooling trap. The yellow residue was taken up in dry THF (20 mL). Then, Et_3N (4.20 mL, 30.4 mmol, 1.50 eq.) was added followed by dropwise addition of phenylhydrazine (2.40 g, 2.64 mL, 22.3 mmol, 1.10 eq.) within 7 minutes, keeping the temperature below 40 °C.

The mixture was stirred for 2 h when TLC (LP:EtOAc 9:1) showed full conversion of imidochloride. Volatiles were removed under reduced pressure, leaving behind a reddish sticky solid, that was taken up in a 2 % solution of AcOH in water (36 mL). Stirring at 70 °C for 45 minutes led to the formation of a solid, that was collected by filtration and washed with cold MeOH.

Next, a mixture of formic acid (8.46 mL, 224 mmol, 23.0 eq.) and Ac_2O (16.6 ml, 175 mmol, 18.0 eq.) was heated to 60 °C and stirred for 15 min. After cooling to rt, the solid obtained in the previous step was slowly added within 10 min. The resulting solution was stirred for 14 h.

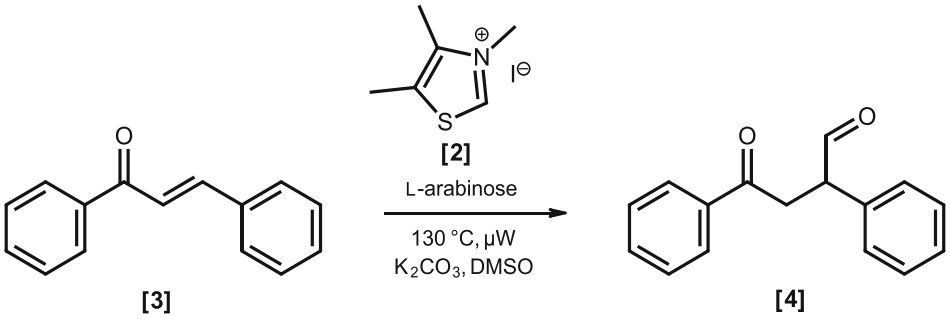
The solvent was then evaporated (40 °C, 15 mbar), and the residue was taken up in perchloric acid (35 %, 16 mL). Finally stirring for 15 min and addition of water (5 mL) lead to the formation of a beige solid, that was collected by filtration and washed with MeOH and H_2O. Drying under reduced pressure gave target material **[14]** in excellent purity, according to NMR analysis.

Yield:	3.46 g (43 %)
Appearance:	beige solid
Melting point:	231.7 – 232.5 °C (EtOH), (lit.[52] 232 – 233 (MeOH))
NMR:	^{1}H NMR (600 MHz, DMSO-d_6) δ 7.49 – 7.57 (m, 4H, Ph-CH), 7.66 – 7.74 (m, 7H, Ph-CH), 7.78 (t, J = 7.3 Hz, 2H, Ph-CH), 8.09 (d, J = 7.9 Hz, 2H, Ph-CH), 11.35 (s, 1H, H5). ^{13}C NMR (101 MHz, DMSO-d_6) δ 120.6 (d, PhCH), 122.3 (s, PhC), 126.5, 129.2, 129.3, 130.2, 130.4, 130.9, 131.5 (7×d, 7×PhCH), 132.0 (s, PhC), 132.3 (d, PhCH), 134.8 (s, PhC), 143.2 (d, C5), 153.2 (s, C3).

Spectral data in accordance with the literature[52,98].

C.3. Synthesis of Chalcone Species

C.3.1. Synthesis of 4-oxo-2,4-diphenylbutanal **[4]**[86]



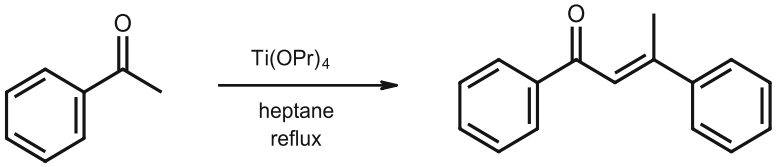
Procedure

A microwave vial was charged with L-arabinose (300 mg, 2.00 mmol, 1.00 eq.), chalcone **[3]** (417 mg, 2.00 mmol, 1.00 eq.), K_2CO_3 (55.3 mg, 0.40 mmol, 0.2 eq.) and trimethyl-thiazolium catalyst **[2]** (102 mg, 0.40 mmol, 0.20 eq.). Next, MeCN (10 mL, HPLC grade) was added, and the mixture was purged with Ar. The mixture was heated to 130 °C for 30 min in the microwave.
Afterwards, the reaction mixture was evaporated, and the brownish residue was directly submitted to column chromatography (MPLC, 40 g SiO_2, gradient LP:EtOAc 20:1 – 8:1, 40 mL/min) to give 350 mg of target material **[4]**, in high purity according to NMR

Yield:	350 mg (73 %)
Appearance:	Brown oil
R_f-value	0.4 (LP:EtOAc 9:1)
NMR:	^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.23 (dd, *J* = 18.0, 4.9 Hz, 1H, H3b), 3.95 (dd, *J* = 18.0, 8.4 Hz, 1H, H3a), 4.46 (dd, *J* = 8.4, 4.9 Hz, 1H, H2), 7.24 – 7.31 (m, 2H, Ph-H3/H5), 7.28 – 7.36 (m, 1H, Ph-H4), 7.35 – 7.44 (m, 2H, Ph-H2/H6), 7.41 – 7.50 (m, 2H, Ph-H3/H5), 7.52 – 7.61 (m, 1H, Ph-H4), 7.91 – 8.06 (m, 2H, Ph-H2/H6), 9.81 (s, 1H, H1).

Spectral data in accordance with the literature[86].

C.3.2. Synthesis of (*2E*)-1,3-Diphenylbut-2-en-1-one **[20]**[95]



[25] **[20]**

Procedure

Following a modified literature procedure[95] a 3-neck flask equipped with a Dean-Stalk trap (half-filled with conc. H_2SO_4) was charged with acetophenone [**25**] (11.0 g, 91.6 mmol, 1.00 eq.) and heptane (20 mL). Tetrapropyl orthotitanate (12.6 mL, 45.8 mmol, 0.50 eq.) was mixed with heptane (10 mL) and added to the reaction mixture at rt. The mixture was stirred under reflux conditions and monitored *via* TLC (LP:EtOAc 10:1). After 5 h the reaction progress slowed down; therefore, another portion of titanate (6.3 mL, 27.9 mmol, 0.25 eq.) was added, and the mixture was further stirred at reflux conditions for 23 h before TLC indicated full conversion of starting material.

The solution was cooled to rt, diluted with heptane (50 mL), and treated with 2N HCl (5 mL). A colorless precipitate formed and the suspension was again heated to reflux conditions for 30 min. The solid material was removed by filtration, and the filtrate was evaporated to give crude target material [**20**] (9.2 g) with ~90% purity according to NMR analysis.

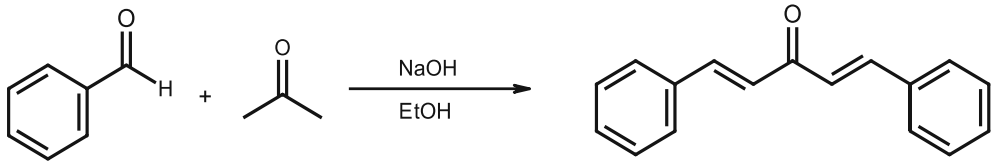
Purification

4.54 g of crude material were further purified *via* column chromatography (300 g SiO_2, LP:EtOAc 20:1 – 10:1, 20 mL fraction size) to give 2.49 g of target material [**20**] in excellent purity (99%, NMR) and a second fraction of 1.50 g of less pure (~90 %, NMR) compound [**20**]

Yield:	overall 8.0 g (79 %), (3.99 g isolated on aliquot purification)
Appearance:	Yellow oil
R_f-value	0.63 (LP:EtOAc 10:1)
NMR:	^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.61 (d, *J* = 1.3 Hz, 3H, H4), 7.18 (q, *J* = 1.3 Hz, 1H, H2), 7.39 – 7.45 (m, 3H, Ph-H4', Ph-H3'/H5'), 7.46 – 7.51 (m, 2H, Ph-H3/H5), 7.53 – 7.65 (m, 3H, Ph-H4, PhH2'/H6'), 7.98 – 8.03 (m, 2H, Ph-H2/H6). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 19.0 (q, C4), 122.2 (d, C2), 126.6 (d, 2×Ph-C2'/C6'), 128.4 (d, 2×Ph-CH), 128.7 (d, 2×Ph-CH), 128.7 (d, 2×Ph-CH), 129.3 (d, Ph-C4'), 132.7 (d, Ph-C4), 139.5 (s, Ph-C1), 142.9 (s, Ph-C1), 155.2 (s, C3), 192.0 (s, C=O).

Spectral data in accordance with literature[93,95].

C.3.3. Synthesis of *(1E,4E)*-1-Methyl-1,5-diphenylpent-1,4-dien-3-one **[22]**



[25] **[22]**

Procedure

Freshly distilled benzaldehyde **[26]** (14.6 g, 138 mmol, 2.00 eq.) was dissolved in EtOH (140 mL). Acetone (4.00 g, 68.9 mmol, 1.00 eq.) was added in one portion followed by dropwise addition of a solution of NaOH (5.5 g, 138 mmol, 2.00 eq.) in H_2O (110 mL) at rt. After 15 minutes, half of NaOH solution was added, and the mixture turned bright orange with a yellow precipitate forming. Upon completion of addition, the mixture was stirred for 4 h at rt, until TLC (LP:EtOAC 20:1) showed full consumption of benzaldehyde. The yellow precipitate was collected by filtration and washed with cold EtOH. The yellow solid was recrystallised from EtOH:H_2O 4:1 to give 12.4 g of pure target material (>95 % purity, NMR)

Yield: 12.4 g (79 %)

Appearance: Yellow needles

Melting point: 112-114 °C (EtOH) (lit.[111] 113-115 °C)

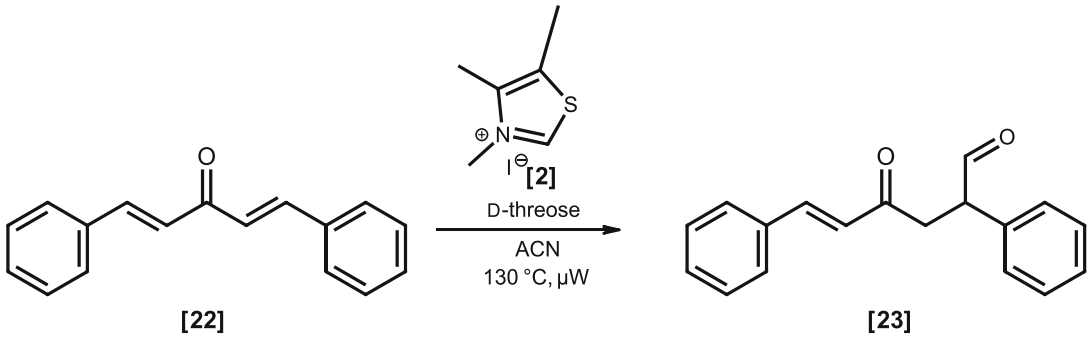
NMR: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (d, J = 16.1 Hz, 2H, H2, H4), 7.45 – 7.50 (m, 6H, 2×Ph-H4, 2×Ph-H3/H5), 7.75 – 7.85 (m, 9H, H1, H5, 2×Ph-H2/H6).

^{13}C NMR (101 MHz, DMSO-d_6) δ 126.1 (d, C2, C4), 129.0 (d, 2×Ph-C2/C6), 129.5 (2×Ph-C3/C5), 131.0 (d, 2×Ph-C4), 135.2 (d, 2×Ph-C1), 143.3 (d, C1, C5), 189.0 (s, C=O).

Spectral data in accordance with literature[111].

