Universität Rostock

Traditio et Innovatio

Application of Glucose-based Salts in Catalysis

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by

Mirai Komabayashi

born 17.08.1997 in Yamagata

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Mirai Komabayashi

Rostock,

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1. Reviewer: Dr. rer. nat. habil. Stefan Jopp, University of Rostock, Germany

2. Reviewer: Prof. Dr. Toshiki Nokami, Tottori University, Japan

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Abstract

Carbohydrates are known as an abundant and readily available natural resource. Scientists have been using this class of compounds for a long time as various materials. Recently, carbohydrates have attracted attention as a promising materials for organocatalysis. They have a natural potential for chiral induction, multiple hydroxyl groups, and biocompatibility.

Despite these benefits, the synthesis of suitable (ionic) carbohydrate-based catalysts needs multiple synthetic steps due to the structural complexity of carbohydrates. The relationship between the carbohydrate structure and the catalytic activity also still remains ambiguous.

Thus, ionic catalysts from glucose were synthesized in short steps in this work. The salts were applied in three different types of reactions: Homogeneous catalysis, metal complex synthesis and phase-transfer catalysis.

In the first project, glucose-based imidazolium ionic liquids (ILs) were employed for aza-Diels alder reactions. The catalysts showed significantly higher activity than an inorganic salt or commercial ILs. The effects of many structural functionalizations on the catalytic activity were studied and the organocatalyst was applied for wide range of dienophile substrates.

In the second project, the glucose-based imidazolium salts were applied for the formation of novel palladium complexes, which were prepared in only 4 steps. The influence of the functionalization of the Pd-complexes for the model Suzuki-Miyaura reaction has been studied. The mesityl-substituted complex was the most reactive catalyst, working with a low catalyst loading of 0.005 mol% with nearly full conversion.

As the third project, new glucose-based ammonium and imidazolium salts bearing different lengths of alkyl chain, glucoside substitution, and protecting groups were synthesized. These catalysts were applied for a phase-transfer Kolbe nitrile synthesis. The best phase-transfer catalyst, bearing methyl-protecting groups and a cationic dodecyl-imidazolium group, reached nearly full conversion and provided a clean nitrile product, which can be collected from the organic phase without any further purification.

Kurzfassung

Kohlenhydrate sind eine weit verbreitete natürliche Ressource, weshalb Wissenschaftler diese schon seit langer Zeit für unterschiedlichste Materialen und Anwendungen untersuchen. Seit kurzem sind Kohlenhydrate als Organokatalysatoren ins Interesse gerückt, aufgrund ihrer natürlichen Fähigkeiten zur chiralen Induktion, Wasserstoffbrückenbindungen und Biokompatibilität.

Trotz dieser Vorteile erschwert die strukturelle Komplexität von Kohlenhydraten die meist mehrstufige Synthese von (ionischen) Kohlenhydrat-basierten Katalysatoren. Außerdem bleibt der Zusammenhang zwischen Kohlenhydratstruktur und katalytischer Aktivität bis heute oft unklar.

Aus diesem Grund wurden in dieser Arbeit neue ionische Glucose-basierte Katalysatoren hergestellt und in drei verschieden Reaktionen untersucht: Homogener Katalyse, Synthese von Metallkomplexen und Phasentransferkatalyse.

Im ersten Projekt wurden Glucose-basierte ionischen Flüssigkeiten (ILs) in einer aza-Diels-Alder Reaktion untersucht. Die Effekte von zahlreichen Funktionalisierungen auf die katalytische Aktivität wurden untersucht und der beste Glucose-basierte Organokatalysator zeigte eine deutlich höhere Aktivität als vergleichbare Metallsalze oder kommerzielle ILs.

Im zweiten Projekt wurden neue Palladiumkomplexe in 4 Schritten aus den Glucose-basierten Salzen hergestellt. Diese Komplexe wurden ausgiebig in einer Suzuki-Miyaura Modellreaktion in ihrer Aktivität in Abhängigkeit von der Struktur der Kohlenhydrate untersucht. Der beste Katalysator erreichte einen vollständigen Umsatz mit nur 0.005 mol% Katalysatorladung.

Als drittes Projekt wurden neue Glucose-basierte Ammonium- und Imidazolium Salze mit unterschiedlichen Alkylresten, Glycosidresten und Schutzgruppen synthetisiert und als Phasentransferkatalysatoren in einer Kolbe Nitril Synthese untersucht. Der beste Katalysator erreichte einen vollständigen Umsatz und das Nitrilprodukt konnte ohne weitere Aufarbeitung in Reinform aus der organischen Phase gewonnen werden.

List of abbreviations

CHILs	Carbohydrate-based Ionic Liquids
RTILs	Room Temperature Ionic Liquids
LUMO	Lowest Unoccupied Molecular Orbital
NHC	*N*-Heterocyclic Carbene
PEPPSI	Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation.
PTC	phase-transfer catalysis
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
OTf	triflate/ trifluoromethanesulfonate
NTf_2	Bistriflimide/ bis(trifluoromethane)sulfonimide
GMIM-I	1-(Methyl-α-D-glucopyranosid-6-yl)-3-methylimidazoliumiodid
AcO-GMIM-I	1-(Methyl-2,3,4-O-acetyl-α-D-glucopyranosid-6-yl)-3-methylimidazolium iodide
PhO-GMIM-I	1-(Phenyl-ß-D-glucopyranosid-6-yl)-3-methylimidazolium iodide
L-GMIM-I	1-(Methyl-α-L-glucopyranosid-6-yl)-3-methylimidazoliumiodid
AcO-GMIM-Ph-I	1-(Phenyl-2,3,4-O-acetyl-ß-D-glucopyranosid-6-yl)-3-methylimidazolium iodide
GDoMe2-I	*N*-Dimethyl-*N*-dodecyl-*N*-(methyl-α-D-glucopyranosid-6-yl) ammonium iodide
NOESY	Nuclear Overhauser Effect Spectroscopy

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1. Introduction

1.1 Carbohydrate-based salts as catalysts

Carbohydrates are one of the most abundant natural resources. Compounds of this class have garnered significant interest in recent years as a sustainable, renewable resource. Recently, several Carbohydrate-Based compounds have been employed as catalysts in asymmetric synthesis.[1]

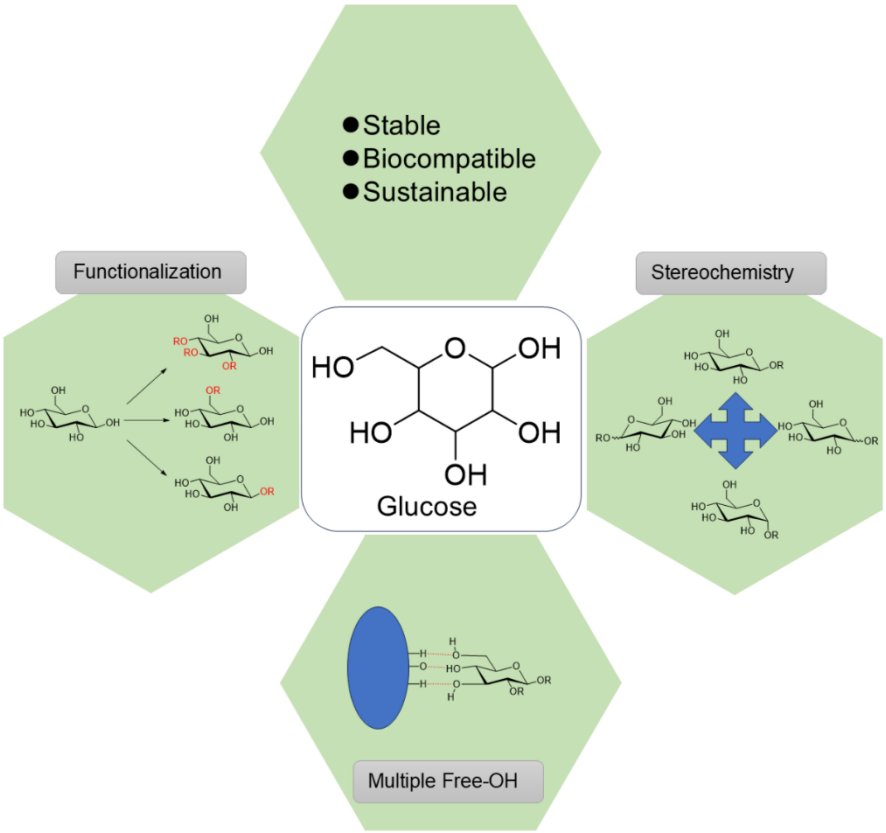
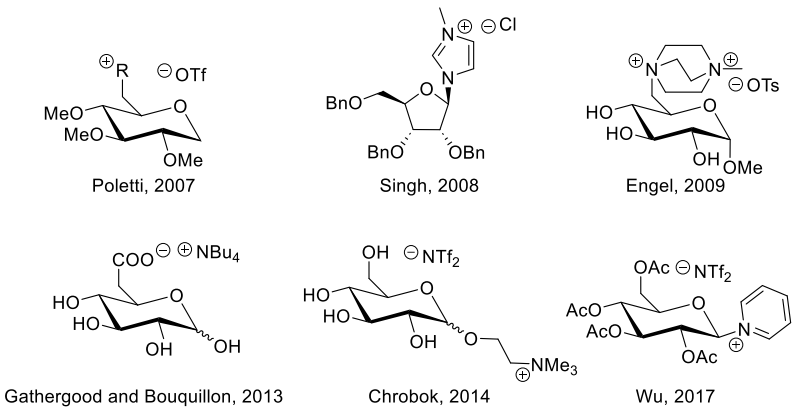


Figure 1. Beneficial properties of carbohydrates for catalyst design

Carbohydrates provide several synthetic benefits for catalysts (Figure 1). First, the notable characteristics of carbohydrates are hydrogen bonding and a wide scope of properties from free hydroxyl groups. Hydroxyl groups can form hydrogen bonds with substrates. They also ensure diversity in introducing functional groups. This synthetic flexibility enables various physical properties and structures to be introduced.

Second, monosaccharide skeletons have an inherent optical activity. This stable structure imposes stereochemical constraints. Combined with multiple hydroxyl groups, it enables control of the ring conformation of the ring. For example, Peddinti *et al*.[2] proposed a mechanism that forms a hydrogen bond in the transition state during the asymmetric Mannich reaction. It results in an effect of selectivity. Chrobok *et al.*[3] also suggested that hydrogen bonding by free hydroxyl groups is involved in the catalytic activity for the Diels-Alder reaction.



Scheme 1. Reported Carbohydrate-besed Ionic Liquids (CHILs).[3–8]

Salts derived from carbohydrates are most commonly in the form of ammonium salts[5,7,8] or uronic acid salts (Scheme 1).[6] Quarternary ammonium salts play an important role in the field of organic synthesis, particularly in Carbohydrate-Based Ionic Liquids (CHILs). The first synthesis of CHILs starting from Glucose was reported by Poletti *et al.* in 2007.[4] Since then, many CHILs of other monosaccharides have been reported over time.[9–11] Homogeneous catalysis is the most popular application of compounds in this class.[9,11] For example, CHILs have been applied for the Michael reaction,[12–14] and selective hydrogenation.[6] Another major application of carbohydrates in catalysis are coordination complexes. The multiple hydrogen bonds from the carbohydrate can stabilize the coordination complex. The confirmation of the monosaccharide ring together with the

introduction of an anchoring group can enhance the coordination ability.[15,16] Some asymmetric synthesis catalyzed by complexes with various metals, like rhodium,[17,18] titanium,[19] and palladium ions,[20,21] have been reported.

1.2 Diels-Alder reaction and its catalysis

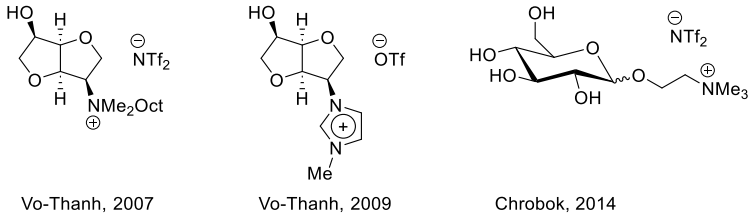
The Diels-Alder reaction is the most famous [4+2] cyclization reaction,[22,23] which provides a six-membered ring from a diene and a dienophile. Since the discovery of the reaction,[24] this straightforward methodology is well known as a strong strategy for natural[25] or pharmaceutical products. Due to the concerting mechanism without a charge transfer, this synthesis affords high stereospecificity.[26,27] This reaction aligns well with green chemistry principles and offers excellent atom economy.[28]

Lewis' acid is a typical example of a catalyst for the Diels-Alder reaction. Since the discovery that aluminum chloride promotes this reaction,[29] it has been widely recognized as a catalyst for the Diels-Alder reaction.[30] This catalytic activity is caused by the LUMO energy of the dienophile and activates the dienophile or reduces Pauli repulsion.[31–33]

Metal salts and complexes are common heterogeneous catalysts. Metal complexes with Zirconium,[34] Copper,[26] and Silver[35] have been reported for the Diels-Alder reaction. Organic compounds were less reported than metal catalysis. However, organocatalyzed Diels-Alder reactions with secondary amines,[36] including imidazolidine and secondary prolinols,[37] have been reported.

CHILs are another direction of organocatalysis. Previous investigations mentioned that interactions such as high polarity and coordination between the cation and the dienophile can affect reaction rate and endo/exo selectivity.[38,39] As a first example, Isosorbide-based CHILs were reported by Vo-Thanh *et al.* (Scheme 2).[40,41] These CHILs were employed in an aza-Diels-

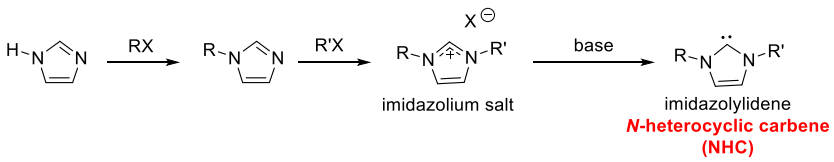
Alder reaction with an imine and Danishefsky's diene. Subsequently, Chrobok *et al.*[3] reported simpler Glucose-based CHILs catalysts (Scheme 1). These Glucose-based catalysts promote the reaction quickly, with high yield and selectivity. Both Vo-Thanh *et al.* and Chrobok *et al.* mentioned the clear differences between acetyl-protected and OH-free CHILs, with free hydroxyl groups being clearly preferable. These results show the possibility that free hydroxy groups contribute to catalytic activity.