C.4. Formylation of DBA

C.4.1. Synthesis of 2,6-Diphenyl-4-oxohex-5-enal **[23]**



Procedure

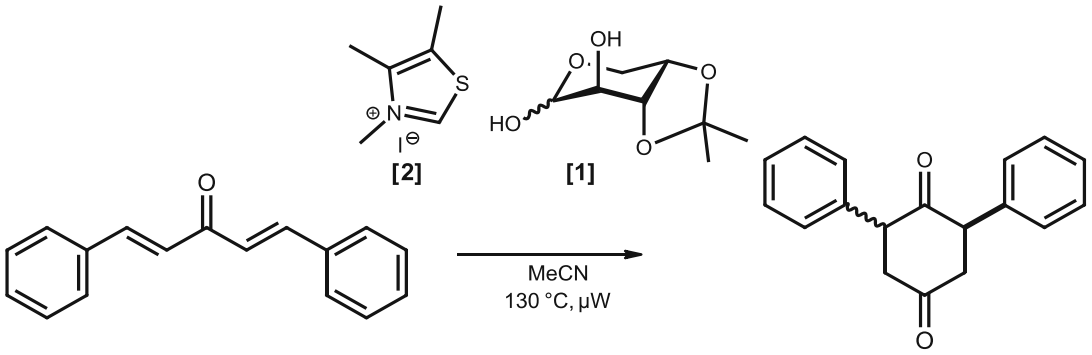
A commercial solution of D-threose **[17]** in H_2O (3.06 mL, 2.13 mmol, 1.00 eq., 0.698 M) was transferred into a microwave vessel and evaporated from water in *vacuo*. Next K_2CO_3 (59.0 mg, 0.43 mmol, 0.20 eq.), DBA **[22]** (1.00 g, 4.27 mmol, 2.00 eq.) and trimethyl triazolium iodide **[2]** (136 mg, 0.53 mmol, 0.25 eq.) were added, and the mixture was dissolved in 20 mL of MeCN.

The reaction mixture was purged with Ar, then heated to 130 °C for 10 min in the microwave. Afterwards, the reaction mixture turned reddish-brown, was treated with conc. acetic acid (1 mL) and the solvents were evaporated. The brown residue was taken up in Et_2O and water, layers were separated, and the organic layer was extracted with water and brine. The combined aqueous layers were treated with 2N HCl (20 mL) and then twice extracted with Et_2O. The combined organic layers were evaporated upon drying over Na_2SO_4 to give the crude material. NMR indicated a mixture of target material **[23]**, starting material and cyclised material **[24]**.

The crude material was submitted to column chromatography (200 g SiO_2, gradient LP:EtOAc 12:1 – 3:1) giving target material **[23]** in good purity (>95 %) according to NMR.

Yield:	190 mg (17 %)
Appearance:	Colourless oil
Rf-value	0.45 (LP:EtOAc 4:1)
NMR:	^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.95 (dd, *J* = 17.6, 5.0 Hz, 1H, H3b), 3.63 (dd, *J* = 17.6, 8.4 Hz, 1H, H3a), 4.38 (dd, *J* = 8.4, 5.1 Hz, 1H, H2), 6.75 (d, *J* = 16.3 Hz, 1H, H5), 7.22 – 7.29 (m, 1H, Ph-H3/H5), 7.29 – 7.35 (m, 1H, Ph-H4), 7.35 – 7.45 (m, 5H, Ph-H3/H5, Ph-H2/H6, Ph-H4), 7.50 – 7.57 (m, 2H, Ph-H2/H6), 7.58 (d, *J* = 16.2 Hz, 1H, H6), 9.77 (d, *J* = 0.6 Hz, 1H, H1). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 41.3 (t, C3), 53.8 (d, C2), 126.0 (d,C5), 128.0 (d, Ph-C4), 128.5 (d, 2×Ph-C), 129.1 (d, 2×Ph-C), 129.2 (d, 2×Ph-C), 129.4 (d, 2×Ph-C), 130.8 (d, Ph-C4), 134.5 (s, Ph-C1), 135.6 (s, Ph-C1), 143.4 (d, C6), 197.3 (s, C4), 199.1 (d, C1).
GC-MS	m/z $[M]^+$ calc. for $C_{18}H_{16}O_2$ 264.3, found 264.0; molecule peak 236.0 corresponds to fragment without aldehyde

C.4.2. Synthesis of 2,6-Diphenylcyclohexan-1,4-dione **[24]**



Procedure

Dibenzalacetone **[22]** (2.00 g, 8.54 mmol, 1.00 eq.), L-arabinose acetonide **[1]** (1.95 g, 10.2 mmol, 1.20 eq.), K_2CO_3 (236 mg, 1.71 mmol, 0.20 eq.) and trimethyl thiazolium iodide **[2]** (544 mg, 2.13 mmol, 0.25 eq.) were split equally between two microwave vessels, and each vial was filled with MeCN (20 mL). The reaction mixtures were purged with Ar and heated to 130 °C for 20 min in the microwave.

Afterwards, MeCN was evaporated, and the residue was taken up in EtOAc (150 mL), extracted twice with water and once with brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to give 2.9 g crude material.

The crude material was purified *via* column chromatography (120 g SiO_2, gradient LP:EtOAc 4:1 – 2:1, dry loading – 20 g Celite, fraction size: 12 mL). To give 360 mg of the pure target compound as diastereomeric mixture cis:trans ~ 3:2 (tentatively assigned according to NMR). The rest of the obtained material was mainly carbohydrate derived residuals.

Yield:	360 mg (13 %)
Appearance:	colourless powder
Melting point:	194.3 – 195.3 (EtOAc)
GC-MS:	m/z $[M]^+$ calc. for $C_{18}H_{16}O_2$ 264.3, found 264.0
NMR (major isomer):	^{1}H NMR (600 MHz, DMSO-d_6) δ 2.71 (dd, J = 17.1, 5.2 Hz, 2H, H3b, H5b), 3.46 (dd, J = 17.1, 13.7 Hz, 2H, H3a, H5a), 4.39 (dd, J = 13.7, 5.2 Hz, 2H, H2,H6), 7.22 – 7.25 (m, 4H, 2×Ph-H3/H5), 7.25 – 7.30 (m, 2H, 2×Ph-H4), 7.32 – 7.35 (m, 4H, 2×PhH2/H6). ^{13}C NMR (151 MHz, DMSO-d_6) δ 43.7 (d, C2, C6), 51.1 (t, C3, C5), 126.9 (d, 2×Ph-C4), 128.3 (d, 2×Ph-C2/C6), 128.6 (d, 2×Ph-C3/C5), 138.4 (s, 2×Ph-C1), 207.9 (s, C=O), 208.5 (s, C=O).

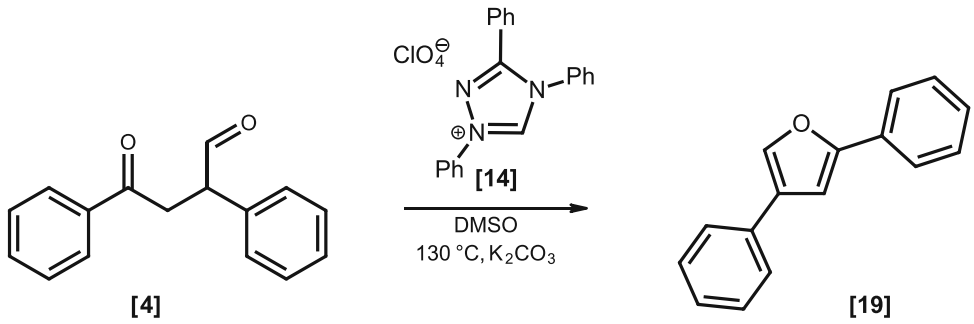
NMR (minor isomer)

^{1}H NMR (600 MHz, DMSO-d_6) δ 3.05 (dd, J = 16.3, 6.6 Hz, 2H, H3b, H5b), 3.12 (dd, J = 16.4, 10.3 Hz, 2H, H3a, H5a), 4.45 (dd, J = 10.2, 6.6 Hz, 2H, H2, H6), 7.17 – 7.21 (m, 4H, 2×Ph-H3/H5), 7.25 – 7.30 (m, 2H, 2×Ph-H4), 7.34 (t, J = 7.6 Hz, 4H, 2×Ph-H2/H6).

^{13}C NMR (151 MHz, DMSO-d_6) δ 44.15 (d, C2, C6), 51.58 (t, C3, C5), 126.95 (d, 2×Ph-C4), 128.33 (d, 4×Ph-C), 128.43 (d, 4×Ph-C), 137.98 (s, 2×Ph-C1), 207.02 (s, C=O), 207.34 (s, C=O).

C.5. Isolation of Dehomologation Side Products

C.5.1. Isolation of 2,4-Diphenylfurane **[19]**



Procedure:

Formylchalcone **[4]** (90.0 mg, 0.38 mmol, 1.00 eq.), triphenyl triazolium catalyst **[14]** (7.5 mg, 0.02 mmol, 0.05 eq.) and K_2CO_3 (2.1 mg, 0.02 mmol, 0.04 eq.) were dissolved in 1 mL of DMSO and stirred at 130 °C in a screw-cap vial. The reaction was monitored *via* TLC (LP:EtOAc 4:1), until after 25 min a new faint apolar spot was forming.

The reaction was cooled to rt and DMSO was removed in *vacuo* (40 °C, 0.3 mbar). The crude material was purified by column chromatography (16 g SiO_2, isocratic LP:EtOAc 17:1) targeting the newly formed species. 8 mg of pure material were isolated and identified as compound **[19]**.

Yield: 8 mg (10 %)

Appearance: colourless solid (melting point lit[112] 110.5-111.0 (MeOH))

NMR ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.97 (d, *J* = 0.9 Hz, 1H, H3), 7.27 – 7.33 (m, 2H, 2×Ph-H4), 7.39 – 7.43 (m, 4H, Ph-H3'/H5', Ph-H3''/H5''), 7.54 (dd, *J* = 8.2, 1.3 Hz, 2H, Ph-H2''/H6''), 7.71 – 7.75 (m, 2H, Ph-H2'/H6'), 7.76 (d, *J* = 0.9 Hz, 1H, H5).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 104.1 (C3), 124.0 (Ph-C2'/C6'), 126.0 (Ph-C2''/C6''), 127.3 (Ph-C4*), 127.7 (Ph-C4*), 128.5 (C4), 128.9 (Ph-C3/C5*), 129.0 (Ph-C3/C5*), 130.8 (Ph-C1'), 132.5 (Ph-C1''), 138.0 (C5), 155.0 (C2).

*Signals could not be unambiguously assigned to the 2-phenyl ring (') or the 4-phenyl ring (")

Spectral data in accordance with literature[112,113].

C.6. General Screening Procedures

C.6.1. GC Calibration

C.6.1.1. GC Calibration of Chalcone species

Preparation of Samples

Stock solutions (50 mM) of all relevant chalcone species ([**3**], [**4**], [**20**], [**22**]) in a solution of methylbenzoate (reference standard) in EtOAc (1 mM) were prepared.

For each analyte the same procedure was performed: First, 100 µL, 80 µL and 40 µL were taken out and filled to 1 mL with methylbenzoate solution in EtOAc (1 mM), giving 3 solutions: **A**: 5 mM; **B**: 4 mM, **C:** 2 mM. From these 3 solutions, further dilutions were prepared by diluting with methylbenzoate in EtOAc (1 mM): Of solution **A**, 200 µL and 150 µL were taken out and filled to 1 mL. Next, 125 µL of solution **B** and **C** were each filled to 1 mL. This procedure delivered analyte-concentrations of 5 mM, 4 mM, 2 mM, 1 mM, 0.75 mM, 0.50 mM, 0.25 mM. Finally, the solution with a concentration of 1 mM was again diluted by filling 100 µL up to 1 mL, to achieve a concentration of 0.10 mM. The samples were filtered through a syringe filter and filled into GC vials.

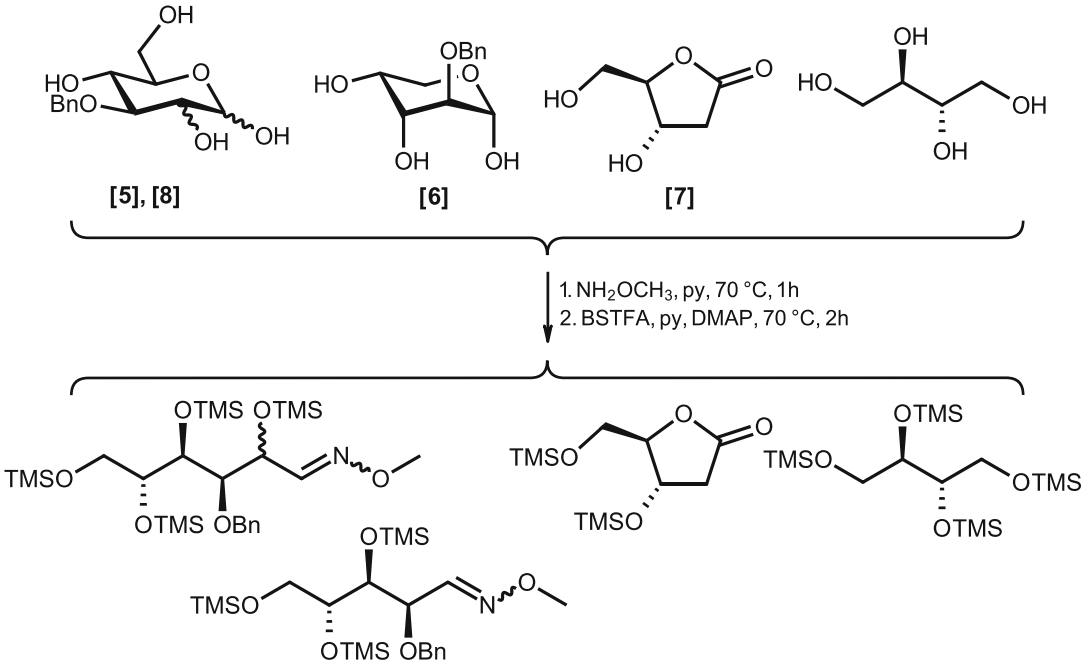
Calculation of linear Calibrations

The samples were measured *via* GC, and the peak areas were normalised to the corresponding methylbenzoate signal (internal standardisation). The resulting normalised peak-area values were correlated to the corresponding analyte concentrations, and linear regressions (in the form $y = k \cdot x + d$) were calculated. The calibration was calculated for both detectors (Front and Back) of the Dual GC system used.

Table 2. Calibration parameters for chalcones in the reaction mixture.

$y = k \cdot x + d$	Front Detector			Back Detector		
	k	**d**	**R^2**	**k**	**d**	**R^2**
Chalcone [3]	1.0665	-0.0341	0.99029	0.9864	-0.1054	0.97925
Formyl-Chalcone [4]	1.0261	-0.045	0.99613	0.8077	-0.0338	0.99239
Methyl Chalcone [20]	0.8292	-0.1713	0.99866	2.4736	0.2208	0.97905
DBA [22]	0.645	-0.0333	0.9966	1.992	-0.0797	0.99648

C.6.1.2. GC Calibration of Carbohydrate derived species



Preparation of Samples

Stock solutions (100 mM in water) of relevant carbohydrates **[5]**, **[6]**, **[8]**, lactone **[7]** and erythritol were prepared. Aliquots of 100 µL were taken out and evaporated to dryness *via* vacuum concentrator (0.4 mbar, 40 °C). For each sample, the following procedure was performed:

A solution of *O*-methylhydroxyl amine hydrochloride in pyridine (400 µL, 40 mg/mL) was added, and the solution was heated to 70 °C for 1 h. Afterwards, a solution of DMAP in pyridine (400 µL, 1.5 mg/mL) and a solution of BSTFA + 1 % TMSCl (400 µL) was added to the mixture. After stirring at 70 °C for 2 h, the solution was cooled to rt and filled to 2 mL with a solution of Methylbenzoate in EtOAc (800 µL, 2.5 mM). This procedure resulted in a concentration of the analyte of 5 mM and 1 mM for the internal standard (Solution **A**). Next 800 µL were taken out and filled with methylbenzoate solution in EtOAc (200 µL, 1 mM) to give solution **B**. Following, solutions **A** and **B** were diluted 3 times 1+1 (500 µL + 500 µL) with a solution of methylbenzoate in EtOAc (1 mM).

Overall analyte concentrations for each analyte of 5 mM, 4 mM, 2.5 mM, 2 mM, 1.25 mM, 1 mM, 0.625 mM, 0.5 mM, 0.3125 mM and 0.25 mM was achieved.

The samples were measured *via* GC to determine the calibration were calculated. (See Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.** for calibration curves).

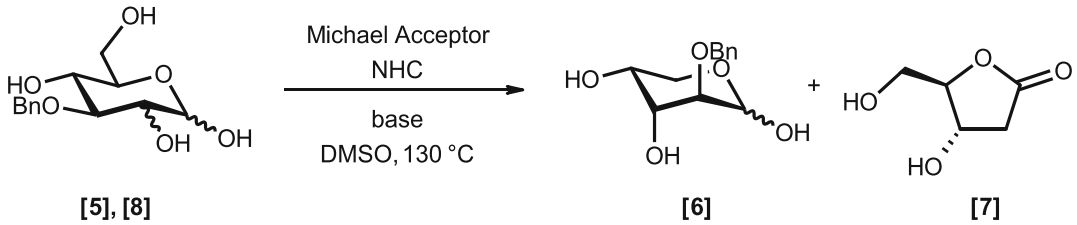
Calculation of linear Calibrations

The samples were measured *via* GC, and the peak areas were normalised to the corresponding methylbenzoate signal (internal standardisation). The resulting normalised peak-area values were correlated to the corresponding analyte concentrations, and linear regressions (in the form $y = k \cdot x + d$) were calculated.

Table 3. Calibration parameters for carbohydrate derived products in the reaction mixture after derivatisation into OTMS-oximes.

$y = k \cdot x + d$	Front Detector			Back Detector		
	k	d	R^2	k	d	R^2
Erythritol	295.623	-40.8741	0.99837	235.0512	-21.0075	0.99966
Lactone [7]	146.132	-17.6315	0.99854	138.7957	-12.2849	0.99969
2-OBn-Arabinose [6]	342.7164	-55.6863	0.99763	279.3352	-24.3607	0.99927
3-OBn-glucose 1 [8]	240.9324	-27.2607	0.99695	220.9677	-5.343	0.99878
3-OBn-glucose 2 [8]	46.9681	-5.3727	0.99829	44.6029	-2.619	0.99877
3-OBn-mannose1 [5]	191.2981	-32.0749	0.9934	205.2263	-25.4111	0.99448
3-OBn-mannose 2 [5]	34.6748	-5.7965	0.98989	35.4563	-2.9196	0.99933

C.6.2. General Procedure for the dehomologation reaction and time-resolved analysis thereof



[5], [8] [6] [7]

Preparing the reaction mixture

Stock solutions of the carbohydrate (160 mM), NHC catalyst (80 mM) and Michael acceptor (640 mM) in DMSO were prepared. The base was weighed into an 8 mL screw-cap vial with a septum. If not noted otherwise for reactions using K_2CO_3, granulated particle size was used (Alfa Aesar, product number: A16625).

Next, 1 mL of carbohydrate solution and subsequently 0.5 mL of NHC and Michael acceptor solution were added to the vial, resulting in a total volume of 2.0 mL DMSO. The mixture was purged with argon. Afterwards, the reaction vial was put into a preheated reaction block at 130 °C (temperature measured *via* reference vial, containing DMSO). At this point, the timing for sampling starts.

Time-resolved sampling

At each time point (commonly: 0, 1, 3, 5, 10, 20, 30 minutes), approx. 0.2 mL of the reaction mixture were taken out and transferred into an Eppendorf vial. To prevent further reactions, the Eppi was cooled to 0 °C with an ice-bath until further processing (max 30 min). Noteworthy, the t0 sample was taken before the mixture was heated.

Processing of aliquotes and derivatisation of carbohydrate derived compounds

Exactly 60 µL of each sample were transferred into an Eppendorf vial, and a solution of erythritole (silylation standard) in H_2O (30 µL, 100 mM, 0.012 mmol) was added. All samples were concentrated in the vacuum concentrator for ~2 h. The following procedure was applied for each sample separately: The residue was taken up in 0.5 mL of an H_2O:MeCN 4:1 solution (vigorous shaking *via* vortexer was applied). Samples showed an increasing tendency to contain insoluble residues with time, however it

was shown, that all relevant materials were fully dissolved in the eluent, therefore the residue was ignored. The solution was transferred onto a LiChrolut RP18 prepacked column (100 mg) and eluted with another 0.5 mL of H_2O:MeCN 4:1. In this step, all apolar side products are separated from the carbohydrate species. The gathered eluent was concentrated in *vacuo* until complete dryness was reached (residual solvent interferes with derivatisation). Next, *O*-methylhydroxylamine hydrochloride solution in pyridine (200 µL, 40 mg/mL) was added to the residue. The solution was heated to 70 °C for 1 h. before a solution of DMAP in pyridine (200 µL, 1.5 mg/mL) and subsequently BSTFA+1 % TMSCl solution (200 µL) was added. And the mixture was again heated to 70 °C for 2 h. Afterwards, the mixture was cooled to rt and filled to 1 mL volume by adding methylbenzoate solution in EtOAc (400 µL, HPLC grade, 2.5 mM). The solutions were filtered through a syringe filter (0.2 µm) and measured *via* GC and quantified.

The concentration of each analyte was determined by first normalising the peak areas to the methylbenzoate signal and calculating an initial concentration *via* the calibrations determined previously. The calculated concentrations were then normalised to match an erythritole concentration of 3.00 mM to account for the potential incompleteness of the derivatisation process.

Processing of aliquotes to analyse chalcone-derived compounds

Exactly 40 µL of each reaction mixture sample were taken into an Eppendorf vial and evaporated to dryness *via* vacuum concentrator. The residue was taken up in 400 µL of water and was extracted twice with 400 µL of methylbenzoate solution in EtOAc (1 mM, HPLC grade). The combined organic layers were dried over Na_2SO_4 and filtered through a syringe filter (0.2 µm) before measuring the samples *via* GC.

The peak areas were normalised to the methylbenzoate signal, and the concentrations of the analytes were directly calculated *via* the calibrations determined previously.

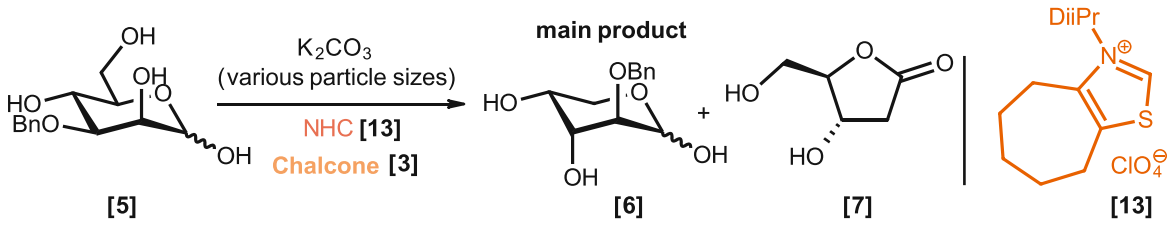
C.6.3. Screening Results

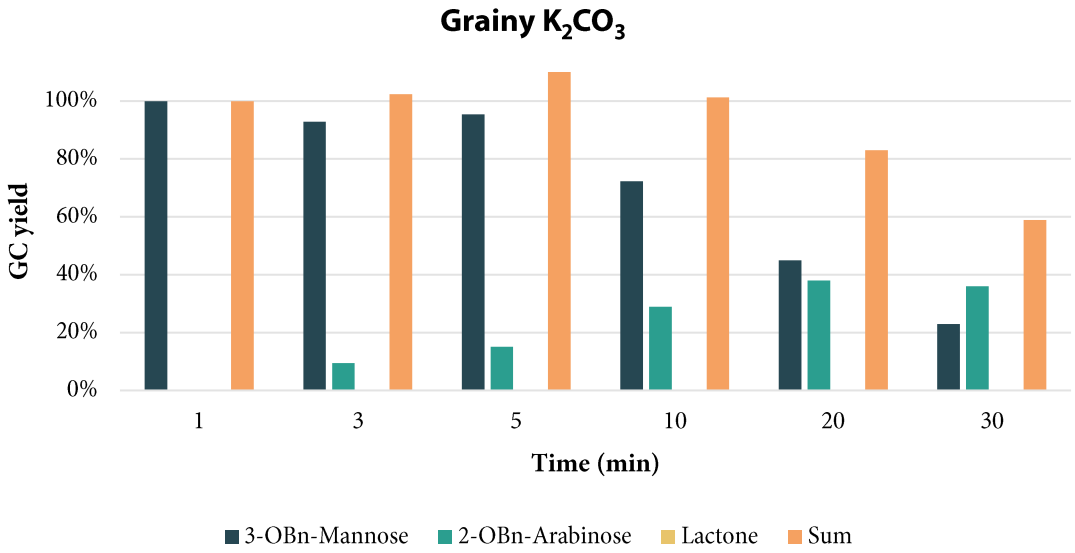
C.6.3.1. Base Screenings with Different Bases

Full timecourses of the screening reactions discussed and summarised in chapters *B.3.1* and *B.3.2* are shown here.