Scheme 2. CHILS-organocatalysts for (aza-)Diels-Alder reactions by Vo-Thanh *et al.*[40,41] and Chrobok *et al.*[3]

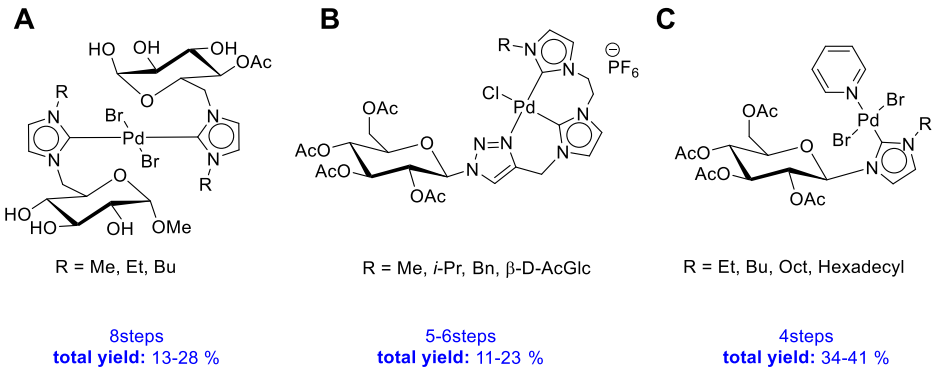
1.3 Palladium-NHC complex catalysis in Suzuki-Miyaura reaction

N-heterocyclic Carbenes (NHCs) are a class of compounds that were first isolated in 1991.[42] As stable and easily isolatable carbenes, this class of compounds was explored as catalysts for a variety of catalytic systems.[43–45] Among several fields, ligands of complexes are the most promising application, since NHCs provide strong σ-donation and very stable carbene-metal bonds. In terms of synthetic routes, NHCs are usually prepared from heterocyclic compounds like imidazole and triazoles, which bear acidic CH bonds that can be deprotonated for carbene formation (Scheme 3). These NHC-metal complexes are generally stable and enable various functionalization and purification.[46]



Scheme 3. Synthesis of NHC from imidazole

Recently, the application of carbohydrate ligands for NHC complexes has been expanding.[47] They have chiral induction ability and high biocompatibility. This catalysis is expected to be an application for pharmacology and biological fields.[48] The improvement of physical properties is another benefit of carbohydrate-based complexes. Solubility in aqueous solution and reusability of NHC complexes can be enhanced through water-soluble carbohydrate ligands into NHC complex. This allows for a greener and more biocompatible reaction.[47]



Scheme 4. Previous works on glucose-based Palladium NHC complexes by A) Lin *et al.*[49], B) Nishioka *et al.*[50] and C) Zhou *et al.*[51]

The Suzuki-Miyamura reaction[52] is a widely known reaction used for the construction of C-C bonds with a palladium complex catalyst. Today, this reaction is essential for the functionalization of aromatic compounds and the synthesis of biaryls. Accordingly, the inherent stability and solubility in water of Carbohydrate-based NHCs are expected to extend the benefits of this coupling reaction. The Suzuki-Miyaura reaction has already been reported with carbohydrate-based pincer[50] and PEPPSI[51,53] complexes (Scheme 4). These reactions proceeded in water or ethanol with high conversion. However, the preparation of these complexes remains difficult, needing many reaction steps with overall low total yields. Furthermore, the structure-activity relationships between

the structure of the carbohydrate-based NHC ligand and the catalytic activity of the metal complex has barely been investigated.

1.4 Carbohydrate-based phase-transfer organocatalysis

Phase-transfer catalysis (PTC) is an emerging alternative method for a wide range of organic synthesis.[54–56] This method is capable of reactions between reagents with different solubilities in different phases.

Many nucleophiles are salts that are insoluble in organic solvents. On the other hand, the substrate or product is often not soluble in water. The range of solvents that are compatible with both the substrate and the nucleophile in these cases is thus limited to aprotic, non-polar solvents such as DMSO or DMF.[57] These solvents have the benefit of a broad solubility range, however, they also have high boiling points and are thus difficult to remove and are sometimes highly toxic, as in the case of DMF.

Therefore, PTC bypasses these problems by placing the nucleophile and the substrate in separate phases (usually aqueous and organic phase) and by promoting their interaction at the interface through phase-transfer catalysts.[54,55] These characteristics are expected to enable green, efficient, and sustainable reactions both at the laboratory and industrial scale. Furthermore, PTC also enables an easy purification process by separating the reagents in different phases.

Phase-transfer catalysts are organic catalysts that transport ions, commonly anions, between the organic and aqueous phases. First, the anion exchange between the phase-transfer catalyst and the nucleophile anion happens aqueous phase. Afterwards, this phase-transfer catalyst salt bearing the nucleophile moves to the organic phase participates in the reaction in the organic phase. Finally, the cation of the catalyst traps the excess anion from the nucleophilic reaction and moves back into the aqueous phase, reenacting the catalytic cycle.

The suggested mechanisms for this process can be divided into two broad types (Figure 2). One of that is a 2-phase mechanism.[58] In this hypothesis, the organic and the aqueous phases are completely separated, and the phase-transer catalyst is directly moving between both phases. Another hypothesis is the middle-phase mechanism.[56] In this case, the phase-transfer catalyst forms a mix phase between two phases. The reaction is carried out on the surface of this mix phase.

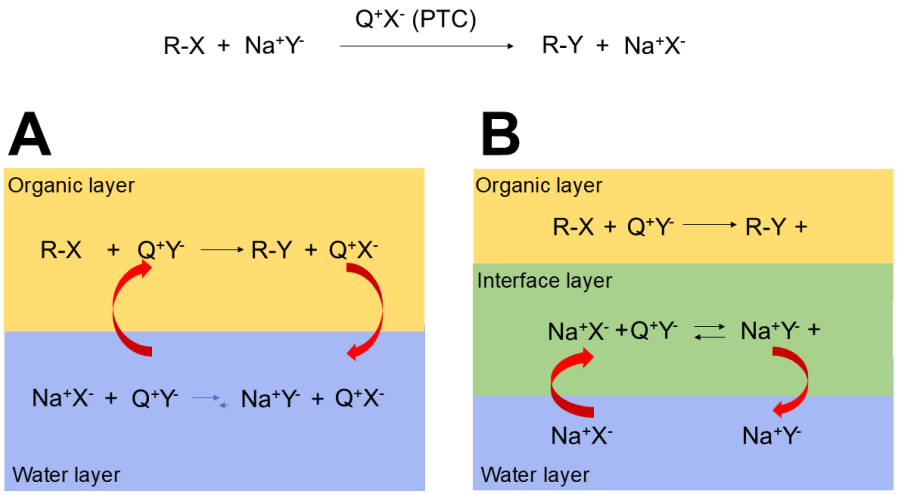


Figure 2. Proposed mechanism by A) Starks[58] and B) Mąkosza *et al.*[56]

The concept and mechanism were established by Charles Starks in 1971.[58] The most well-known and successful example of PTC is the Maruoka catalyst.[59,60] This catalysis was developed two decades after it was first mentioned by Starks. A binaphthyl-based chiral tertiary ammonium salt was applied for the asymmetric amino acid synthesis. After simplification for improvement, this PTC was also commercialized for the industrial field.

Carbohydrates are also suitable compounds for phase-transfer catalysis, due to their multiple hydroxyl groups and the potential to adjust their polarity by the introduction of functional groups. For example, Bakó *et al.*[61,62] applied glucose- and galactose-based azacrown ethers as phase-transfer catalysts for several asymmetric synthesis and Chrobok *et al.*[57] reported glucose-

based phase-transfer catalysts for the synthesis of chloroprene. The study of Chrobok *et al.* also gave insights into the cytotoxicity and biodegradability of their glucose-based phase-transfer catalysts.

Despite this progress in using carbohydrate-based phase-transfer catalysts for the PTC process, the direct influence of the carbohydrate and its functionalization on the phase-transfer catalysts solubility in aqueous and organic phases remains to be studied.

2. Goals of this PhD thesis

This PhD thesis aims to expand the range of applications of carbohydrate-based catalysts and to explore the interaction between the catalytic activity and the structure of the carbohydrate-based catalysts.

For a simple synthetic strategy, all glucose-based salts will be derived from a common starting material. These glucose-based salts will then be employed as catalysts in a homogeneous reaction, a metal complex synthesis, and for phase-transfer catalysis (Figure 3), proving the wide application range of these glucose-based salts in catalysis. In all three projects, the focus lies in the synthesis of several novel glucose-based salts with different functionalizations and in the study of the structure-activity relationships in a chosen model reaction.

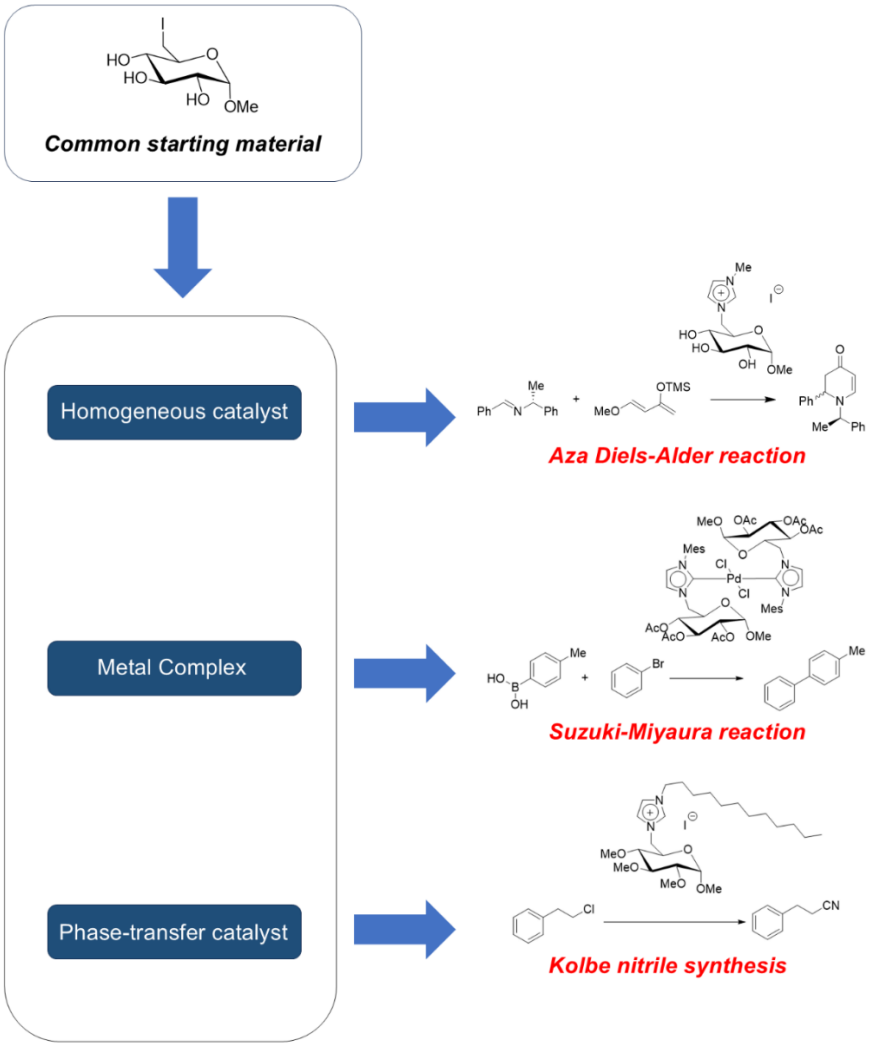
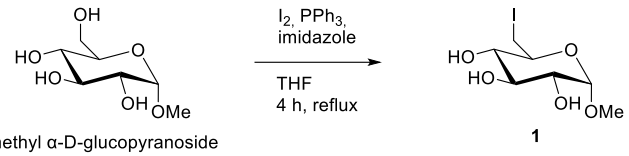


Figure 3. Overall view of project plan starting from common starting material.

3. Results and Discussion

3.1 The common synthetic pathway for the preparation of all organocatalysts

Most catalysts for the three projects of this thesis started from the common starting material **1** derived from methyl α-D-glucopyranoside (Scheme 5). This procedure was established in a previous work from the group of Jopp *et a*l.[63] In this Appel reaction, the hydroxyl group at the 6-position of the glucopyranoside is regioselectively transformed into an iodine group. This iodine will then act as a leaving group and subsequently as an anion for all catalyst synthesis discussed in the following parts.

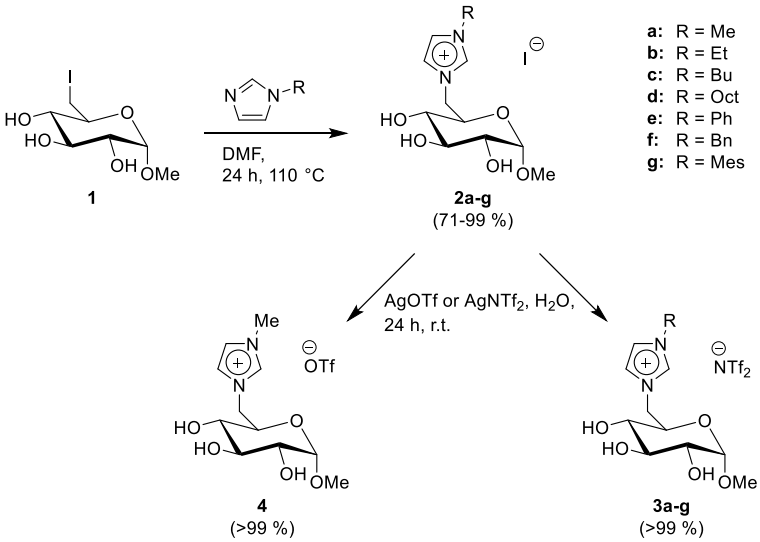


Scheme 5. Preparation of common starting material **1**

3.2 Aza Diels-Alder catalysis

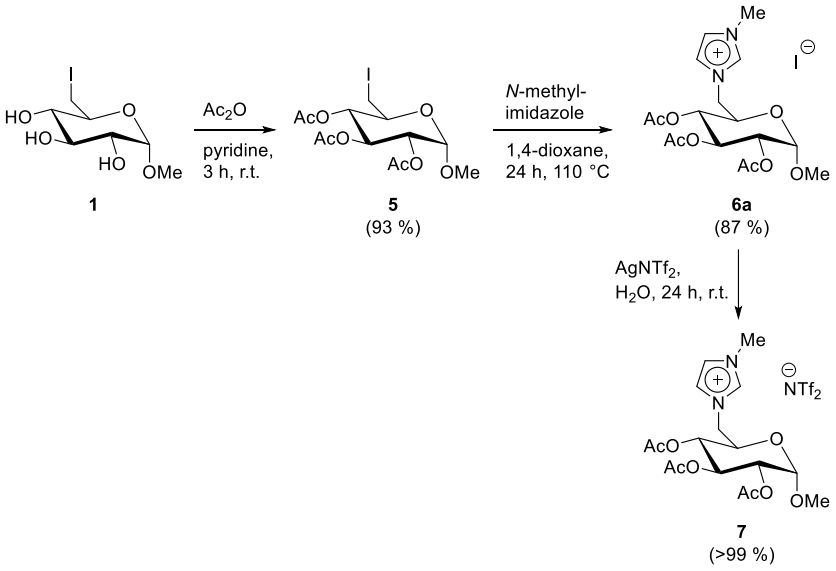
3.2.1 Preparation of the glucose-based organocatalysts

The synthesis was started from *N*-alkyl imidazolium salts along with basic procedure (Scheme 6). For evaluation of relationship between structure and catalytic activity, imidazole bearing linear alkyl chain from methyl to octy **2a-d** and aromatic substitutions, phenyl, benzyl and methyl **2e-g** group were introduced to 6-position. All these reactions were carried out in DMF, 110 °C. Both OTf- **4** and NTf_2- **3a-g** catalysts were obtained via anion exchange with silver salts. These anions were reported to improve catalytic activity in previous reports.[3,40,41] The anion exchange proceeds in nearly quantitative amounts.



Scheme 6. Synthesis of glucosyl imidazolium ionic liquids with varying *N*-substituted imidazoles and varying anions.

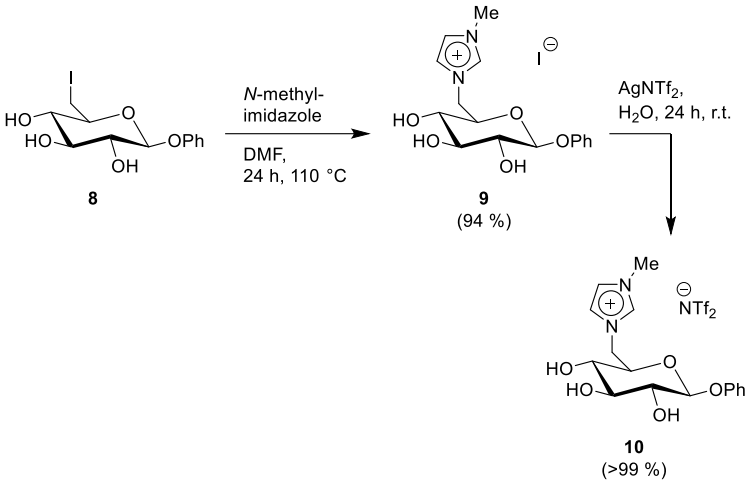
A protected catalyst was also prepared with the aim of studying the effect of hydrogen bonding coming from free hydroxyl groups.[3,40,41] For this reason, **1** was converted to the acetyl-protected product **5**. After this reaction, the introduction of *N*-methyl imidazole and the subsequent anion exchange resulted in catalyst **7**.