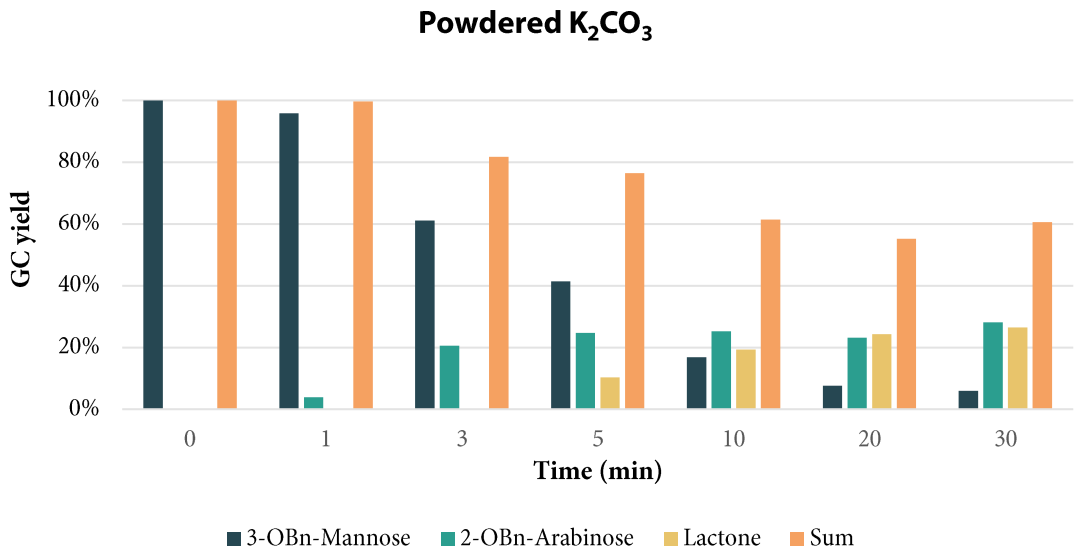
Comparison of the Reaction Outcome Depending on K_2CO_3 with Different Particle Size

3-*O*Bn-mannose **[5]** (1.00 eq) was dehomologated according to the general procedure described above, with DiiPr catalyst **[13]** (0.25 eq.), chalcone **[3]** (2.00 eq.) and K_2CO_3 (0.20 eq.) with grainy or powdered particle size. (Summary and discussion of the shown results: *Chart 8* on page 53)





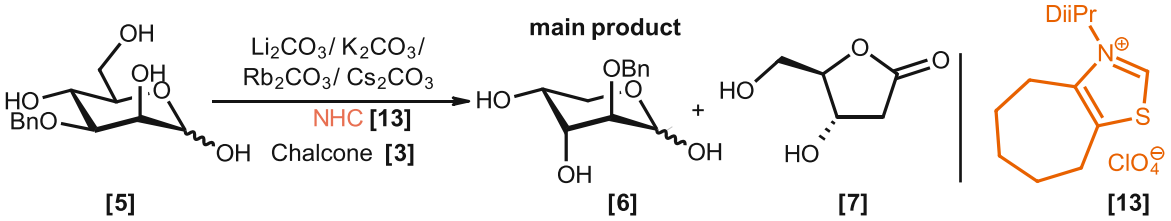
TIME	[5]	[6]	[7]	SUM
1 min	100%	0%	0%	100%
3 min	93%	10%	0%	102%
5 min	95%	15%	0%	110%
10 min	72%	29%	0%	101%
20 min	45%	38%	0%	83%
30 min	23%	36%	0%	59%

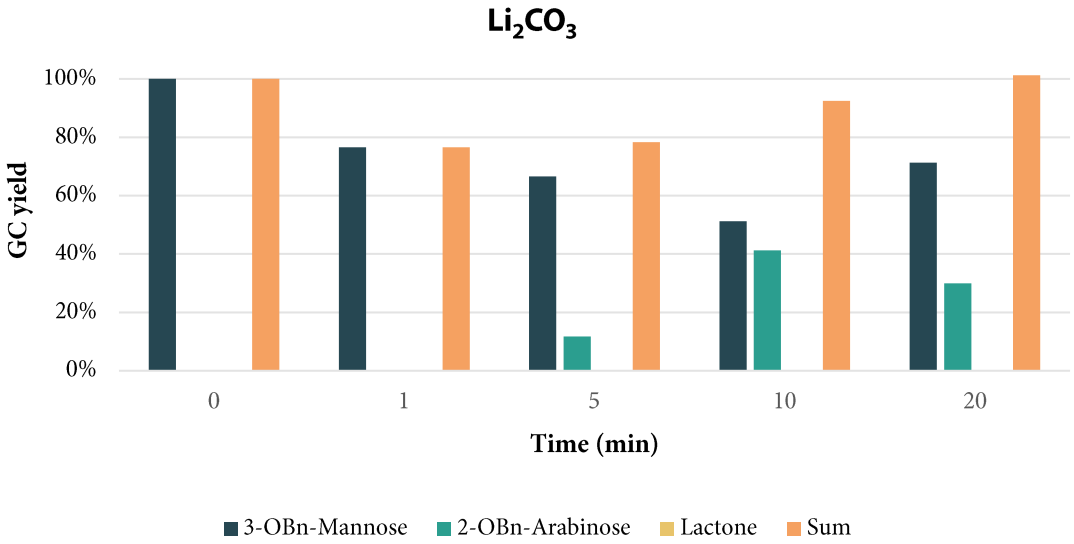


TIME	[5]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	96%	4%	0%	100%
3 min	61%	21%	0%	82%
5 min	41%	25%	10%	76%
10 min	17%	25%	19%	61%
20 min	8%	23%	24%	55%
30 min	6%	28%	26%	61%

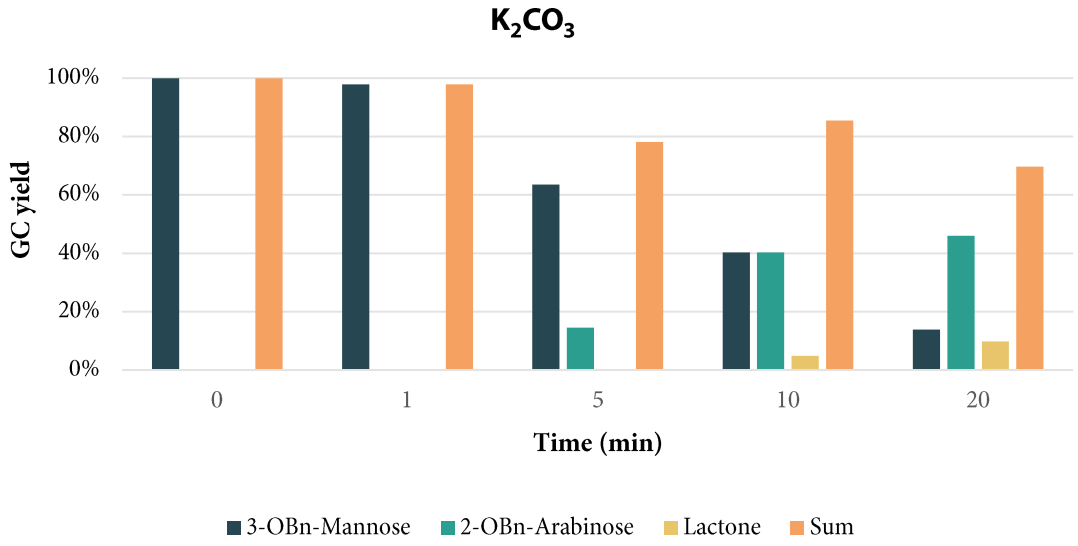
3-*O*Bn-Mannose [5] with DiiPr-Catalyst [13]

3-*O*Bn-mannose **[5]** (1.00 eq) was dehomologated according to the general procedure described above, with DiiPr catalyst **[13]** (0.25 eq.), chalcone **[3]** (2.00 eq.) and different bases (Li_2CO_3, K_2CO_3, Rb_2CO_3, Cs_2CO_3) (0.20 eq.). (Summary and discussion of the shown results: *Chart 9* on page *55*)

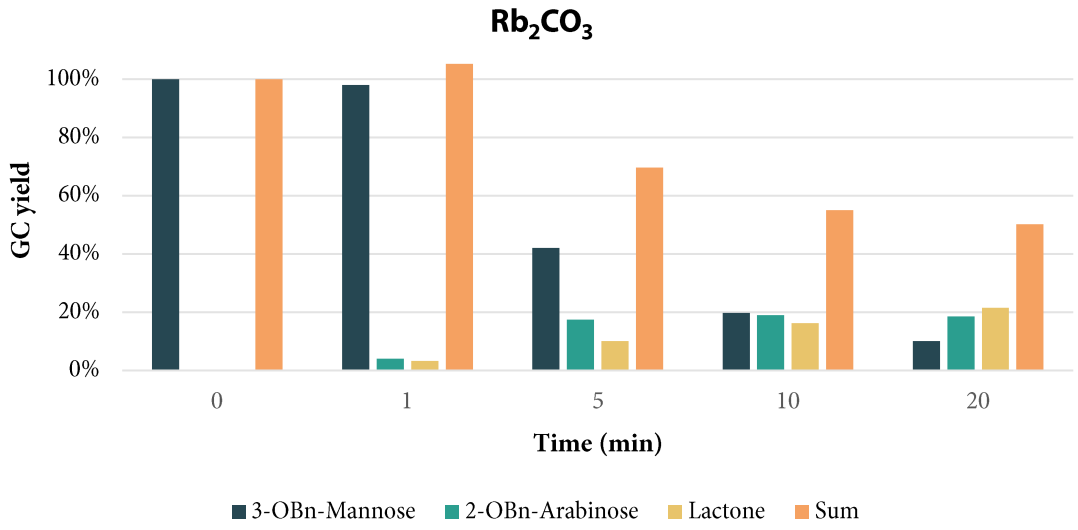




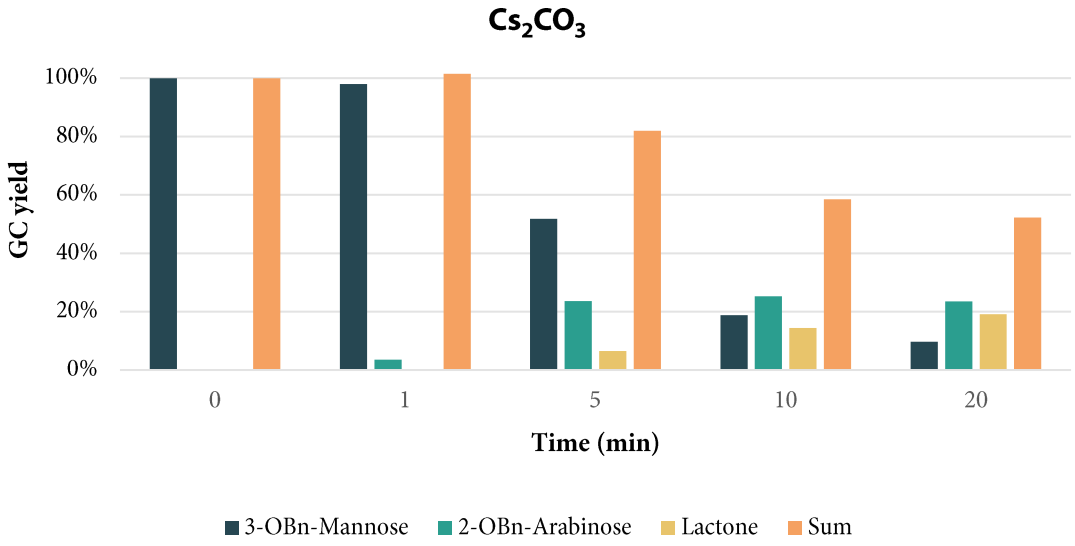
TIME	[5]	[6]	[7]	SUM
0 min	77%	0%	0%	77%
1 min	67%	12%	0%	78%
5 min	51%	41%	0%	92%
10 min	71%	30%	0%	101%
20 min	77%	0%	0%	77%
30 min	67%	12%	0%	78%