Scheme 7. Synthesis of acetyl-protected glucosyl imidazolium ionic liquid **7**.

An *O*-glucoside derivative, to reveal the effect of the 1-position substituent, was also prepared (Scheme 8). PhO-GMIM-I **10**

was derived from 6-iodo-phenyl-beta-D-glucoside **8** following the common procedure via **9**.

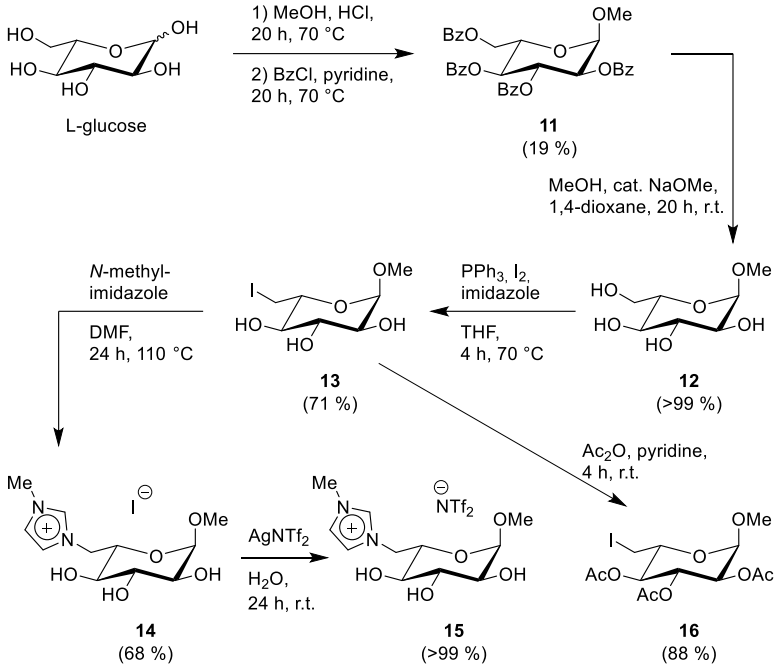


Scheme 8. Synthesis of phenyl b-D-glucopyranoside organocatalyst **10**

The stereochemistry of carbohydrate cation moiety could affect catalytic activity, especially stereoselectivity. Thus, L-glucose-based L-GMIM-NTf_2 **15** was derived for comparison with the D-form catalyst GMIM-NTf_2 **3a** (Scheme 9). Since methyl α-L-glucoside **12** is not commercially available, the synthesis was started from native L-glucose. The benzyl protected precursor **11** was obtained from L-glucose with Fischer glycosylation followed by benzyl protection. The resulting alpha/beta mixture was separated by column chromatography with the method reported by Taniguchi and Monde.[64] The pure alpha compound was obtained in 19% yield after these steps,[65] and a final Zemplén deprotection led to methyl α-L-glucoside **12**. The common pathway for the Appel reaction towards **13** was applied, *N*-methyl imidazole was inserted to achieve product **14** and finally the iodine anion was exchanged to NTf_2 to convert to **15**.

The salt with unprotected hydroxyl groups was difficult to crystallize due to hygroscopicity. For structural determination of the L-form, crystallization was necessary. Therefore, the acetyl-protected 6-iodo product **16** was prepared, which was easily crystallizable from chloroform. X-ray Crystal structure

analysis of acetyl-protected precursor provides the actual conformation of the L-glucoside skeleton by ORTEP (Figure 4).



Scheme 9. Synthesis of the L-glucose-based organocatalyst **15**.

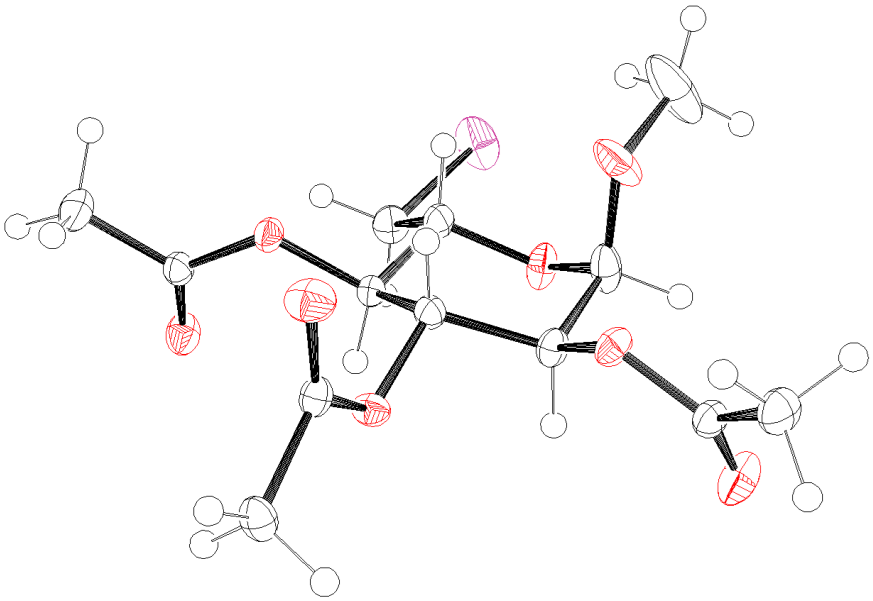
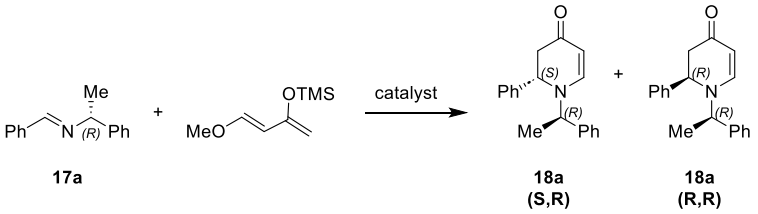


Figure 4. ORTEP of acetyl-protected 6-iodo L-glucose product **16**.

3.2.2 Application for aza Diels-Alder reaction

As the model reaction, an Aza Diels-Alder reaction with a chiral dienophile, synthesized from benzaldehyde and (R)-

phenylethyl amine, and Danishefsky's diene was investigated (Scheme 10). This model reaction was chosen as a reference to research of Vo-thanh *et al*.[40,41] Because the diastereomeric products **18a (S,R)** and **18a (R,R)** have two asymmetric centers, evaluation of stereoselectivity can be performed via NMR.[40] Thus, both the yield and diastereomeric excess were calculated from ^{1}H-NMR measurement.



17a **18a (S,R)** **18a (R,R)**

Scheme 10. Model aza-Diels-Alder reaction.

Table 1. Optimization of the aza-Diels-Alder reaction between **17a** and Danishefsky's diene to **18a**.[a]

Entry	Catalyst	Amount (eq)	t (h)	Yield (%)[b]	de of major diastereomer (%)[b]
1	none	-	2	n.d.	n.d.
2	methyl a-D-glucopyranoside	0.5	2	n.d.	n.d.
3	$ZnCl_2$	0.1	2	42	45
4	$ZnCl_2$	0.5	2	78	38
5	HO-EMIM-NTf_2	0.5	2	31	60
6	GMIM-I (**2a**)	0.5	2	38	43
7	GMIM-OTf (**4**)	0.5	2	9	20
8	GMIM-NTf_2 (**3a**)	0.5	2	73	70
9	GEIM-NTf_2 (**3b**)	0.5	2	69	63
10	GBIM-NTf_2 (**3c**)	0.5	2	79	61
11	GOIM-NTf_2 (**3d**)	0.5	2	73	58
12	GPhIM-NTf_2 (**3e**)	0.5	2	88	53
13	GBnIM-NTf_2 (**3f**)	0.5	2	76	63
14	GMesIM-NTf_2 (**3g**)	0.5	2	77	60
15	PhO-GMIM-NTf_2 (**10**)	0.5	2	65	67

16	AcO-GMIM-NTf_2 (**7**)	0.5	2	43	78
17	L-GMIM-NTf_2 (**15**)	0.5	2	84	64
18	GMIM-NTf_2 (**3a**)	0.3	2	66	66
19	GMIM-NTf_2 (**3a**)	0.1	2	23	67
20	GMIM-NTf_2 (**3a**)	0.3	5	80	67
21	GMIM-NTf_2 (**3a**)	0.3	18	93	67

[a] Reaction conditions: chiral imine **17a** (1.0 mmol), Danishefsky's diene (1.5 mmol), catalyst (amount as given in each entry), time as given in each entry, room temperature. [b] Yield of **18a** and diastereomeric excess of **18a (S,R)** as determined by NMR from the raw reaction mixture.

First, the optimizations started with control experiments. The blank condition showed no conversion (table 1 entry1). Non-iconic carbohydrate, raw methyl-alpha-D-glucoside, did not provide any catalytic activity (table 1 entry 2). To show how important the presence of glucose-based catalyst is, no catalyst and typical inorganic catalyst,[66,67] zinc chloride were tested. 10 mol% ZnCl performed 42% yield, 45% de (table 1 entry 3). It must be noted that the yield was not reproducible and median has been given in the table. The results show significant variation between 24 to 65 % yield and 33 to 54 % de. This error was observed only with this entry. ZnCl has hygroscopicity and the water content was not controlled, which could affect this result. In case the loading was increased to 50 mol%, the yield improved to 78% (table 1 entry 4). The commercial ionic liquid hydroxyethyl methyl imidazolium bis-triflyl-imide (HO-EMIM-NTf_2) led to a lower yield of 31%, but an increased de of 60% (table 1 entry 5).

For the comparison of different anions, glucose-based catalysts bearing iodine **2a**, OTf **4** and NTf_2 **3a** have been applied to the model reaction (table 1 entry 6-8). These anions performed with high reactivity in previous reports.[3] The iodine and OTf catalysts led to overall low yields and de. Interestingly, NTf_2 shows a sharp increase to 73% yield and from to 70% de.

Chiappe *et al*.[68] reported that the suitable size of cavity, which is created by the interaction between the anion and the cation, contributes to the reactivity. This effect mainly comes from the structure of the anion. Thus the “softer” anion, NTf_2, marked the highest reactivity.[69]

Both **3a** (NTf_2) and **4** (OTf) were room temperature ionic liquids (RTILs) and miscible in the reaction mixture. The iodine salt **2a** on the other hand was solid at room temperature and insoluble in the reaction mixture. This suggests that solubility itself does not affect the reactivity, since **2a** led to notably better results than **4**.

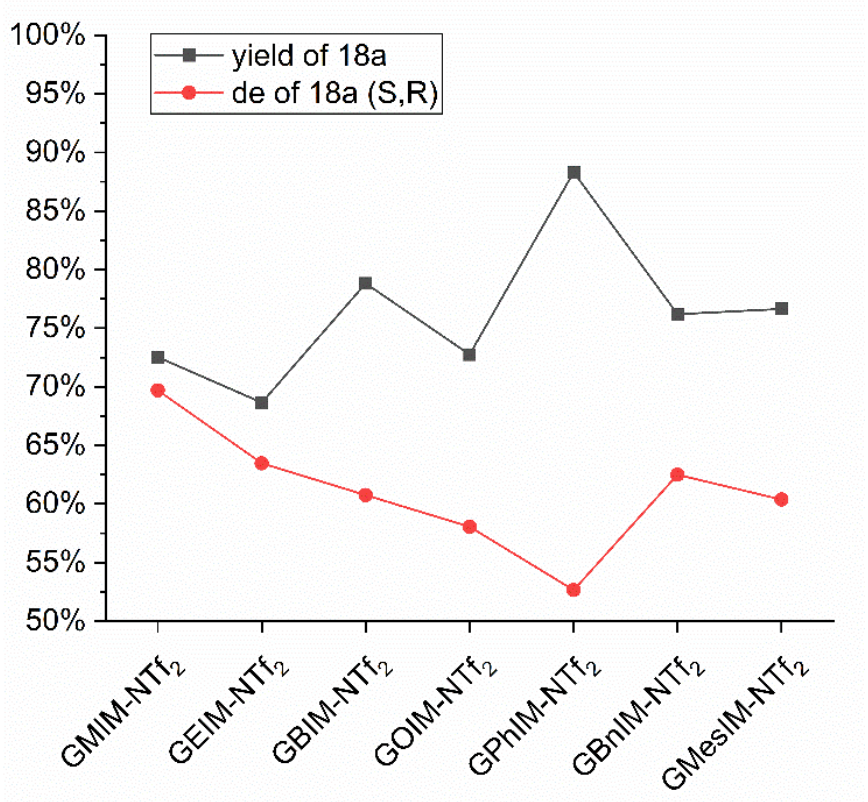


Figure 5. Yield of **18a** and diastereomeric excess of **18a (S,R)** synthesized with the organocatalysts **3a-g**.

The glucose-based organocatalysts **3a-g**, bearing different *N*-substitution, were tested next (table 1 entry 8-14). Generally, longer alkyl chains and aryl groups enhance the yield. It suggests that the electron density on imidazolium ring plays

an important role in the reactivity. At the same time, the selectivity decreased along with high conversion. This trend is nearly like a mirrored trend (Figure 5). Therefore, an increase in reactivity coming from +I and +M effects is accompanied by the loss of selectivity. The hydrogen bonding ability of the C-2 hydrogen on the imidazolium ring is reduced by the electron-donating substituent. In addition, it is also considered that the ionic interactions are weakened, resulting in the change of solvation cavity size. This counting effect can explain these mirrored results.[68] GMIM-NTf_2 **3a** was concluded as the best middle ground for the different *N*-substitutions.

The phenyl-beta-GMIM-NTf_2 **10** and acetyl protected GMIM-NTf_2 **7** catalysts were tested next (table 1 entry 15-16). The yield of both entries dropped to 65% and 43%, respectively. The drop of yield for catalyst **7** in comparison to **3a**, which has free hydroxyl groups and led to 73% yield, proves the importance of free hydroxyl groups. The functionalization of the glycosidic position, as in catalyst **10**, however didn't influence the yield or de notably in comparison to **3a**.

The enantiomeric effect was studied by L-GMIM-NTf_2 **15** (table 1 entry 17). Only D-glucose-based catalysts have been reported before this work. The results of the catalyst L-GMIM-NTf_2 **15** are very similar to the results of D-GMIM-NTf_2 **3a**, showing that the stereochemistry of the glucose itself does not influence the diastereoselectivity of the tested aza-Diels-Alder reaction.

Overall, CHILs-based organocatalysis was found to lead to improved yields and de in comparison to metal salts or commercial ILs, likely due a favorable combination of traits like free hydroxyl groups and NTf_2-anions.

Finally, the reaction conditions of the aza-Diels-Alder reaction were further optimized using the best catalyst **3a** (table 1, entry 18-21). A catalyst loading of 30 mol% and a reaction time of

18 hours led to the overall best results with 93% yield and 67% de (table 1 entry 21).

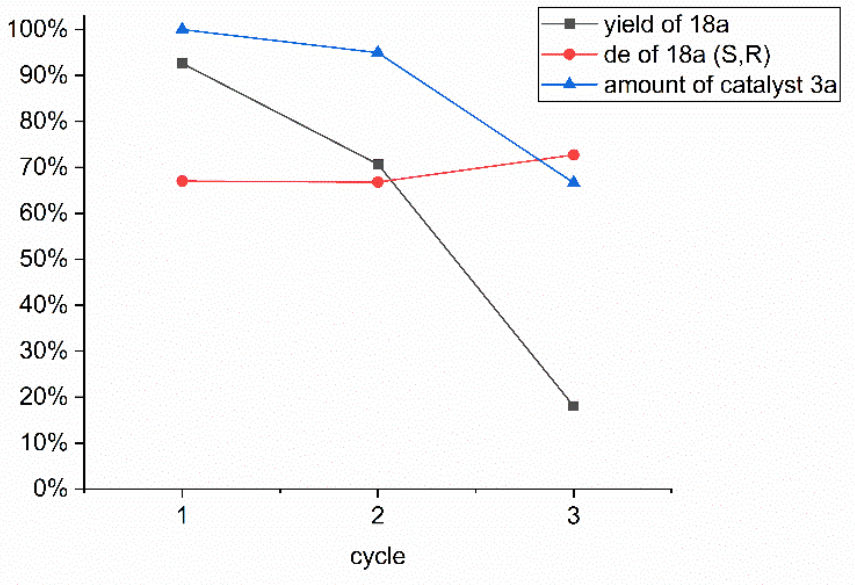
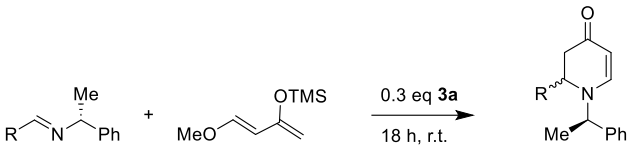


Figure 6. Recycling experiments (3 cycles) with organocatalyst **3a**. Reaction conditions: chiral imine **17a** (1.0 mmol), Danishefsky's diene (1.5 mmol), **3a** (0.3 mmol), 18 h, room temperature. Yield of **18a** and diastereomeric excess of **18a (S,R)** as determined by NMR from the raw reaction mixture.

This model of an aza Diels-Alder reaction takes place under solvent-free conditions. To achieve a more environmentally friendly and atom-economical system, recyclability is also an important factor. After the reaction, the crude product was extracted with water and diethyl ether. The product and the salt were separated through this procedure. To evaluate how reusable this catalyst is, the recycling experiments were carried out. As a procedure, **3a** from the previous water phase was reused for the next cycle. However, due to the partial solubility of **3a** in diethyl ether, all the salt could not be recovered, and around 30% of the original catalyst amount was lost by the third cycle. Accordingly, the yield also dropped to only 20% (Figure 6).



17a-g 18a-g

a: R = Ph
b: R = *n*-propyl
c: R = *t*-Bu
d: R = *p*-F-Ph
e: R = *p*-MeO-Ph
f: R = *m*-MeO-Ph
g: R = *o*-MeO-Ph

Scheme 11. Aza-Diels-Alder reactions with different imines.

Table 2. Scope of differently substituted imines.[a]

Entry	Product	R	Yield (%)[b]	de of major diastereomer (%)[b]
1	**18a**	Ph	93	67
2	**18b**	*n*-propyl	13	24
3	**18c**	*t*-Bu	9	49
4	**18d**	*p*-F-Ph	53	68
5	**18e**	*p*-MeO-Ph	71	78
6	**18f**	*m*-MeO-Ph	68	67
7	**18g**	*o*-MeO-Ph	88	52

[a] Reaction conditions: chiral imine **17a-g** (1.0 mmol), Danishefsky's diene (1.5 mmol), **3a** (0.3 mmol), 18 h, room temperature. [b] Yield and diastereomeric excess as determined by NMR from the raw reaction mixture.

For the further exploration of the application of this novel organocatalytic aza-Diels-Alder reaction, the scope of imine substrates was investigated. The imines **17a-g** (Scheme 11) were prepared from *(R)*-phenylethylamine with benzaldehyde, *t*-butyraldehyde, pivalaldehyde, *p*-fluorbenzaldehyde, or *o*-/ *m*-/ *p*-methoxybenzaldehyde, as reported before.[70,71] All these imines were reacted with Danishefsky's diene under the optimized conditions using **3a** as glucose-based organocatalyst. The major product of all reactions was separated by silica gel column chromatography analyzed by NOESY-2D-NMR spectrum.

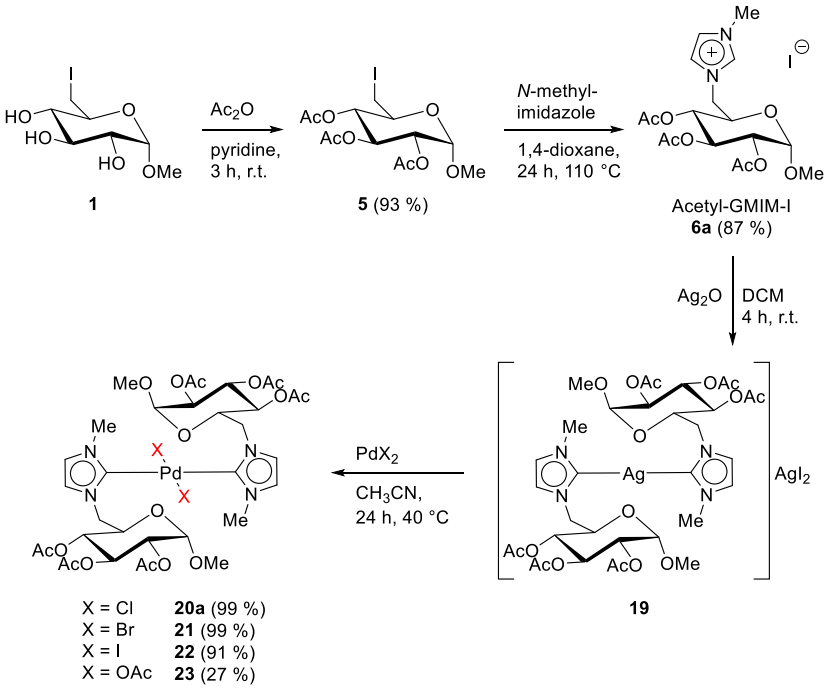
Alkyl-substitution showed drastically reduced yields of 13 and 9%. The diastereomeric excess was also reduced to 24 % and

49 % (table 2 entry 2-3). Next, phenyl-substituted imines were tested. The electron-withdrawing substituent, *p*-fluor, led to lower reactivity of 53% and similar selectivity of 68% (table 2 entry 4). In case of substituents that have an electron-donating group in several positions, *o*/ *m*-/ *p*- methoxy, overall, the yield was lowered to 68% to 88%. Regarding selectivity, only *p*-methoxy performed higher to 78% de (table 2 entry 5). The other 2 substrates, *m*- and *o*-, had no improvement, and led to similar de (table 2 entry 6,7). Alkyl substitutions and chemical modification of the aromatic ring have almost no positive effect on the reaction. The trend in the effects of electron-withdrawing or electron-donating groups and their position shows that this catalytic system has a broad aryl-substrate scope regardless of the substrate structure.

3.3 NHC complex catalysis

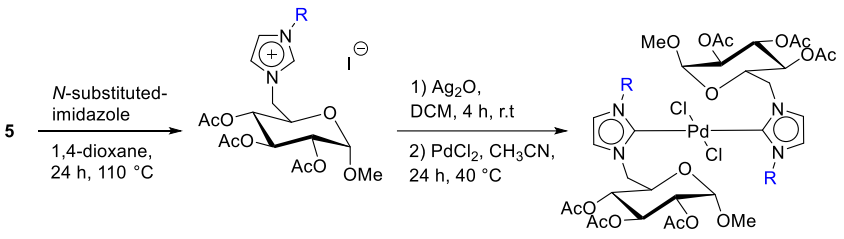
3.3.1 Preparation of the glucose-based Pd(II) NHC complexes

The synthesis of the NHC complexes starts from the common starting material, 6-iodo methyl glucoside **1**. The acetylation of **1** to **5** and its conversion to the salt **6a** with *N*-methylimidazole has been carried out like in the previous project (refer to chapter 3.2.1). Afterwards, Acetyl-GMIM-I **6a** was converted into the bis(NHC) complex **19** with 0.5 equivalents of silver(I) oxide (Scheme 12). This complex and all analogue silver complexes were usually not isolated due to their low stability under light, however, the complex formation could be proven my NMR. **19** was then converted into the palladium (II) complexes **20a** and **21-23** bearing different anions (Scheme 12). The palladium bis(NHC) complex formation and the existence of the anions was proven via NMR and MS.



Scheme 12. Synthesis of Pd^{II}-bis(NHC) complexes with different anions on the palladium.

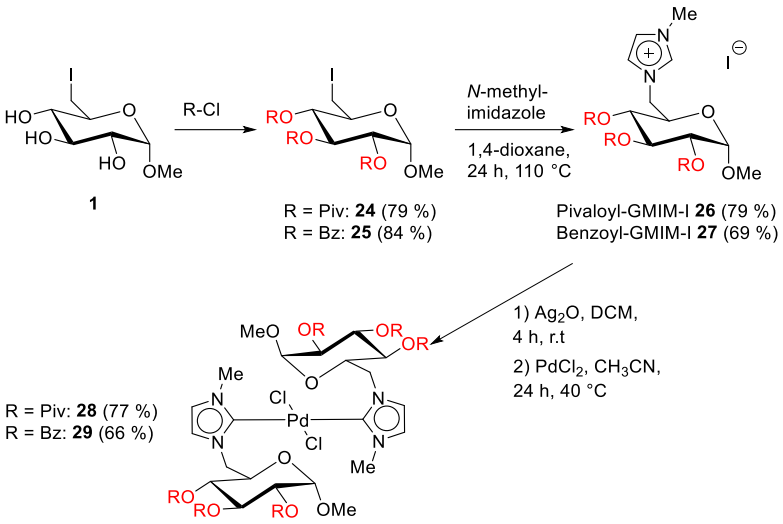
The acetylated methyl 6-iodo glucoside **5** was then used to produce a number of new salts **6b-h** and complexes **20b-h**, following the same synthetic procedure as previously shown in scheme 12. These products differ from **6a** and **20a** in the *N*-substitution at the imidazole, bearing longer alkyl chains, a vinyl group, or different aryl groups (Scheme 13).



Scheme 13. Synthesis of Pd^{II}-bis(NHC) complexes with different alkyl- and arylgroups at the imidazolylidene.

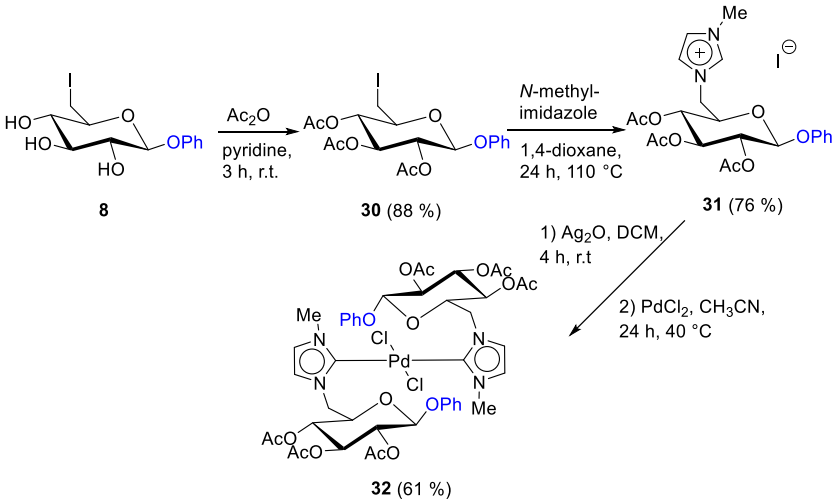
The acetyl protecting groups, as used in the syntheses shown in schemes 12 and 13, are necessary for enhancing the

solubility of the salts **6a-h** in organic solvents. Without these protecting groups, the salts are insoluble in DCM and thus the formation of the silver and palladium complexes fails, as has been tested in this work. To further investigate effect of protecting groups, benzoyl- and pivaloyl-protected salts were prepared by the same pathway as **6a**. Afterwards, these salts **24-25** were quarternized with *N*-methylimidazole and subsequently converted to the palladium complexes **28-29** (Scheme 14). The synthesis of **28-29** performed with generally slightly lower yields in all steps than the comparable acetyl-protected complexes, likely due to the bigger sterical hindrance of the pivaloyl- or benzoyl-groups.



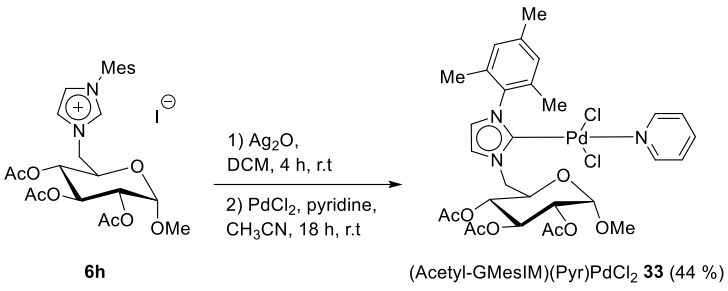
Scheme 14. Synthesis of Pd^{II}-bis(NHC) complexes with different acyl-protecting groups on the glucose.

Lastly, the complex AcO-GMIM-Ph-I **32** was synthesized starting from phenyl 6-iodo-glucoside **8** (refer to chapter 3.2.1) to study the *O*-glucoside effect**,** using the same synthetic pathway as previously used for all NHC complex syntheses (Scheme 15). Like previously seen with the bigger acyl groups (Scheme 14), the comparatively bigger phenyl glucoside also leads to lower yields due to steric effects.



Scheme 15. Synthesis of a PdII-bis(NHC) complex with a beta-phenyl glycoside.

For a deeper understanding of the complexes and their reactivity in the model Suzuki-Miyaura reaction, glucopyranoside-based PEPPSI complex **33** was also prepared (Scheme 16). This complex was produced to serve as comparison to existing works using PEPPSI complexes.[73] The strategy also started with the formation of the silver complex, however, palladium chloride and pyridine were then added in equimolar amounts. The selectivity of the complex formation was lower than for the bis(NHC) complexes. In the end, the desired complex was obtained in only 44% yield.



Scheme 16. Synthesis of a PEPPSI complex from **6h**.

The structures of the acyl-protected 6-iodo glucopyranosides **5** and **24** (Figure 7) and the acetyl-protected salts **6a-b** (Figure 8) have also been confirmed by X-ray analysis.

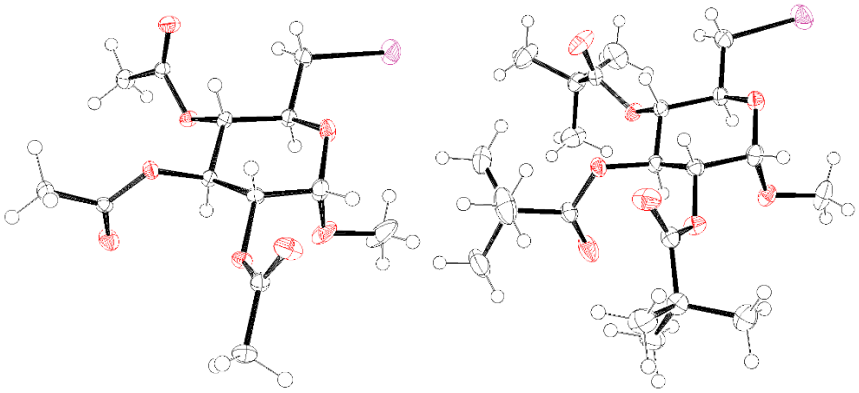


Figure 7. ORTEP plots of **5** (left) and **24** (right).