TIME	[5]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	98%	0%	0%	98%
5 min	64%	15%	0%	78%
10 min	40%	40%	5%	86%
20 min	14%	46%	10%	70%
30 min	100%	0%	0%	100%



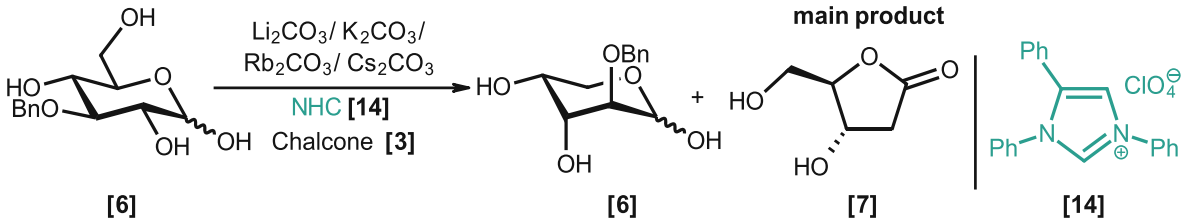
TIME	[5]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	98%	4%	3%	105%
5 min	42%	17%	10%	70%
10 min	20%	19%	16%	55%
20 min	10%	19%	22%	50%

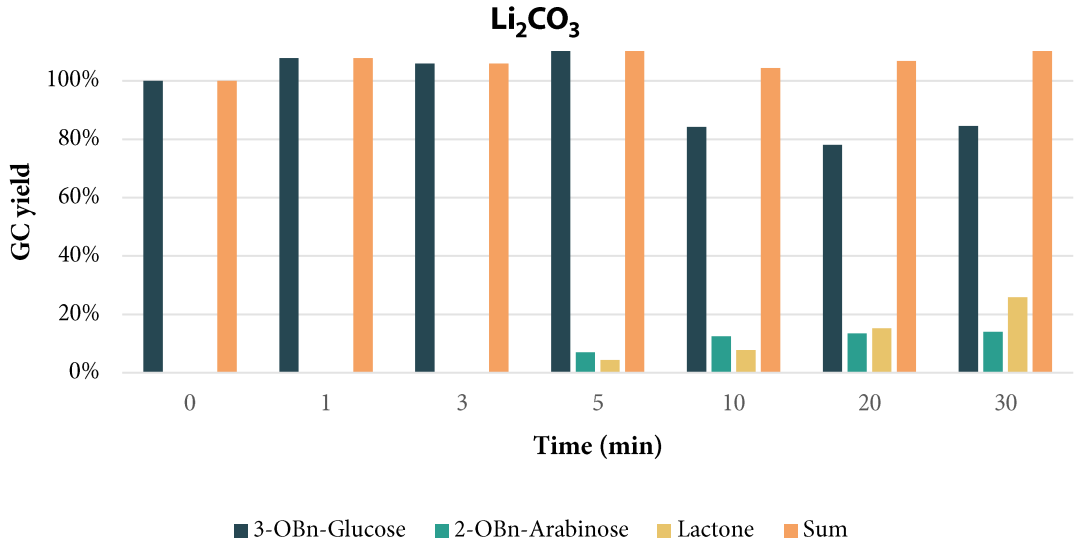


TIME	[5]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	98%	3%	0%	102%
5 min	52%	24%	6%	82%
10 min	19%	25%	14%	59%
20 min	10%	23%	19%	52%

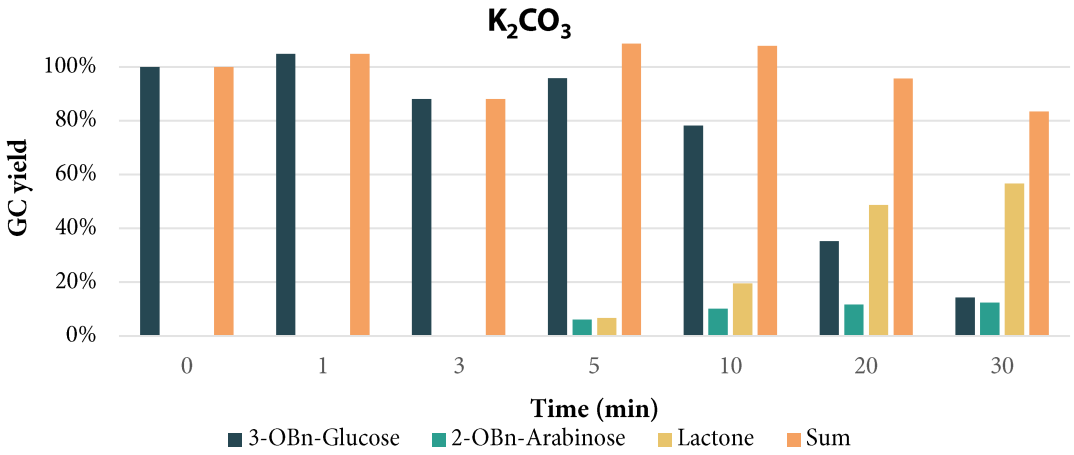
3-*O*Bn-Glucose [8] with Triphenyl triazolium catalyst [14]

3-*O*Bn-glucose[**8**] (1.00 eq) was dehomologated according to the general procedure described above, with triphenyl triazolium catalyst [**14**] (0.25 eq.), chalcone [**3**] (2.00 eq.) and different bases (Li_2CO_3, K_2CO_3, Rb_2CO_3, Cs_2CO_3) (0.20 eq.). (Summary and discussion of the shown results: *Chart 9* on page *55*)

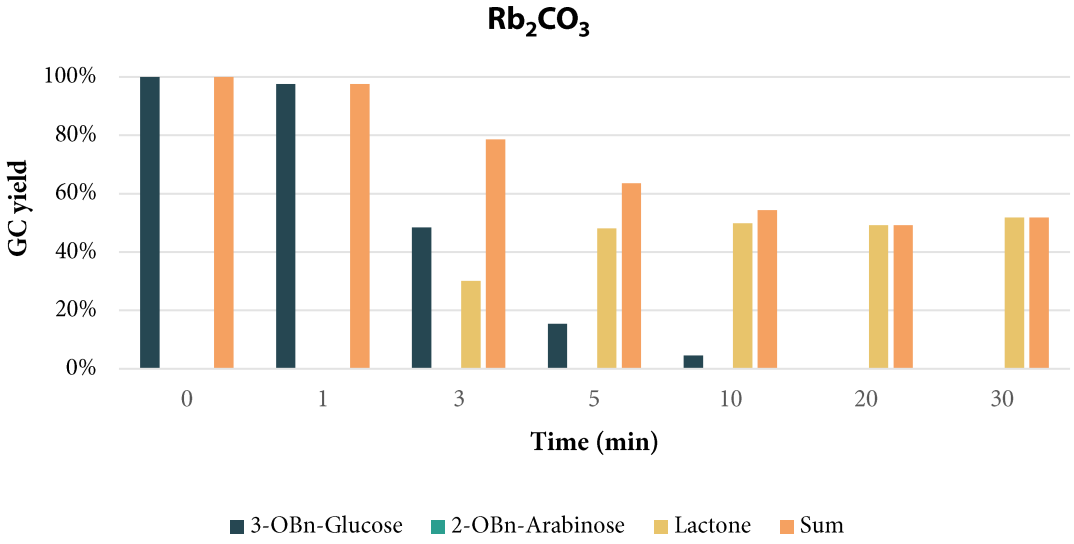




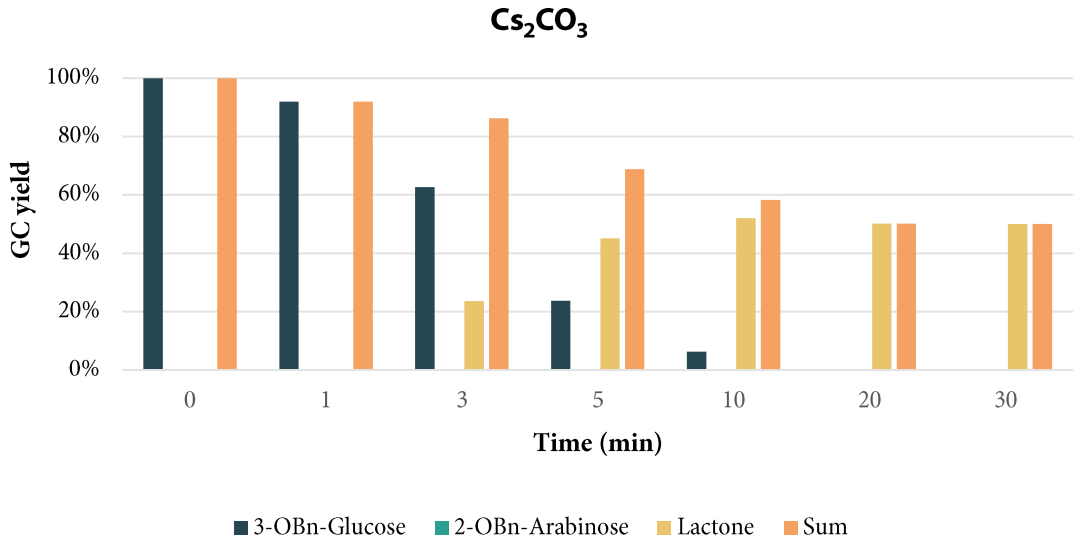
TIME	[8]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	108%	0%	0%	108%
3 min	106%	0%	0%	106%
5 min	113%	7%	4%	124%
10 min	84%	12%	8%	104%
20 min	78%	13%	15%	107%
30 min	85%	14%	26%	124%



TIME	[8]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	105%	0%	0%	105%
3 min	88%	0%	0%	88%
5 min	96%	6%	7%	109%
10 min	78%	10%	20%	108%
20 min	35%	12%	49%	96%
30 min	14%	12%	57%	83%



TIME	[8]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	98%	0%	0%	98%
3 min	49%	0%	30%	79%
5 min	15%	0%	48%	64%
10 min	5%	0%	50%	54%
20 min	0%	0%	49%	49%
30 min	0%	0%	52%	52%



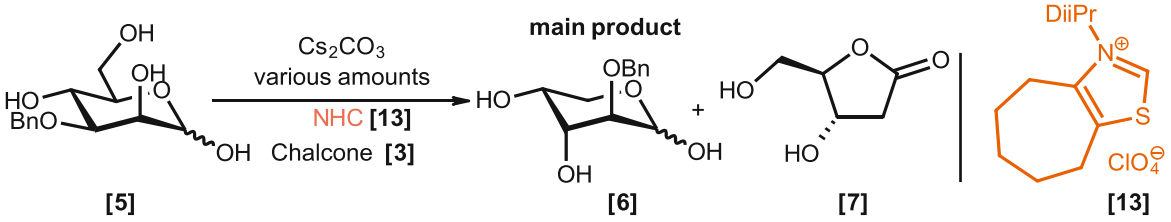
TIME	[8]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	92%	0%	0%	92%
3 min	63%	0%	24%	86%
5 min	24%	0%	45%	69%
10 min	6%	0%	52%	58%
20 min	0%	0%	50%	50%
30 min	0%	0%	50%	50%

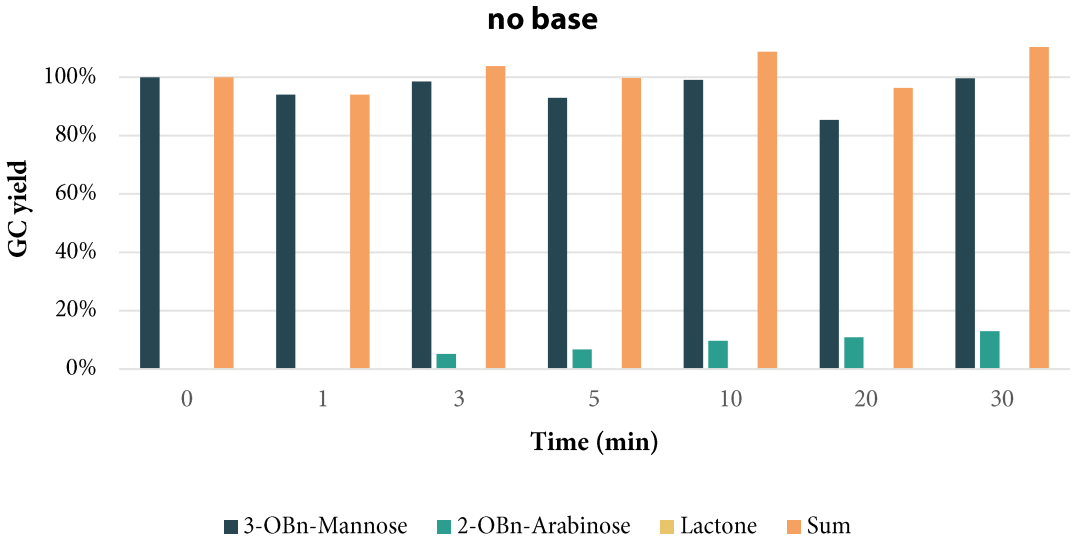
C.6.3.2. Screening with alternating amounts of Cs_2CO_3.