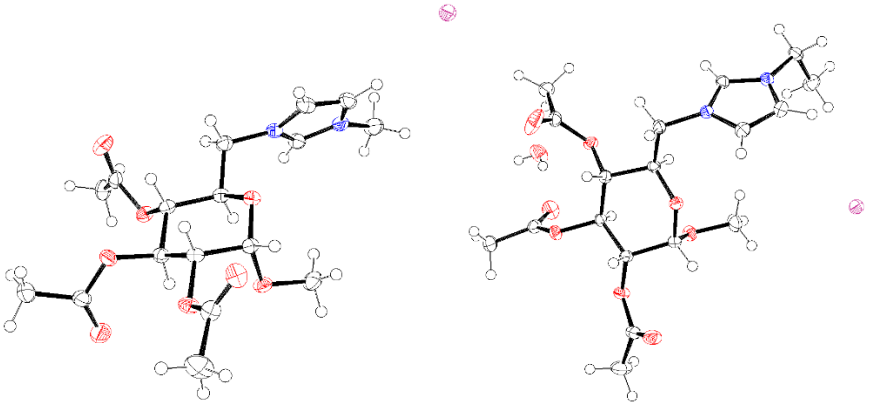
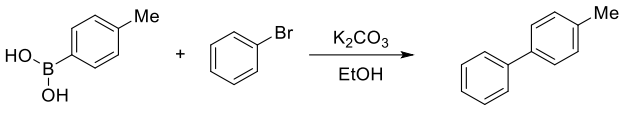


Figure 8. ORTEP plots of Acetyl-GMIM-I **6a** (left) and Acetyl-GEIM-I **6b** (right).

3.3.2 Application for Suzuki-Miyaura reaction

The simple Suzuki-Miyaura reaction of bromobenzene and 4-methylphenylboronic acid was chosen as a model reaction (Scheme 17).



34 **35** **36**

Scheme 17. Model Suzuki-Miyaura reaction with 4-toluneboronic acid **34** and bromobenzene **35** to 4-methylbiphenyl **36**.

The investigation of the glucose-based bis(NHC) palladium(II) complexes started with the different substituents on the palladium center of the complex. Table 3 shows the results of Cl, Br, I, and acetyl. Among the different halogens, the chloride was found to lead to the best results (table 3, entry 1-3). The

reactivity decreased with increasing size of the halogen atom. The acetyl complex led slightly lower yield than the chloride salt (table 3, entry 4). Lastly, a change of solvent from chloroform to ethanol improved the yield from 40 to 56% (table 3, entry 5). Many different unpolar, polar and polar protic solvents have been tested, but all led to worse results than chloroform and ethanol.

Table 3. Influence of the catalysts **20a** and **21-23** on a Suzuki-Miyaura model reaction.[a]

Entry	Catalyst	Catalyst name	Solvent	Yield (%)[b]
1	**20a**	(Acetyl-GMIM)$_2$PdCl$_2$	$CHCl_3$	40
2	**21**	(Acetyl-GMIM)$_2$PdBr$_2$	$CHCl_3$	25
3	**22**	(Acetyl-GMIM)$_2$PdI$_2$	$CHCl_3$	4
4	**23**	(Acetyl-GMIM)$_2$Pd(OAc)$_2$	$CHCl_3$	34
5	**20a**	(Acetyl-GMIM)$_2$PdCl$_2$	EtOH	56

[a] Reaction conditions: bromobenzene (1.0 mmol), 4-tolueneboronic acid (1.25 mmol), K_2CO_3 (2.0 mmol), catalyst (0.05 mmol), solvent (3 mL), 60 °C, 5 h. [b] Yield of 4-methylbiphenyl determined by GC, using nitrobenzene as internal standard, with 3 individual samples taken from each reaction.

Next, a variety of alkyl **20a-e** and aryl **20f-h** substituents on the imidazole ring (table 4, entry 1-8) were tested. The length of the alkyl chain on the imidazoylidene was found to be inconsequential, leading to similar results between 53 and 56% for all complexes. The vinyl complex **20e** shows no catalytic activity (table 4, entry 5). With aryl substituents, the phenyl- **20f** and mesityl-containing complexes **20h** achieved significantly higher yields with 80% and over 99%, respectively (table 4, entry 6,8). These results prove that a +M effect on the imidazoylidene significantly improves the reactivity of the complexes, with the even electron-richer mesityl group leading to the best results.

Next, different functionalizations on the carbohydrate were tested. First, the effect of *O*-protecting groups was

investigated. The bulkier pivaloyl substituent as in complex **28** clearly dropped the yield to 19% (table 4, entry 9), in comparison to 56% for the analogue acetyl protected complex **20a**. Interestingly, the similarly bulky benzoyl groups **29** led to a slightly increased yield of 63% (table 4, entry 10). Similarly, the phenyl glucoside complex **32** reached 60% yield (table 4, entry 11).

It can be concluded that the introduction of aryl groups on the imidazole has the strongest effect for performance. The functionalization of the carbohydrate (acyl protecting groups or glycosidic group) also influences the reactivity of the catalyst, but only very slightly. Overall, chemical modification with aromatic substituents proved to be effective.

To confirm minimum load of catalyst, the amount of the mesityl-substituted catalyst **20h** was stepwise decreased from 5 mol% to 0.5, 0.05, 0.005, 0.001 and 0.0005 (table 4, entry 12-16). The reactivity keeps full conversion until 0.005 mol% (table 4, entry 14) and 81% yield even with 0.001 mol% loading (table 4, entry 15). Eventually, 0.0005 mol% loading led only 8% yield (table 4, entry 16). The best condition of 0.005 mol% loading still achieved 90% yield for less reactive 4-fluorophenyl boronic acid (table 4, entry 17).

Even compared to the commercial catalyst $(PPh_3)_2PdCl_2$, which led to 74% yield (table 4, entry 18), complex **20h** was more reactive.

Lastly, the PEPPSI complex **33** was tested (table 4, entry 19-20). This PEPPSI complex is also substituted with the mesityl-group, which proved to be the most reactive substituent for the bis(NHC) complexes investigated in this work. This PEPPSI catalyst **33** led to similar results as **20h** for both 0.005 mol% and 0.0001 mol% loading, leading to full conversion and 76%, respectively. Nevertheless, based on the selectivity and yield during the catalyst synthesis, **20h** can be conclude as the best catalyst.

Table 4. Influence of the catalysts **20a-h** and **28**, **29** and **33** on a Suzuki-Miyaura model reaction. [a]

Entry	Catalyst	Catalyst name	Amount (mol%)	Yield (%)[b]
1	**20a**	$(AcO\text{-}GMIM)_2PdCl_2$	5	56
2	**20b**	$(AcO\text{-}GEIM)_2PdCl_2$	5	52
3	**20c**	$(AcO\text{-}GBIM)_2PdCl_2$	5	52
4	**20d**	$(AcO\text{-}GOIM)_2PdCl_2$	5	53
5	**20e**	$(AcO\text{-}GVIM)_2PdCl_2$	5	traces
6	**20f**	$(AcO\text{-}GPhIM)_2PdCl_2$	5	80
7	**20g**	$(AcO\text{-}GBnIM)_2PdCl_2$	5	56
8	**20h**	$(AcO\text{-}GMesIM)_2PdCl_2$	5	>99
9	**28**	$(PivO\text{-}GMIM)_2PdCl_2$	5	19
10	**29**	$(BzO\text{-}GMIM)_2PdCl_2$	5	63
11	**32**	$(AcO\text{-}PhO\text{-}GMIM)_2PdCl_2$	5	60
12	**20h**	$(AcO\text{-}GMesIM)_2PdCl_2$	0.5	>99
13	**20h**	$(AcO\text{-}GMesIM)_2PdCl_2$	0.05	>99
14	**20h**	$(AcO\text{-}GMesIM)_2PdCl_2$	0.005	>99 (99)[d]
15	**20h**	$(AcO\text{-}GMesIM)_2PdCl_2$	0.001	81
16	**20h**	$(AcO\text{-}GMesIM)_2PdCl_2$	0.0005	8
17[c]	**20h**	$(AcO\text{-}GMesIM)_2PdCl_2$	0.005	90[d]
18	*/*	$(PPh_3)_2PdCl_2$	0.005	74
19	**33**	$(AcO\text{-}GMesIM)(Pyr)PdCl_2$	0.005	>99
20	**33**	$(AcO\text{ -}GMesIM)(Pyr)PdCl_2$	0.001	76

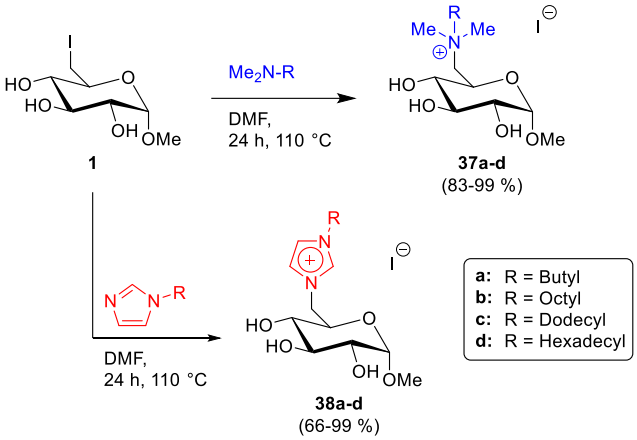
[a] Reaction conditions: bromobenzene (1.0 mmol), 4-tolueneboronic acid (1.25 mmol), K_2CO_3 (2.0 mmol), catalyst, abs. EtOH (3 mL), 60 °C, 5 h. [b] Yield of 4-methylbiphenyl determined by GC, using nitrobenzene as internal standard, with 3 individual samples taken from each reaction. [c] 4-Fluorophenyl boronic acid was used. [d] Isolated yield.

3.4 Phase-Transfer Catalysis

3.4.1 Preparation of the glucose-based phase-transfer catalysts

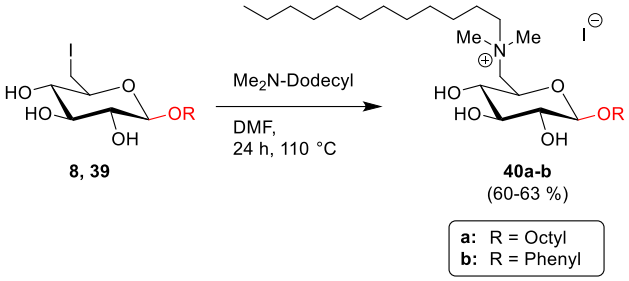
Most syntheses started from the 6-iodo glucopyranoside common starting material **1**, as used in all projects presented

in this thesis. As the next step, *N*-substituted dimethylamines or imidazoles were introduced, following the previously in this work established procedure in DMF (Scheme 18). For the synthesis of glucose-based phase transfer catalysts, long alkyl chains were necessary for the solubility of the salts in the organic phase. Thus, the ammonium salts **37a-d** and the imidazolium salts **38a-d** with alkyl chains ranging from butyl to hexadecyl were synthesized.



Scheme 18. Synthesis of the ammonium- and imidazolium-organocatalysts **37a-d** and **38a-d**, with varying alkyl chain lengths.

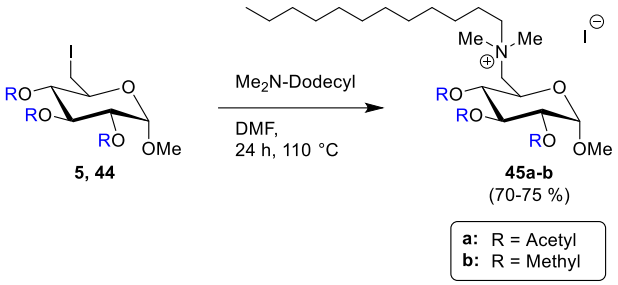
To compare the influence of the 1-position, catalysts starting from beta octyl and beta phenyl glucopyranoside were prepared (Scheme 19). Hereby, phenyl 6-iodo beta-D-glucopyranoside **8** was reused from a previous project (refer to chapter 3.2.1) and octyl 6-iodo beta-D-glucopyranoside **39** was prepared from commercially available octyl beta-D-glucopyranoside using the common Appel reaction pathway. Next, dimethyl dodecyl amine was introduced into these starting materials to achieve the salts **40a-b**.



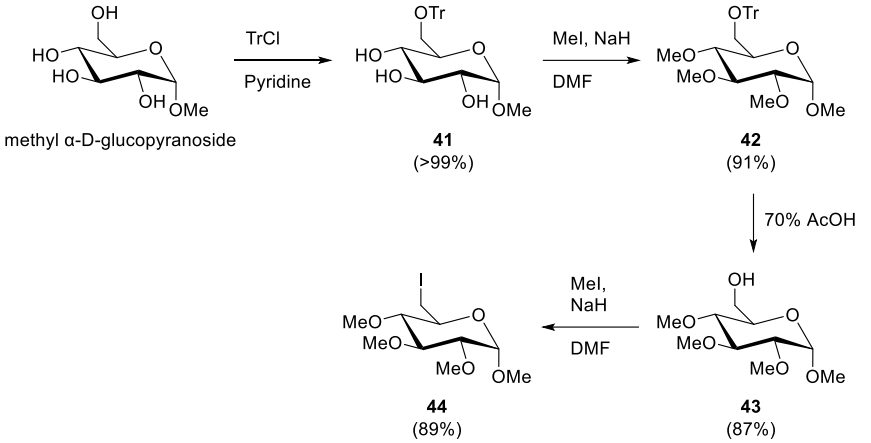
Scheme 19. Synthesis of organocatalysts **40a-b** with varying glycosidic groups.

Like in the previously discussed projects of this thesis, *O*-protected catalysts (Scheme 20) were also prepared. For acetyl protection, starting material **5** was used (refer to chapter 3.2.1). Additionally, methyl ether protection was investigated in this work. For this, commercially available methyl alpha-D-glucopyranoside was first protected with a trityl group in 6-position to achieve **41**, then methylated via sodium hydride and methyl iodide towards **42**, then the trityl group was deprotected with acetic acid to achieve product **43** and finally the free OH group in 6-position of **43** was converted into an iodine using an Appel reaction to **44** (Scheme 21).

Both *O*-protected 6-iodo starting materials **5** and **44** were then converted into the glucose-based phase-transfer catalysts **45a-b** with dimethyl dodecyl amine (Scheme 20).



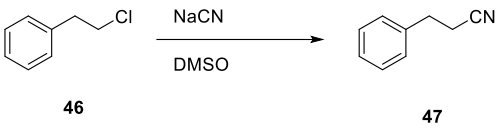
Scheme 20. Synthesis of the ester- and ether-protected organocatalysts **45a-b**.



Scheme 21. Synthesis of methyl protected starting material **44**.

3.4.2 Application for biphasic Kolbe nitrile synthesis

As a model reaction, the Kolbe nitrile synthesis of 2-chloroethyl benzene **46** to 3-phenylpropionitrile **47** was chosen (Scheme 22). Due to the lower reactivity of the aryl-substituted chloroalkane than its respective bromo- or iodo-counterparts, this model reaction can prove the wide adaptability for substrates. Both **46** and **47** show distinct signals in ^{1}H-NMR, allowing for the analysis of this reaction and the calculation of its yield from ^{1}H-NMR.



Scheme 22. Model Kolbe nitrile synthesis between 2-chloroethyl benzene **46** and sodium cyanide to 3-phenylpropionitrile **47**.

Since these substrates have not been used in a Kolbe nitrile synthesis before, the conditions for the standard Kolbe nitrile synthesis in DMSO were tested before moving on to the biphasic Kolbe nitrile synthesis. This was necessary to establish the limits of the standard protocol and to have a comparison for the novel biphasic protocol. The optimization of the classical Kolbe nitrile synthesis in DMSO (Table 5) shows that the reaction works best at 40 °C with 2 to 3

equivalents of sodium cyanide at 24 hours reaction time (Table 5, entry 4-5).

Table 5 Optimization of the classical Kolbe nitrile synthesis of **46** and sodium cyanide to **47**.[a]

Entry	T (°C)	NaCN amount (eq)	t (h)	Yield (%)[b]
1	r.t.	5.0	24	74
2	40	5.0	24	>99
3	70	5.0	24	>99
4	40	3.0	24	>99
5	40	2.0	24	>99
6	40	1.5	24	79
7	40	1.1	24	80
8	40	2.0	4	73
9	40	2.0	8	90
10	40	2.0	16	98

[a] Reaction conditions: **46** (1.0 mmol) and the given amount of NaCN in DMSO (3.0 mL) at the given time and temperature. [b] Yield of **47** as determined by NMR from the raw reaction mixture.

Secondly, to design the novel biphasic system for the Kolbe nitrile synthesis, several organic solvents were tested (table 6). With n-heptane at 70 °C, the reaction led to only 8 % yield, while the yield rose to 39% at 100 °C (table 6, entry 1-2), showing the necessity of high temperatures in comparison to the standard protocol. Thus, all solvents, cyclohexane (table 6, entry 3), toluene (table 6, entry 4), ethyl acetate (table 6, entry 5), diethyl ether (table 6, entry 6) and chloroform (table 6, entry 7) were applied at 100 ºC. Heptane was concluded as the best solvent for biphasic reaction.

Next the effects of the amounts of sodium cyanide and catalyst were investigated. Rising the NaCN amount from 2.0 equivalents to 3.0 and 5.0 results in a slight increase of yield

to 52% (table 6, entry 8-9). Increasing the catalyst amount from 0.25 equivalents to 0.5 or 1.0 equivalents leads to a stark increase of the yield up to 93% (table 6, entry 10-11). However, 25 mol% of catalyst were still used for further investigations, to keep the reaction catalytic and to use less catalyst per reaction. Lastly, performing the reaction with no catalyst (table 6, entry 12) or with commercially available tetrabutylammonium iodide (table 6, entry 13) leads to low activity.

Table 6. First optimization of reaction parameters, using **37c** as model catalyst[a]

Entry	T (°C)	Solvent	NaCN amount (eq)	Catalyst amount (eq)	Yield (%)[b]
1	70	*n*-heptane	2.0	0.25	8
2	100	*n*-heptane	2.0	0.25	39
3	100	cyclohexane	2.0	0.25	28
4	100	toluene	2.0	0.25	15
5	100	ethyl acetate	2.0	0.25	-
6	100	diethyl ether	2.0	0.25	22
7	100	chloroform	2.0	0.25	10
8	100	*n*-heptane	3.0	0.25	42
9	100	*n*-heptane	5.0	0.25	52
10	100	*n*-heptane	5.0	0.5	72
11	100	*n*-heptane	5.0	1.0	93
12[c]	100	*n*-heptane	5.0	-	4
13[d]	100	*n*-heptane	5.0	0.25	27

[a] Reaction conditions: **46** (1.0 mmol) and the given amounts of NaCN and organocatalyst **37c** in an organic solvent (1.5 mL) and water (1.5 mL) at the given temperature for 24 h. [b] Yield of **47** as determined by NMR from the raw reaction mixture. [c] The reaction was performed without catalyst. [d] Tetrabutylammonium iodide was used as organocatalyst.

Next, the previously prepared different glucose-based phase transfer catalysts, bearing different alkyl chain

functionalizations, different cationic groups and varying groups at the carbohydrate were investigated in the biphasic Kolbe nitrile synthesis (table 7).

Table 7. Comparison of different organocatalysts[a]

Entry	Catalyst	Catalyst name	Yield (%)[b]
1	**37a**	MeGlu(OH)-NMe_2Bu-I	5
2	**37b**	MeGlu(OH)-NMe_2Oct-I	13
3	**37c**	MeGlu(OH)-NMe_2Dodec-I	52
4	**37d**	MeGlu(OH)-NMe_2Hexadec-I	51
5	**38a**	MeGlu(OH)-ImBu-I	7
6	**38b**	MeGlu(OH)-ImOct-I	19
7	**38c**	MeGlu(OH)-ImDodec-I	57
8	**38d**	MeGlu(OH)-ImHexadec-I	48
9	**40a**	OctGlu(OH)-NMe_2Dodec-I	62
10	**40b**	PhGlu(OH)-NMe_2Dodec-I	39
11	**45a**	MeGlu(OAc)-NMe_2Dodec-I	40
12	**45b**	MeGlu(OMe)-NMe_2Dodec-I	71

[a] Reaction conditions: **46** (1.0 mmol), NaCN (5.0 eq), organocatalyst (0.25 eq), *n*-heptane (1.5 mL), water (1.5 mL), 100 °C, 24 h. [b] Yield of **47** as determined by NMR from the raw reaction mixture

The dimethyl alkyl ammonium and *N*-alkyl imidazole salts baring several lengths of alkyl chain from butyl to hexadecyl were tested first (table 7, entry 1-8). Both types of salts have similar trends in increasing yield along with the longer alkyl chain length, showing their optimum at dodecyl (Figure 9). The yields drops with the catalysts bearing the even longer hexadecyl chain, suggesting that an appropriate alkyl length is necessary. Imidazolium catalysts had overall higher catalytic activity than ammonium catalysts.

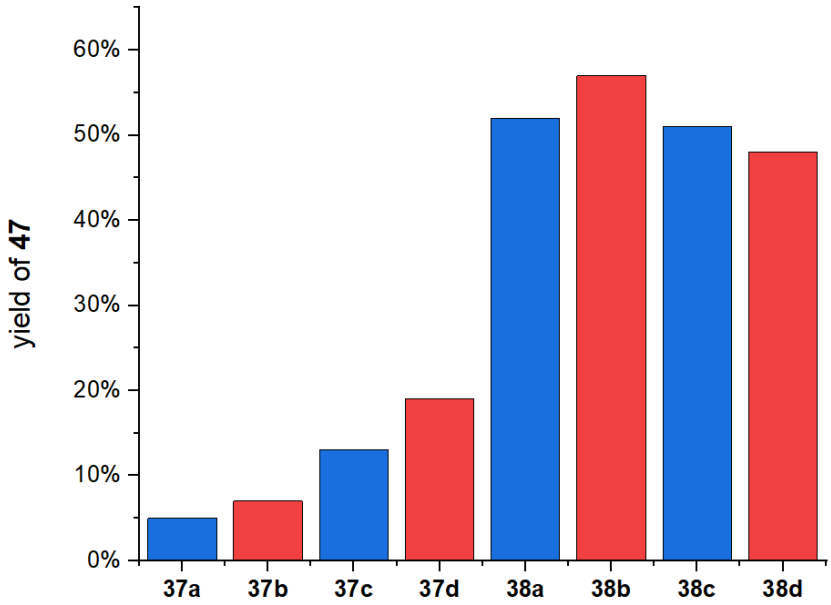
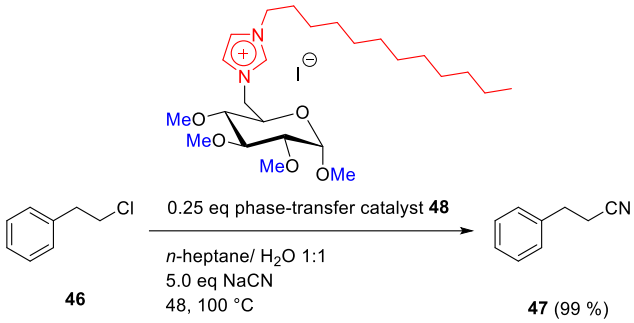


Figure 9. Performance of the ammonium catalysts **37a-d** and the imidazolium catalysts **38a-d** (**a** = butyl, **b** = octyl, **c** = dodecyl, **d** = hexadecyl).

Next entries (table 7, entry 9-10) were the catalysts which have an octyl and a phenyl glycosidic group on 1-position of the carbohydrate. Octyl glucoside **40a** led to better activity than the analogue methyl glucoside **37c**. However, **40a** was detected in the organic phase by ^{1}H-NMR. In this case, it will be difficult to isolate the nitrile product **47** after the reaction, as the goal of this biphasic reaction is for the phase-transfer catalyst to remain in the aqueous phase after the reaction, which has been the case for all other glucose-based phase-transfer catalysts in this work. The phenyl glucoside **40b** led to a lower reactivity than **37c**.

Lastly, *O*-protected catalysts which bear acetyl and methyl groups were investigated. The result of the acetylated catalyst **45a** is 10% less activity than the comparative catalyst **37c** with free hydroxyl groups. There is a possibility that a deprotection happened during the reaction due to the disappearance of the signal of the acetyl groups in ^{1}H-NMR. The methyl protected catalyst **45b** performs as the best catalyst with 71% yield.

Finally, taking all results into account, glucose-based phase-transfer catalyst **48** was synthesized. This catalyst combines the methyl protected glucose with *N*-dodecylimidazole, which is the combination of the best functionalizations as found in table 7. With catalyst **48**, 78% yield were achieved under optimized reaction conditions as used in table 7, under a further extension of the reaction time to 48 hours led to 99% yield (Scheme 23).



Scheme 23. Optimized model biphasic Kolbe nitrile synthesis using phase-transfer catalyst **48** (yield of **47** as determined by NMR from the raw reaction mixture).

To further explore the capabilities of this new glucose-based phase-transfer catalyst **48**, we investigated the recyclability of the catalyst. The reaction was performed in glass pressure tube. After each reaction, the organic phase was removed and additional 1 mmol of starting material **46** and sodium cyanide was added, as these amounts will theoretically by used up during each step. Unfortunately, a constant loss of activity can be seen for each cycle (Figure 10). The first cycle starts at 99 %, then it became 85 %, 69 %, 56 % and finally 47 %. As a notable thing, a brown color mix phase between the water phase and the organic phase was observed (Figure 11B). It could not be avoided that this mix phase was partially removed during the recycling experiments shown in figure 10.

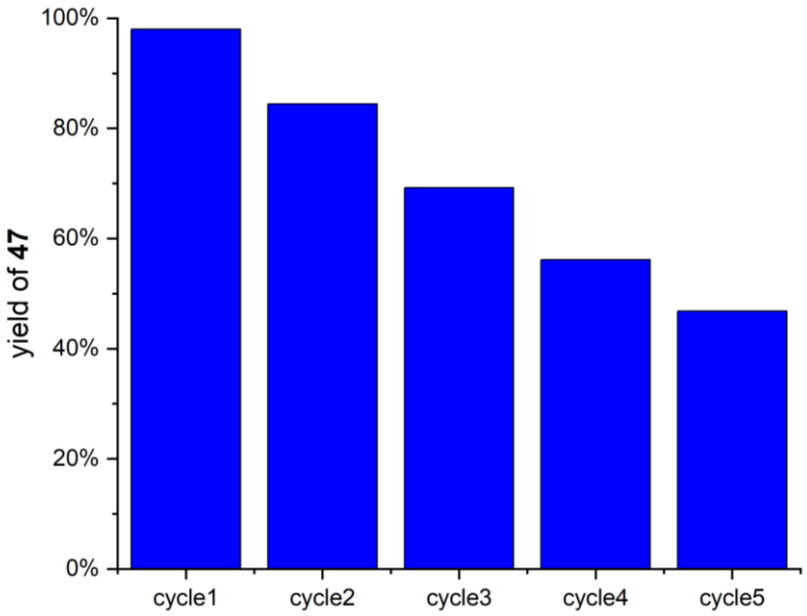


Figure 10. Recycling studies part 1. The first cycle starts with **46** (1.0 mmol), NaCN (5.0 mmol), PTC **48** (0.25 mmol), *n*-heptane (1.5 mL) and water (1.5 mL) at 100 °C for 48 h. After each cycle, the organic phase was removed and **46** (1.0 mmol), NaCN (1.0 mmol) and *n*-heptane (1.5 mL) were added to the remaining aqueous phase. Yield of **47** as determined by NMR from the raw reaction mixture.

To test the influence of this mix-phase and its partial removal on the previous recycling experiments, another recycling experiment where the mix-phase was fully removed after the first cycle was performed (Figure 11A). Here, only 10% yield was achieved in the second cycle. This result proved that this "third phase" plays an important role for the catalytic system. Methyl protection demonstrates appropriate solubility in the both organic and water phases. Forming the third phase has reported to accelerate the reaction.[74,75] Existence of "hard salt" and high temperature may also contribute to form the phase.[76] It suggests that the combination of structure and condition is responsible for this high catalytic activity.

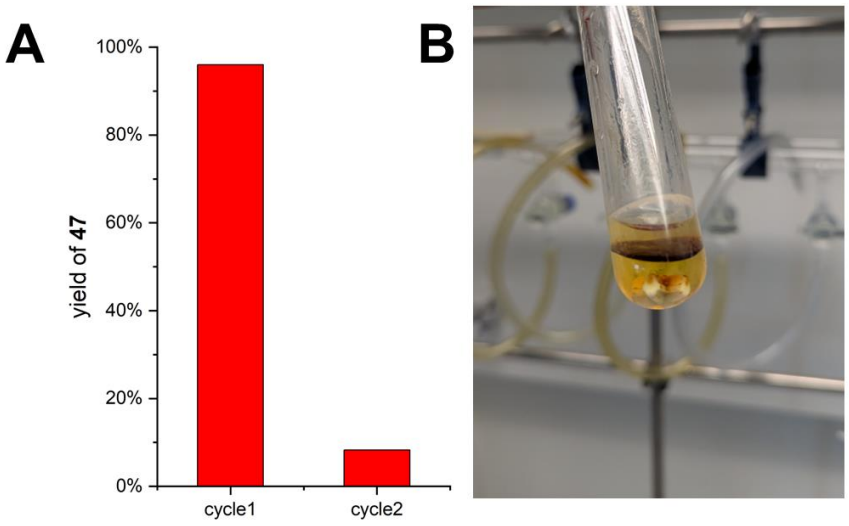


Figure 11. A) Recycling studies part 2. The first cycle starts with **46** (1.0 mmol), NaCN (5.0 mmol), PTC **48** (0.25 mmol), *n*-heptane (1.5 mL) and water (1.5 mL) at 100 °C for 48 h. After the first cycle, the organic phase and the brown-colored mix-phase were removed and **46** (1.0 mmol), NaCN (1.0 mmol) and *n*-heptane (1.5 mL) were added to the remaining aqueous phase. Yield of **47** as determined by NMR from the raw reaction mixture.

4. Conclusion

Overall three different catalytic applications for glucose-based salts have been presented in this thesis and in the three publications accompanying this cumulative PhD thesis. Over the course of these 3 publications, dozens of novel glucose-based salts have been synthesized, varying in their cationic head-groups, the different alkyl- or aryl-groups located at these cationic head-groups, and the different *O*-functionalizations on the glucose. The synthetic protocols used for the synthesis of all these salts have proven to be widely applicable for many different structural variations.

In publication I, 10 novel glucosyl imidazolium bis-triflylimide ionic liquids, including both D- and L-glucose, were synthesized in up to 89% yield. These glucose-based ILs were employed as organocatalysts for an aza-Diels-Alder reaction between a chiral imine dienophile and Danishefsky's diene. The diastereomeric selectivity of the resulting piperidin-4-one product depended on the structure of the catalysts. The prepared glucosyl imidazolium bis-triflylimide ionic liquids were significantly more active than commercial ILs or metal salts. In general, yield and diastereomeric excess were in inverse proportion, with catalysts of higher reactivity also leading to a lower diastereoselectivity. From all experiments, GMIM-NTf_2 was found to be the best catalyst. Notably, L-GMIM-NTf_2 was the first report of a L-glucose-based ionic liquid catalyst. However, this enantiomer catalyst did not show any unique selectivity for the aza-Diels-Alder reaction. Lastly, the model aza-Diels-Alder reaction was also expanded onto other imine substrates, and aryl imines were found to be vastly more reactive than alkyl imines.