Full timecourses of the screening reactions discussed and summarised in chapter *B.3.3* are shown here.

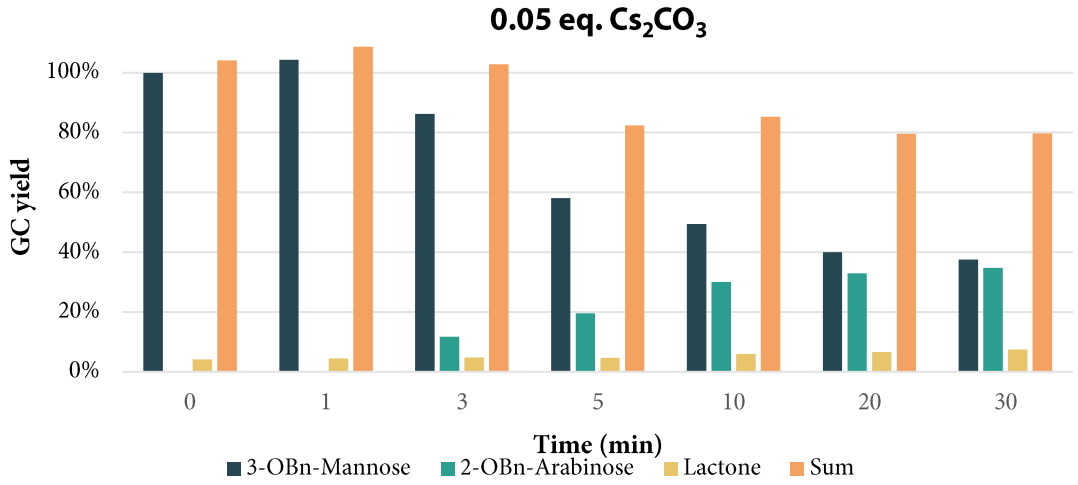
3-*O*Bn-Mannose [5] with DiiPr-Catalyst [13]

3-*O*Bn-mannose **[5]** (1.00 eq) was dehomologated according to the general procedure described above, with DiiPr catalyst **[13]** (0.25 eq.), chalcone **[3]** (2.00 eq) and different concentration of Cs_2CO_3 (0 eq., 0.05 eq., 0.10 eq., 0.20 eq., 0.30 eq.). (Summary and discussion of the shown results: *Chart 11* on page 57)

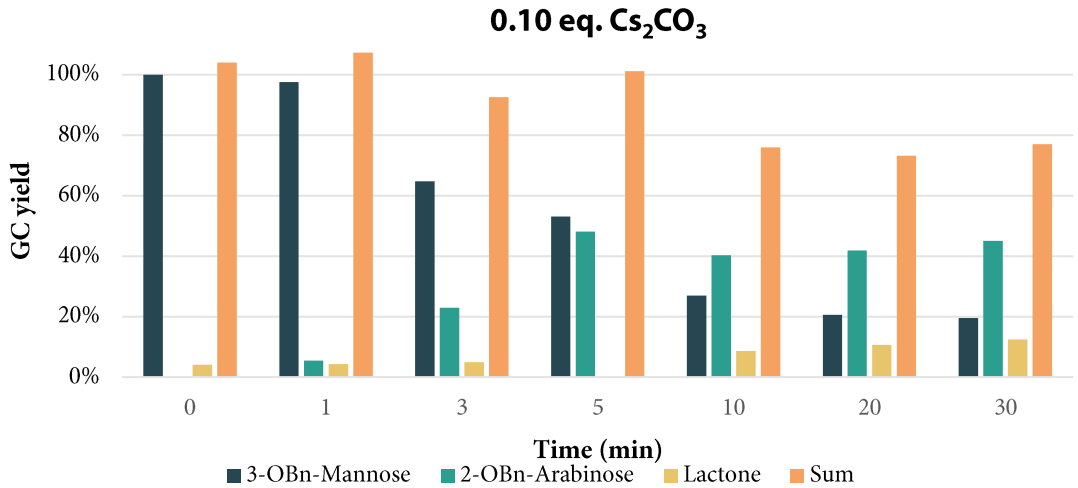




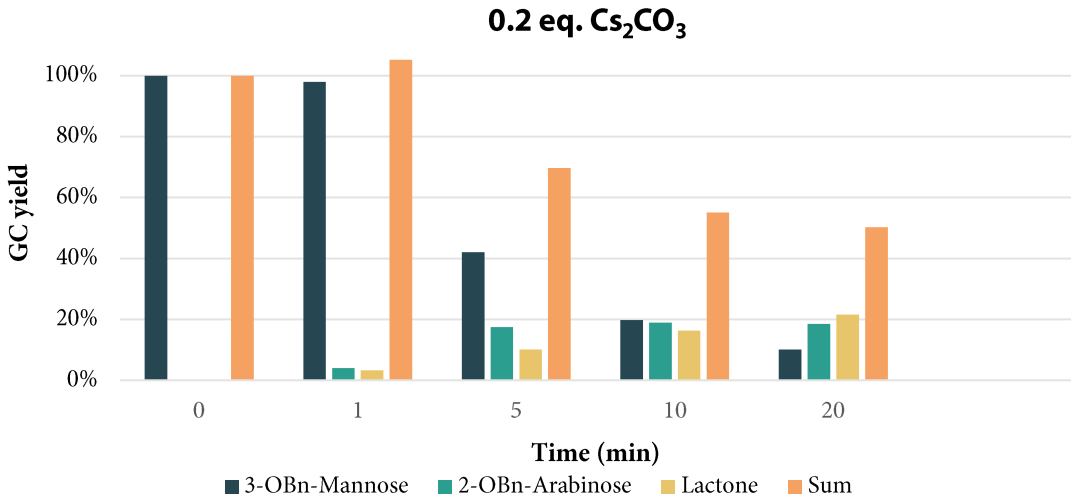
TIME	[5]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	94%	0%	0%	94%
3 min	99%	5%	0%	104%
5 min	93%	7%	0%	100%
10 min	99%	10%	0%	109%
20 min	85%	11%	0%	96%
30 min	100%	13%	0%	113%



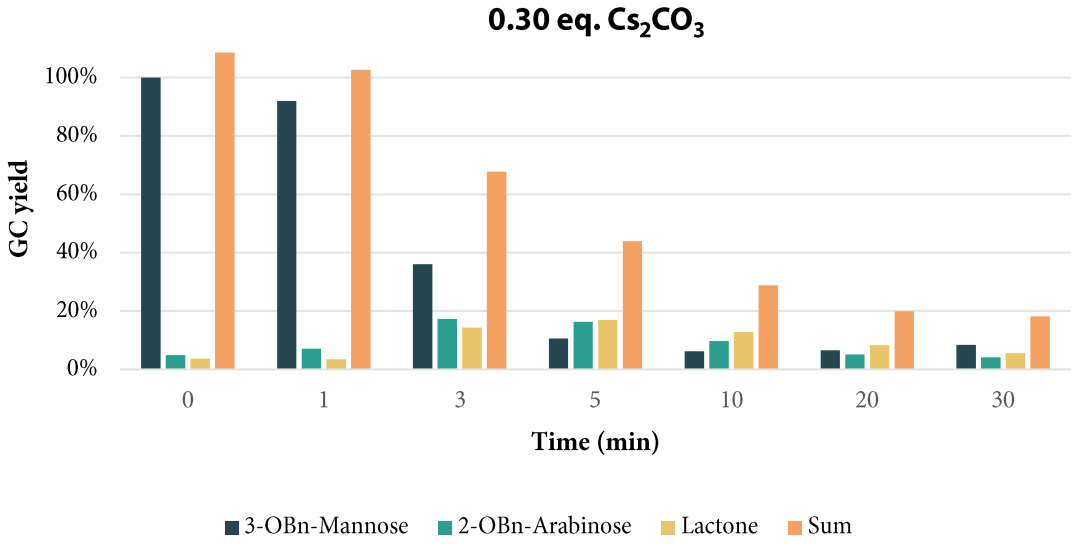
TIME	[5]	[6]	[7]	SUM
0 min	100%	0%	4%	104%
1 min	104%	0%	4%	109%
3 min	86%	12%	5%	103%
5 min	58%	20%	5%	82%
10 min	49%	30%	6%	85%
20 min	40%	33%	7%	80%
30 min	37%	35%	7%	80%



TIME	[5]	[6]	[7]	SUM
0 min	100%	0%	4%	104%
1 min	98%	6%	4%	107%
3 min	65%	23%	5%	93%
5 min	53%	48%	0%	101%
10 min	27%	40%	9%	76%
20 min	21%	42%	11%	73%
30 min	20%	45%	12%	77%



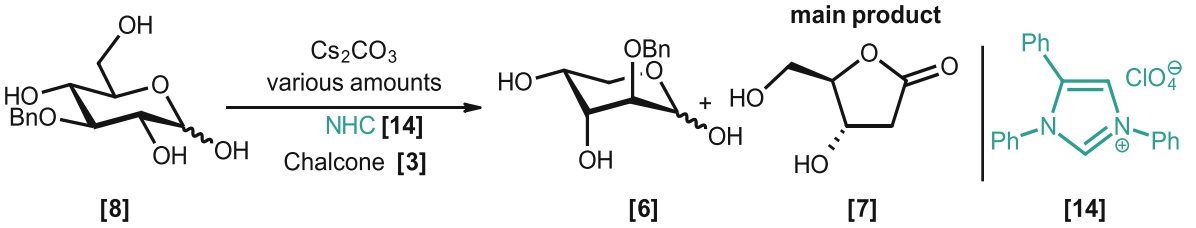
TIME	[5]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	98%	4%	3%	105%
5 min	42%	17%	10%	70%
10 min	20%	19%	16%	55%
20 min	10%	19%	22%	50%

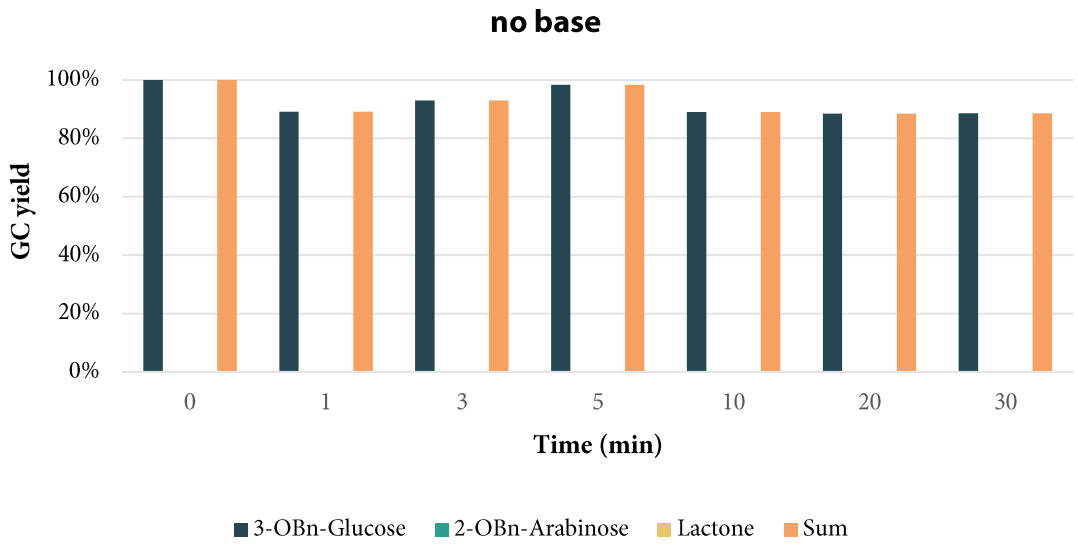


TIME	[5]	[6]	[7]	SUM
0 min	100%	5%	4%	109%
1 min	92%	7%	4%	103%
3 min	36%	17%	14%	68%
5 min	11%	16%	17%	44%
10 min	6%	10%	13%	29%
20 min	6%	5%	8%	20%
30 min	8%	4%	6%	18%

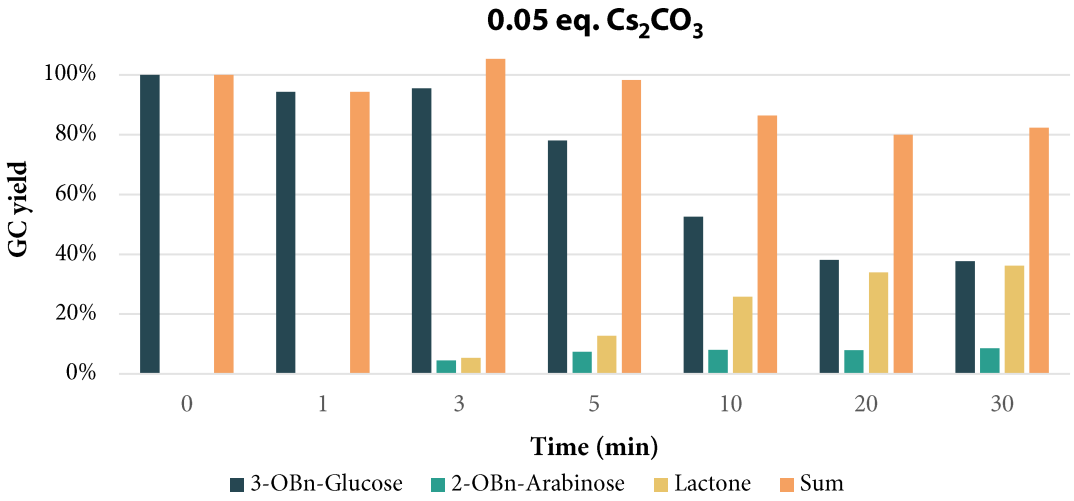
3-*O*Bn-Glucose [8] **with Triphenyl triazolium Catalyst** [14]

3-*O*Bn-glucose**[8]** (1.00 eq) was dehomologated according to the general procedure described above, with triphenyl triazolium catalyst **[14]** (0.25 eq.), chalcone **[3]** (2.00 eq.) and concentrations of Cs_2CO_3 (0 eq., 0.05 eq., 0.10 eq., 0.20 eq., 0.30 eq.). (Summary and discussion of the shown results: in *Chart 12* on page 58)

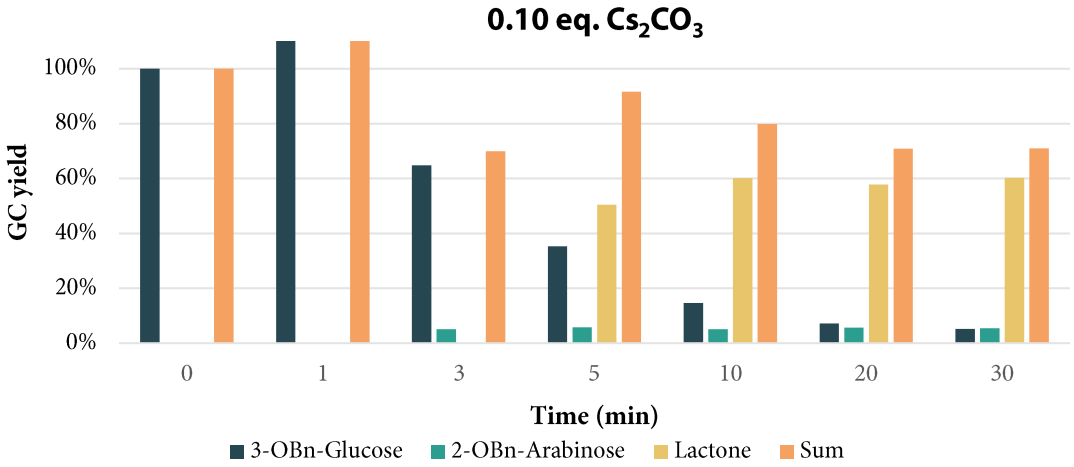




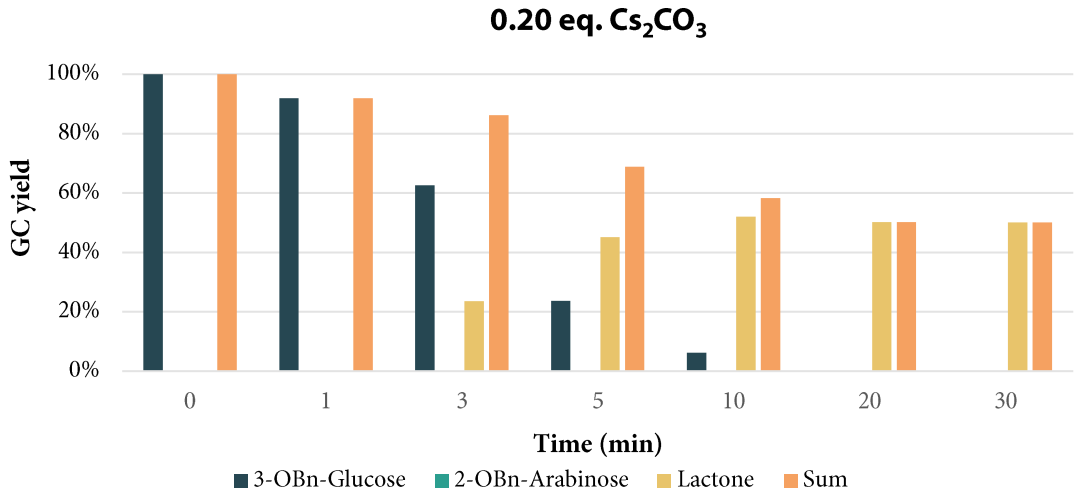
TIME	[8]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	89%	0%	0%	89%
3 min	93%	0%	0%	93%
5 min	98%	0%	0%	98%
10 min	89%	0%	0%	89%
20 min	89%	0%	0%	89%
30 min	89%	0%	0%	89%



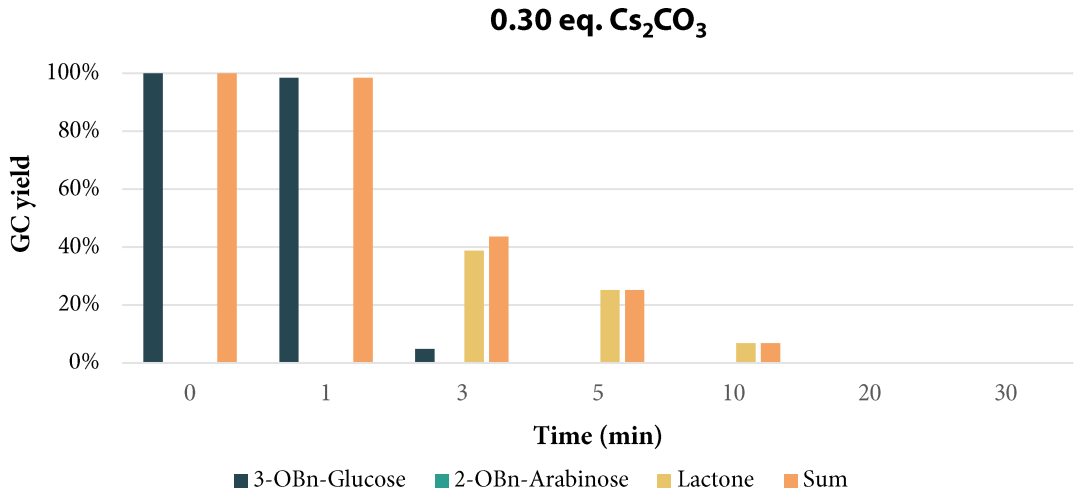
TIME	[8]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	94%	0%	0%	94%
3 min	95%	5%	5%	105%
5 min	78%	7%	13%	98%
10 min	53%	8%	26%	86%
20 min	38%	8%	34%	80%
30 min	38%	9%	36%	82%



TIME	[8]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	115%	0%	0%	115%
3 min	65%	5%	0%	70%
5 min	35%	6%	50%	92%
10 min	15%	5%	60%	80%
20 min	7%	6%	58%	71%
30 min	5%	5%	60%	71%



TIME	[8]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	92%	0%	0%	92%
3 min	63%	0%	24%	86%
5 min	24%	0%	45%	69%
10 min	6%	0%	52%	58%
20 min	0%	0%	50%	50%
30 min	0%	0%	50%	50%



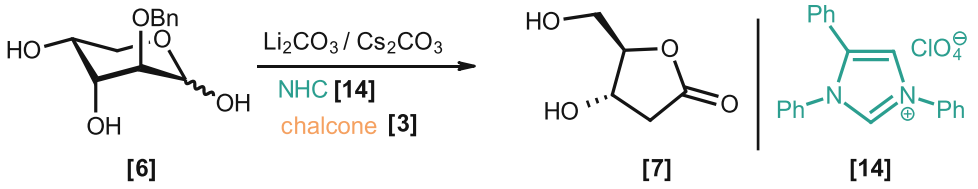
TIME	[8]	[6]	[7]	SUM
0 min	100%	0%	0%	100%
1 min	99%	0%	0%	99%
3 min	5%	0%	39%	44%
5 min	0%	0%	25%	25%
10 min	0%	0%	7%	7%
20 min	0%	0%	0%	0%
30 min	0%	0%	0%	0%

C.6.3.3. Lactone Formation from 2-OBn-Arabinose ***[6]***

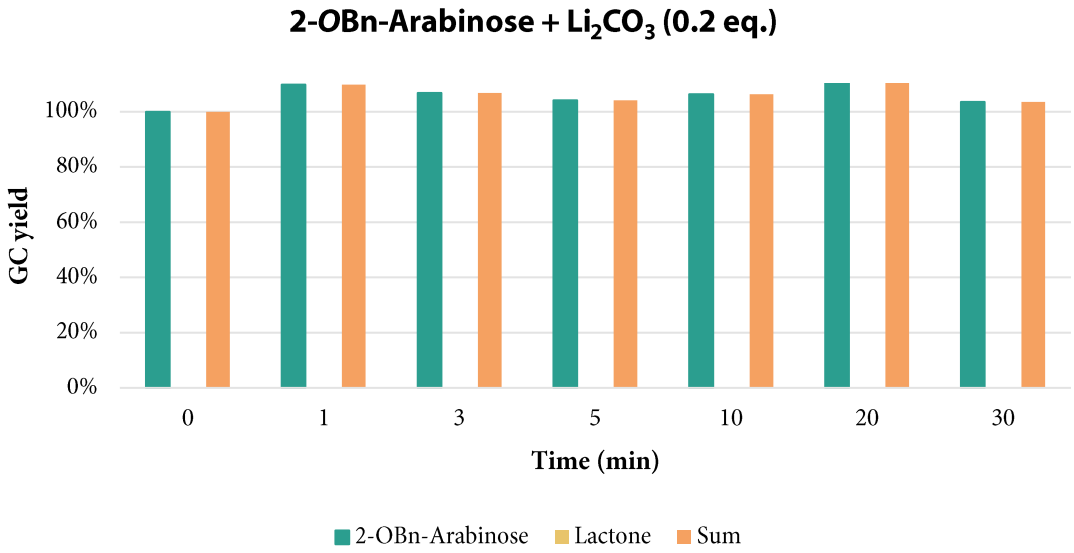
Full timecourses of the screening reactions discussed and summarised in chapter *B.4.2* are shown here.