In publication II, 15 novel bis(NHC)-palladium(II) complexes were derived from 11 novel acyl protected glucose-based imidazolium salts. These NHC complexes were designed with several substituents on the imidazolium moiety, as well as different protecting groups and glucosidic groups on the carbohydrate. The complexes were achieved in 4 steps with up to 73% yield, vastly surpassing known literature in which similar complexes were synthesized in up to 40% yield.

The catalytic activity of the novel glucose-based bis(NHC) palladium complexes was investigated in a Suzuki-Miyaura reaction. Most of the new complexes showed a mediocre reactivity. Functionalizations on the carbohydrate influenced the catalytic activity only slightly, but the substituents on the imidazole proved to be more influential. Specifically, aryl-substituted imidazoles led to a stark increase in reactivity. The best complex, bearing a mesityl group, was found to be more reactive than a commercial palladium complex, leading to 99% with a low catalyst loading of only 0.005 mol%.

In publication III, 13 novel ammonium and imidazolium glucose-based phase-transfer catalysts were achieved in simple procedure. The catalysts were employed for biphasic Kolbe nitrile synthesis. Different length of *N*-alkyl chain and different protecting groups and *O*-glucosides were compared and investigated in the relationship between structure and catalytic activity. Generally, longer alkyl substituents lead higher activity, and the imidazolium glucose-based phase-transfer catalysts were more reactive than their ammonium counterparts. The yield reached its peak with a dodecyl group, then slightly dropped with hexadecyl. It suggests that there is a suitable balance range between hydrophilicity and hydrophobicity. This property is essential to move and transport an anion between the water and organic phase. Despite the fact that methyl protection of hydroxyl groups of glucose should lead to lower hydrophilicity, this catalyst demonstrated the highest activity among all the salts. Interestingly, this catalyst formed a mix-phase between the organic and water phase. This formation seems to enhance the reactivity. Although a higher reaction temperature was needed than in the classical Kolbe reaction in DMSO, phase-transfer catalysis provides the product via a significantly simpler purification with less handling of toxic sodium cyanide. The recyclability of the glucose-based phase-transfer catalyst was also investigated. Unfortunately, the catalyst loses its catalytic activity after several cycles.

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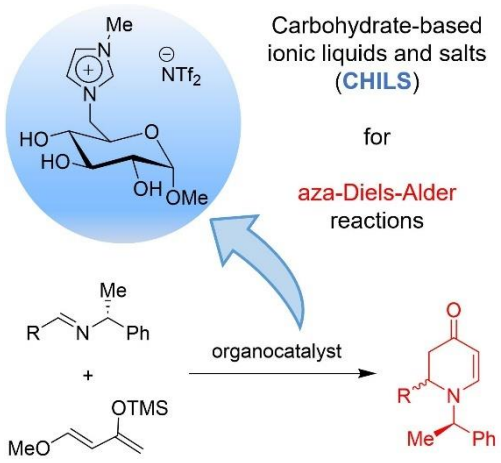
6. Publication I: Glucose-based Ionic Liquid Organocatalysts for Asymmetric aza-Diels-Alder Reactions



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Mirai Komabayashi did all experiments and analysis in this work. The publication was written by Mirai Komabayashi as first author.

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Glucose-based Ionic Liquid Organocatalysts for Asymmetric aza-Diels-Alder Reactions

Mirai Komabayashi[a] and Stefan Jopp*[a]

Carbohydrate-based ionic liquids and salts (CHILS) have recently emerged as an uprising sub-class of ionic liquids. Their starting materials are available in abundant natural resources from plants and fauna. Carbohydrates are not only sustainable; they also exhibit natural chirality. To use this, novel glucosyl imidazolium NTf_2 ionic liquids were synthesized and applied as organocatalysts in aza-Diels-Alder reactions in this work, where we used aldimines and Danishefsky's diene as substrates. We investigated the structure-activity relationships of these glucosyl imidazolium NTf_2 organocatalysts through several functionalizations on the carbohydrate and the imidazole and compared them with common metal catalysts and ionic liquids. Our organocatalysts improved the yield of the model aza-Diels-Alder reaction highly and also had a positive effect on the overall diastereomeric excess.

Introduction

Carbohydrate-based ionic liquids and salts (CHILS) have attracted organic chemists since their first synthesis in 2007 and their community has been growing steadily.[1] Generally, ionic liquids (ILs) are defined as salts with a melting point under 100 °C. As a remarkable feature, ILs are usually non-volatile and non-flammable solvents. As so-called "Designer solvents",[2] ILs can exhibit a wide range of properties by modifying the structure and combination of anion and cation.[3]

Carbohydrates have a chiral structure and OH-groups for potential hydrogen bonding by nature. Due to these features, common applications of CHILS are as catalysts for (asymmetric) synthesis[4–14] and for chiral recognition.[15–17] The most promising results have been achieved for (aza-)Diels-Alder reactions (Figure 1).[4–6]

Aza-Diels Alder reactions are a well-known strategy to synthesize *N*-heterocyclic compounds.[18] In common cases, Lewis and Brønsted acid catalysts lower the LUMO energy of the dienophile and activate it via protonation or complexation.[18] Most of the catalysts for this reaction are organic metal salts or complexes from metals like zirconium,[19] silver[20–21] and copper.[21]

In their previous works, Vo-Thanh and co-workers reported the catalytic activity of isosorbide-based CHILS for aza-Diels-Alder reactions.[4–5] These are the first reports of CHILS as asymmetric organocatalysts. The ammonium- and imidazolium-substituted

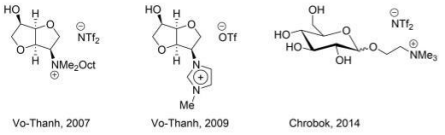

Figure 1. CHILS-organocatalysts for (aza-)Diels-Alder reactions by Vo-Thanh *et al.* and Chrobok *et al.*[4–6]

isosorbide CHILS were synthesized in up to 7-step synthesis with total yields between 20 and 30%. The best results of these organocatalysts (74% yield, 68% de) were close in yield for the non-CHILS catalyst $ZnCl_2$ (60% yield, 32% de), but showed a notable influence on the diastereomeric excess. Chrobok and co-workers also reported the catalysis of Diels-Alder reactions by glucose-based CHILS.[6] These CHILS were obtained through a notably shorter 3-step synthesis with total yields between 40 and 50%. In difference to the works of Vo-Thanh and co-workers, their organocatalysts led to vastly higher reaction rate and full conversion in comparison to the metal catalyst $Y(OTf)_3$, which is attributed to the hydrogen bonds of the OH-groups of the sugar, but had only a small influence on the diastereomeric excess (86% de for the glucose-based CHILS, 80% de for the metal catalyst).

Judging from these aforementioned works, three major components seem to be favorable for highly reactive CHILS-organocatalysts for (aza-)Diels-Alder reactions: Imidazolium cation, OTf or NTf_2 anion and a large number of free OH-groups. To achieve novel CHILS-organocatalysts with these structural elements combined, we used our previously developed synthesis of biocompatible glucosyl imidazolium iodide salts as a basis.[22] In this work, glucosyl imidazolium NTf_2 ionic liquids were synthesized including a high number of structural functionalizations on the carbohydrate and the imidazole, to investigate the structure-activity relationships in aza-Diels-Alder reactions. To get a deeper understanding of the influence of the carbohydrate on the

[a] *M. Komabayashi, Dr. S. Jopp*
Department Life, Light & Matter
University of Rostock
Albert-Einstein-Str. 25, 18059 Rostock, Germany
E-mail: stefan.jopp@uni-rostock.de

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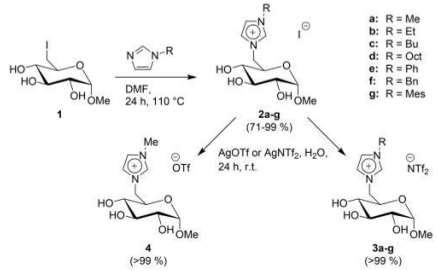
diastereomeric excess we also synthesized L-glucose organocatalysts for the first time.

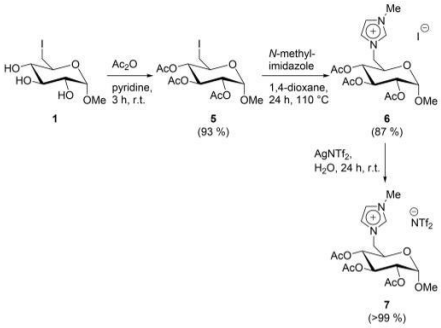
Results and Discussion

Synthesis of the Organocatalysts

Starting from commercially available methyl α-D-glucopyranoside, an Appel reaction is performed to achieve **1** in 91% yield. Next, *N*-substituted imidazoles were introduced into the 6-position, converting the sugars to the glucosyl imidazolium iodide salts **2a**–**g** in yields between 71 and 99%. These first two steps have previously been reported by our group.[22] Lastly, anion exchange with the corresponding silver salts in water leads to NTf_2-organocatalysts **3a**–**g** in full conversion, out of which only **3a** was previously reported by our group.[22] Additionally, the OTf-organocatalyst **4** was also prepared in full conversion in the same manner.[23] The CHILS-organocatalysts **3a**–**g** and **4** are thus synthesized in three steps in total yields between 64 and 89% (Scheme 1).



Scheme 1. Synthesis of glucosyl imidazolium ionic liquids with varying *N*-substituted imidazoles and varying anions.



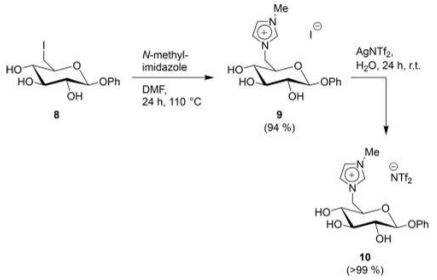
Scheme 2. Synthesis of acetyl-protected glucosyl imidazolium ionic liquid **7**.

Besides the variation of anions and imidazole substitution, we were also interested in the effect of other substitutions on the carbohydrate on the model aza-Diels-Alder reaction. For this, we synthesized the acetyl-protected organocatalyst **7** as well as organocatalyst **10**, which has a phenyl group at the anomeric center instead of the otherwise used methyl group.

For the synthesis of **7** (Scheme 2), **1** was acetylated to **5** in 93% yield and quarternized with *N*-methylimidazole to **6** in 87% yield. This product has recently been used by our group as precursor for organometallic NHC-complexes.[24] Herein, **6** was further converted to **7** by anion exchange with silver bis-trifylimide in full conversion.

In case of **10** (Scheme 3), the same reaction pathway as shown in scheme 1 was applied, this time however using commercially available phenyl β-D-glucopyranoside as starting material for the synthesis 6-iodo sugar **8** with 57% yield, followed by quarternization with *N*-methylimidazole to **9** in 94% yield.[22] The aimed for novel organocatalyst **10** was, again, achieved by anion exchange with silver bis-trifyl-imide in full conversion.

Since the overall influence of the chirality of the carbohydrate on the diastereomeric excess of (aza)-Diels-Alder reactions is ambiguous, as explained in the introduction, our final synthetic goal to shed light on this question was to synthesize the enantiomer of D-glucosyl imidazolium organocatalyst **3a**. Since methyl α-L-glucopyranoside **12** is not commercially available, a prolonged 6-step reaction pathway had to be applied for the synthesis of **15** (Scheme 4). First, L-glucose was converted to benzoyl-protected **11** in a two-step one pot procedure of Fischer glycosylation with methanol followed by benzoyl protection. The resulting alpha/beta (~80/20) mixture can in case of **11** be separated via column chromatography, as reported by Taniguchi and Monde *et al.*,[25] to achieve pure alpha anomer with 46% yield after two steps. A direct separation of the alpha/beta mixture after Fischer glycosylation, as reported by Lipták and Pozsgay *et al.*,[26] was not possible in our case. **12** was then achieved after Zemplén deprotection with sodium methanolate in full conversion. Afterwards, the same procedure as previously applied was used, first using the Appel reaction with iodine to achieve **13** in 71% yield, then quarternizing **13** with *N*-



Scheme 3. Synthesis of phenyl β-D-glucopyranoside organocatalyst **10**.

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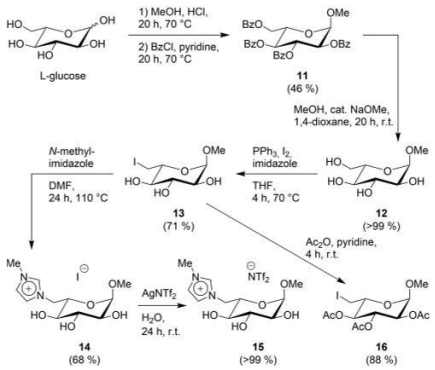


Scheme 4. Synthesis of the L-glucose-based organocatalyst **15**.

methylimidazole to **14** in 68% yield and finally anion exchange to achieve the L-glucosyl imidazolium organocatalyst **15** in full conversion. Since the NMR spectra of all L-glucose products **12** to **15** are identical to the respective D-glucose counterparts synthesized in this work, we aimed to prove the stereochemistry by crystal structure. However, all L-glucose products were difficult to crystalize, likely due to the free OH groups. Thus, **13** was converted to **16** by acetyl protection with 88% yield and a crystal structure of **16** was achieved by crystallization from chloroform and heptane (Figure 2).

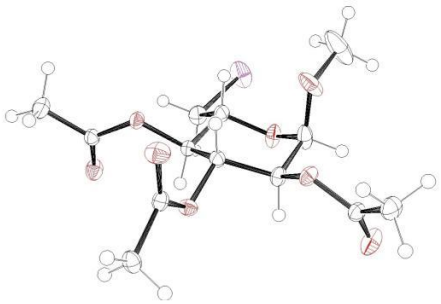
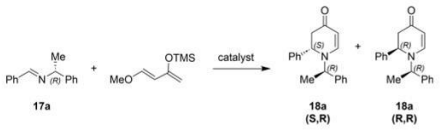


Figure 2. ORTEP of acetyl-protected 6-iodo L-glucose product **16**.[27]



Scheme 5. Model aza-Diels-Alder reaction.

Optimization of Aza-Diels-Alder Reaction

The model aza-Diels-Alder reaction used in this work was the cyclisation of chiral imine **17a**, which was prepared from benzaldehyde and *(R)*-phenylethylamine as previously reported,[28–29] and Danishefsky's diene to the piperidin-4-one product **18a** (Scheme 5). This model reaction was also previously used by Vo-Thanh *et al.*,[4–5] which allows us a direct comparison of our results with their work. In **18a**, one new asymmetric center is formed, leading to the two distinguishable diastereomers **18a (S,R)** and **18a (R,R)**. Since the NMR data of these diastereomers is known in literature,[5] both yield and diastereomeric excess could be calculated from NMR from the raw reaction mixtures.