2-*O*Bn-Arabinose [6] **with Triphenyl Catalyst** [**14**]

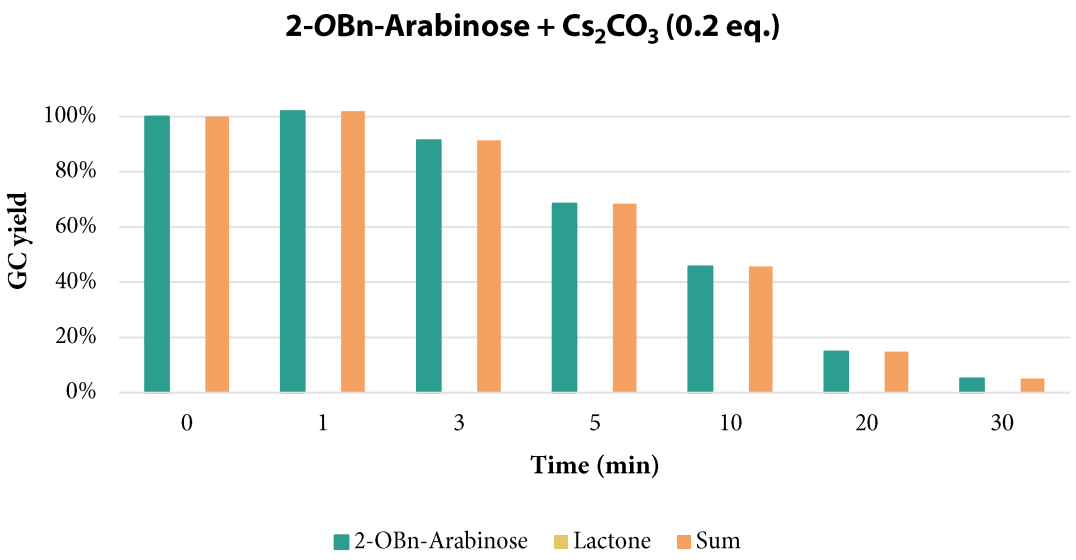
2-*O*Bn-arabinose [**6**] (1.00 eq) was directly used in the general dehomologation procedure described above, with triphenyl triazolium catalyst [**14**] (0.25 eq.), standard chalcone [**3**] (2.00 eq) and either Li_2CO_3 (0.20 eq.) or Cs_2CO_3 (0.20 eq.). (Summary and discussion of the shown results: *Chart 15* on page 61)



[6] [7] [14]



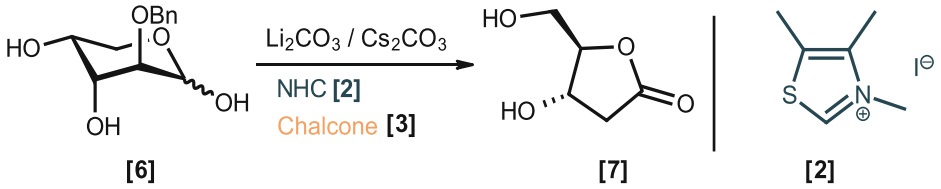
TIME	[6]	[7]	SUM
0 min	100%	0%	100%
1 min	110%	0%	110%
3 min	107%	0%	107%
5 min	104%	0%	104%
10 min	106%	0%	106%
20 min	114%	0%	114%
30 min	104%	0%	104%



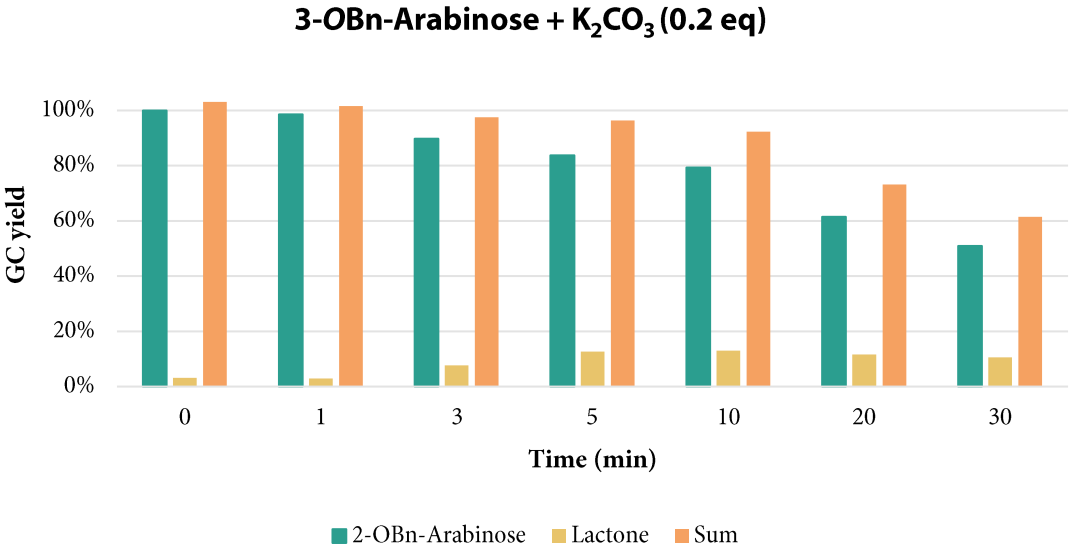
TIME	[6]	[7]	SUM
0 min	100%	0%	100%
1 min	102%	0%	102%
3 min	91%	0%	91%
5 min	68%	0%	68%
10 min	46%	0%	46%
20 min	15%	0%	15%
30 min	5%	0%	5%

2-*O*Bn-Arabinose [6] with Trimethyl Catalyst [14]

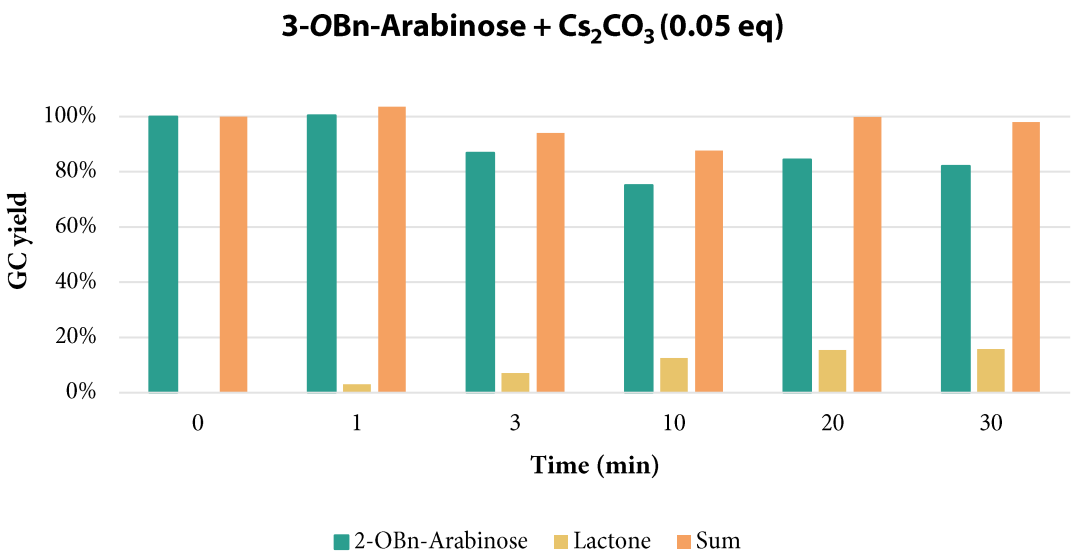
2-*O*Bn-arabinose **[6]** (1.00 eq) was directly used in the general dehomologation procedure described above, with triphenyl triazolium catalyst **[14]** (0.25 eq.), chalcone **[3]** (2.00 eq) and either K_2CO_3 (0.20 eq.) or Cs_2CO_3 (0.05 eq.). (Summary and discussion of the shown results: *Chart 16* on page 62)



[6] **[7]** **[2]**



TIME	[6]	[7]	SUM
0 min	100%	3%	103%
1 min	99%	3%	102%
3 min	90%	8%	98%
5 min	84%	13%	96%
10 min	79%	13%	92%
20 min	62%	12%	73%
30 min	51%	11%	61%



TIME	[6]	[7]	SUM
0 min	100%	0%	100%
1 min	101%	3%	104%
3 min	87%	7%	94%
10 min	75%	13%	88%
20 min	84%	16%	100%
30 min	82%	16%	98%

D. Appendix

Curriculum vitae

Christoph Suster

Wassergrabenweg 6A, A-2384 Breitenfurt | christoph.suster@tuwien.ac.at

Education

May 2018 – today

TU Wien, Vienna, Austria

Master study programme Technical Chemistry with focus on synthetic organic chemistry (066 490)

October 2014 – May 2018

TU Wien, Vienna, Austria

Bachelor study programme in Technical Chemistry

Thesis: Rapid decoration of thio-*manno*-heptosides towards Lipopolysaccharide substructures. Supervised by Prof. Dr. Mihovilovic and Dr. Christian Stanetty

September 2008 – Juni 2013

HBLVA17 Rosensteingasse, Vienna, Austria

Specialisation in Biochemistry

Thesis: Modellierung zur Glykosylierung von Deoxynivalenol und anschließender Entschützung mit Schweineleberesterase

Supervision: Prof. Dr. Johannes Fröhlich and Dr. Philipp Frumann

Publications

February 2021

Efficient Acylation of Sugars and Oligosaccharides in Aqueous Environment Using Engineered Acyltransferases

*Simon P. Godehard, Henrik Müller, Christoffel P. S. Badenhorst, Christian Stanetty, **Christoph Suster**, Marko D. Mihovilovic, and Uwe T. Bornscheuer**

ACS Catalysis

Citation: ACS Catalysis 2021 11 (5), 2831-2836 DOI: 10.1021/acscatal.1c00048

May 2020

Straight Forward and Versatile Differentiation of the L-*glycero* and D-*glycero*-D-*manno* Heptose Scaffold

***Christoph Suster**, Ian R. Baxendale, Marko D. Mihovilovic, Christian Stanetty**

Frontiers in Chemistry

Citation: Front. Chem. 8:625. doi: 10.3389/fchem.2020.00625

Work Experience

2013 - 2018 Summer Internships (11 months total)	Baumit GmbH, Waldegg/Wopfing, Austria **Analytical Laboratory for cement production** RFA, XRD, Laser diffraction
August 2019 – March 2021	Scientific co-worker @ BSC Research Group for contracted NMR-analysis by cooperation partners (academia & industry)
2016-2020	TU Wien, Vienna, Austria **Tutorials in several Laboratory courses** Instrumental and Bioanalytical Laboratory, Synthesis Laboratory Course

Extracurricular Activities

October 2018 – June 2019	Chess Teacher in elementary schools for the organisation SPIDS (Schachpädagoik in die Schulen)
May 2017, May 2018	Volunteer at TEDxTUWien, annual meeting, TU Wien, Vienna, Austria
September 2013 - today	Voluntary work as ambulance driver and paramedic at Samariterbund Lower Austria (Gaaden im Wienerwald)

Additional Skills

Fond Computer Skills	Programming: C#, JavaScript (Typescript, React), PHP, HTML, VBA Office MS-Office: Word, Excel, Access, PowerPoint Chemistry related software: MestReNova (including programming of scripts), ChemDraw, ChemDoodle, SciFinder, Reaxys, Berkeley Madonna, Origin Pro
Peer Mediation	16 h course in Peer Mediation in 2010
Paramedic	“Rettungssanitäter”, since 2013.

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