With all our organocatalysts in hand, we investigated their reactivity in the aforementioned model reaction. First, the reactions were performed using no catalyst and the starting material methyl α-D-glucopyranoside (Table 1, entries 1–2). Both reactions had no conversion of the substrates, showing the importance of an ionic catalyst for this reaction. Using 10 mol% of zinc chloride as catalyst, as previously also reported Vo-Thanh *et al.*,[5] led to 42% yield and 45% de (Table 1, entry 3). It should be noted that these values are medians, as the control experiments with zinc chloride led to vastly varying yields between 24 to 65% and de values between 33 to 54%. This limited reproducibility of the results with $ZnCl_2$ is not observed with other catalysts investigated in this work. $ZnCl_2$ was used without further purification and might thus have varying results due to hygroscopy. For a better comparison with our CHILS-organocatalysts, which were initially used with 50 mol%, we also employed zinc chloride with a loading of 50 mol% (Table 1, entry 4), which led to an increase of the yield to 78%. The commercially available ionic liquid hydroxyethyl methyl imidazolium bis-trifyl-imide (HOEMIM-NTf_2) achieved a lower yield of 31%, but a notably higher de with 60% (Table 1, entry 4).

When comparing different anions, glucosyl methyl imidazolium iodide (GMIM-I) yielded 38% of the product with 43% de, while GMIM-OTf had only 9% yield and 20% de. GMIM-NTf_2 on the other hand had the best results with 73% yield and 70% de (Table 1, entries 6–8). Interestingly, both GMIM-OTf and GMIM-NTf_2 are room temperature ionic liquids and dissolved in the reaction mixture, while GMIM-I, as a salt with higher melting point, did not dissolve visibly. $ZnCl_2$ on the other hand is also soluble in the reaction mixture. Thus, the big differences in the results do not stem from solubility alone, but the anion itself seems to influence the reaction highly, with NTf_2 being the preferred anion.

Next, we investigated the influence of the *N*-substitution on the reactivity of the catalysts (Table 1, entries 8–14). With rising alkyl chain length from methyl (GMIM-NTf_2) to ethyl (GEIM-NTf_2) to butyl (GBIM-NTf_2) and finally to octyl (GOIM-NTf_2), the yield varies between 69 and 79% without a clear trend, while the de sinks stepwise from 70 to 53%. The aromatic substituents phenyl (GPhIM-NTf_2), benzyl (GBnIM-NTf_2) and mesityl (GMesIM-NTf_2) all lead to higher yields than GMIM-NTf_2, but lowered the diastereomeric excess. This is most notable in GPhIM-NTf_2 (Table 1, entry 12), which leads to 88% yield with only 53% de. If this phenyl substitution however is situated at the anomeric center

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Table 1. Optimization of the aza-Diels-Alder reaction between **17a** and Danishefsky's diene to **18a**.[a]

Entry	Catalyst	Catalyst amount	t (h)	Yield (%)[b]	de of **18a (S,R)** (%)[b]
1	none		2	n.d.	n.d.
2	methyl α-D-glucopyranoside	0.5 eq	2	n.d.	n.d.
3	$ZnCl_2$	0.1 eq	2	42	45
4	$ZnCl_2$	0.5 eq	2	78	38
5	HOEMIM-NTf_2	0.5 eq	2	31	60
6	GMIM-I (**2a**)	0.5 eq	2	38	43
7	GMIM-OTf (**4**)	0.5 eq	2	9	20
8	GMIM-NTf_2 (**3a**)	0.5 eq	2	73	70
9	GEIM-NTf_2 (**3b**)	0.5 eq	2	69	63
10	GBIM-NTf_2 (**3c**)	0.5 eq	2	79	61
11	GOIM-NTf_2 (**3d**)	0.5 eq	2	73	58
12	GPhIM-NTf_2 (**3e**)	0.5 eq	2	88	53
13	GBnIM-NTf_2 (**3f**)	0.5 eq	2	76	63
14	GMesIM-NTf_2 (**3g**)	0.5 eq	2	77	60
15	PhO-GMIM-NTf_2 (**10**)	0.5 eq	2	65	67
16	Acetyl-GMIM-NTf_2 (**7**)	0.5 eq	2	43	78
17	L-GMIM-NTf_2 (**15**)	0.5 eq	2	84	64
18	GMIM-NTf_2 (**3a**)	0.3 eq	2	66	66
19	GMIM-NTf_2 (**3a**)	0.1 eq	2	23	67
20	GMIM-NTf_2 (**3a**)	0.3 eq	5	80	67
21	GMIM-NTf_2 (**3a**)	0.3 eq	18	93	67

[a] Reaction conditions: chiral imine **17a** (1.0 mmol), Danishefsky's diene (1.5 mmol), catalyst (amount as given in each entry), time as given in each entry, room temperature. [b] Yield of **18a** and diastereomeric excess of **18a (S,R)** as determined by NMR from the raw reaction mixture.

instead of the imidazole (Table 1, entry 15), this same trend cannot the seen. The organocatalyst PhO-GMIM-NTf_2 leads to similar results as GMIM-NTf_2, proving the importance of the electronical situation of the imidazolium ring.

As seen in figure 3, the yield and de reached by each organocatalyst **3a–g** behave in a nearly mirrored fashion, where higher yield is mirrored by lower de. Overall, +M substituents seem to enhance the reaction rate while at the same time losing selectivity. Thus, GMIM-NTf_2 **3a** is the best middle ground for the different *N*-substitutions.

The previous works of Vo-Thanh and co-workers and Chrobok and co-workers have investigated the importance of free OH groups for the reactivity of CHILS-organocatalysts due to hydrogen bonding.[4–6] This trend has been further proven by us, as the yield drops with Acetyl-GMIM-NTf_2 (Table 1, entry 16) to 43%.

Lastly, we investigated L-GMIM-NTf_2 **15** (Table 1, entry 17), which is the enantiomer of GMIM-NTf_2 **3a** (Table 1, entry 8). As discussed in the introduction and as can also be seen from our results, the diastereomeric excess of the aza-Diels-Alder reaction is influenced by several factors like the anion and the overall reaction rate, making it unclear if the CHILS-organocatalyst exhibits any direct chiral induction. Since L-GMIM-NTf_2 **15** leads to 64% de, a result nearly unchanged from GMIM-NTf_2 **3a** with its 70% de, and since **15** did not lead to a higher selectivity towards the minor product **18a (R,R)**, it must be concluded that the CHILS-organocatalyst to not exhibit a chiral induction. Rather, the increased de observed with the CHILS-organocatalysts in

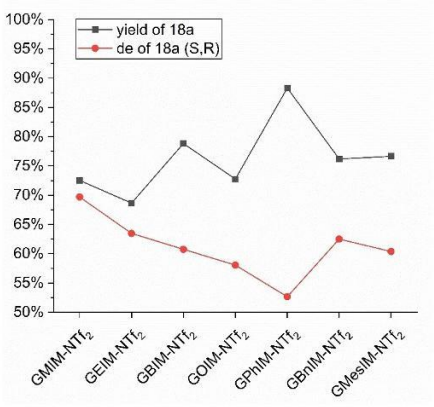

Figure 3. Yield of **18a** and diastereomeric excess of **18a (S,R)** synthesized with the organocatalysts **3a–g**.

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comparison to metal catalysts like $ZnCl_2$ seems to stem from a favorable combination of structural elements, like imidazolium, free OH groups and NTf_2 anion.

In the end we optimized the catalyst amount and reaction time while using the optimal CHILS-organocatalyst GMIM-NTf_2 **3a**. Reducing the catalyst amount from 0.5 eq to 0.3 eq leads to only a small decrease of the yield from 73% to 66%, while further decreasing the catalyst amount to 0.1 eq leads to a drop of the yield down to 23% (Table 1, entries 8 and 18–19). We chose to continue with 0.3 eq **3a** and prolonged the reaction time to 5 h and 18 h, which led to an increase of the yield to 80 and 93%, respectively (Table 1, entries 20–21). For all these experiments, the de was unaffected between 66 and 70%.

With the final optimized conditions of 30 mol% catalytic loading and 18 h reaction time, **3a**, a CHILS-organocatalyst that can be synthesized in in 3 steps with a total yield of 89%, has been found to lead to 93% yield and 67% de in the aza-Diels-Alder reaction between *(R)*-phenylethylamine and Danishefsky's diene. These results surpass comparative catalysts like zinc chloride and the ionic liquid HOEMIM-NTf_2 in both yield and de. Our catalysts lead to higher yields and a similar diastereomeric excess than the ones reported by Vo-Thanh *et al.*,[5] but are comparatively easier and more efficient in their preparation.

Recycling Experiments

The model aza-Diels-Alder reaction was always performed under solvent-free conditions. After the reaction time, water and diethyl ether were added and the aqueous phase was extracted with diethyl ether to separate the CHILS-organocatalyst in the aqueous phase from the substrates and products in the organic phase.

For recycling experiments, the aqueous phase was concentrated and the catalyst GMIM-NTf_2 **3a** was reused for the next experiment (Figure 4). However, due to the partial solubility of **3a** in diethyl ether, some percentage of **3a** was lost after each cycle, with only 2/3 of the original catalyst amount remaining after the second cycle, which in tandem led to decreased product yields (Figure 4). The de on the other hand is, as expected, unaffected by this loss of catalyst. We also investigated this recycling with chloroform, ethyl acetate, toluene and cyclopentyl methyl ether to potentially achieve a better separation of **3a**, but these extraction solvents all led to worse results.

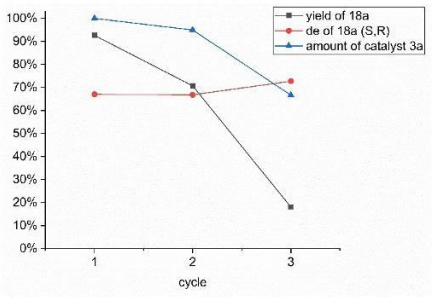


Figure 4. Recycling experiments (3 cycles) with organocatalyst **3a**. Reaction conditions: chiral imine **17a** (1.0 mmol), Danishefsky's diene (1.5 mmol), **3a** (0.3 mmol), 18 h, room temperature. Yield of **18a** and diastereomeric excess of **18a (S,R)** as determined by NMR from the raw reaction mixture.

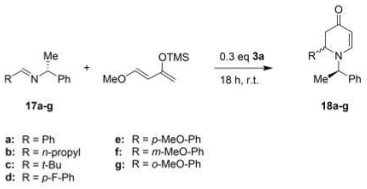
Imine Scope

For further application of our novel CHILS-organocatalysts, we investigated the scope of imine substrates. The synthesis of the imines **17a–g** started from benzaldehyde, butyraldehyde, pivaldehyde, *p*-fluorobenzaldehyde or *o*-/ *m*-/ *p*-methoxybenzaldehyde together with *(R)*-phenylethylamine, as reported in literature.[28–29] All aza-Diels-Alder reactions of **17a–g** with Danishefsky's Diene were carried out under optimized reaction conditions with **3a** as organocatalyst (Scheme 6).

While **18a** and its diastereomers **18a (S,R)** and **18a (R,R)** have previously been reported in literature,[4–5,30] all other products **18b–g** are reported for the first time in this work. The yields and de of all products are given in Table 2.

In comparison to the phenyl-substituted **18a** and its optimized yield and de of 93 and 67% (Table 2, entry 1), alkyl-substitution leads to a drastically reduced yield and diastereomeric excess of 13 and 24%, respectively, in case of *n*-propyl substituted product **18b** (Table 2, entry 2). The more sterically hindered *t*-Bu product **18c** was not formed under the given conditions. This leads us to believe that alkyl-substituted imines are generally very unreactive in this aza-Diels-Alder reaction.

We next explored substituted phenyl substrates. The electron-withdrawing fluorine atom in *para*-position in **18d** (Table 2, entry 4) leads to a lower yield of 53% in comparison to the unsubstituted phenyl product **18a**. The de on the other hand remains unchanged with 68%. In case of the electron-donating methoxy-group in *para*-position in **18e** (Table 2, entry 5), its yield with 71% is higher than **18d** but still lower than **18a**, but a heightened de of 78% was observed. When comparing the position of the group, both *para*- and *meta*-methoxy lead to similar results, while *ortho*-methoxy **18f** leads to a high yield of 90%, very similar to **18a**, but a lowered de of 51%. Overall, most substitutions on the aromatic ring influence the product yield and de negatively in comparison to the model substrate **18a**, and no clear trends in the effects of electron-withdrawing or



Scheme 6. Aza-Diels-Alder reactions with different imines.

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Table 2. Scope of differently substituted imines.[a]

Entry	Product	R	Yield (%)[b]	de of major diastereomer (%)[b]
1	18a	Ph	93	67
2	18b	*n*-propyl	13	24
3	18c	*t*-Bu	–	–
4	18d	*p*-F-Ph	53	68
5	18e	*p*-MeO-Ph	71	78
6	18f	*m*-MeO-Ph	68	67
7	18 g	*o*-MeO-Ph	88	52

[a] Reaction conditions: chiral imine **17a–g** (1.0 mmol), Danishefsky's diene (1.5 mmol), **3a** (0.3 mmol), 18 h, room temperature. [b] Yield and diastereomeric excess as determined by NMR from the raw reaction mixture.

electron-donating groups or their positions in the aromatic ring can be found.

All products **18c–g** have been isolated via column chromatography as diastereomeric mixtures. A separation of the diastereomers was not possible, which has been tested with several different eluent mixtures. Only in case of **18b** a separation of the major diastereomer was achieved via column chromatography. Furthermore, it was not possible to determine the absolute configuration of the newly formed stereocenter in **18b–g** via NOESY-2D-NMR experiments.

Conclusions

Overall 10 new glucosyl imidazolium based bis-triflyl-imide ionic liquids have been synthesized in this work, including variations of the *N*-substitution on the imidazolium, protecting groups on the sugar, different glycosidic groups and the use of both L- and D-glucose. The synthesis of all carbohydrate-based ionic and salts (CHILS) described in this work was optimized to achieve high total yields up to 89%.

All of these CHILS were investigated as organocatalysts in a model aza-Diels-Alder reaction between an imine, produced from benzaldehyde and *(R)*-phenylethylamine, and Danishefsky's diene, leading to a diastereomeric piperidin-4-one compound. Both the yield and the diastereomeric excess of this piperidin-4-one product are heavily influenced by the structure of the catalyst. It was found that the *N*-glucosyl *N'*-alkyl/aryl substituted imidazolium ionic liquids prepared in this work lead to notably higher yields and diastereomeric excess' than comparative dialkyl-substituted imidazolium ionic liquids or metal catalysts. Furthermore, a direct correlation between the reactivity of the CHILS organocatalyst and the de was found, with higher reactivities leading to lower de values. Overall, glucosyl methyl imidazolium bis-trifyl-imide (GMIM-NTf_2) **3a** was found the be the best organocatalyst for the model reaction. Its enantiomer, L-GMIM-NTf_2 **15**, has also been prepared, which marks the first L-glucose CHILS described in literature so far. Interestingly, no specific change in the stereoselectivity of the model aza-Diels-Alder reaction was observed with **15** as organocatalyst.

Finally, the aza-Diels-Alder model reaction used in this work and also by other groups before has, for the first time, also been investigated in its scope of different imine starting materials. Overall, alkyl-substituted imines were difficult to convert, but aryl-substituted imines could be easily be converted with both electron-withdrawing and electron-donating groups and also with a more sterically hindered *meta*- and *ortho*-substitution.

Experimental Section

The NMR spectra were recorded on a Bruker AVANCE 250 II, Bruker AVANCE 300 III, Bruker AVANCE 500 NEO or JEOL ECZL 400. $CDCl_3$ was calibrated as 7.27 (^{1}H) and 77.00 (^{13}C). DMSO-d_6 was calibrated as 2.49 (^{1}H) and 39.50 (^{13}C). D_2O was calibrated as 4.80 (^{1}H). MeOH-d_4 was calibrated as 3.31 (^{1}H) and 49.00 (^{13}C).

ESI-MS was measured in an Agilent 1200/6210 Time-of-Flight LC–MS or a Thermo Scientific Exactive ESI/DART FTMS. The specific rotations were measured with a Dr. Kernchen Gyromat-HP Digital Automatic Polarimeter with concentrations given in mg per mL.

Compounds **1**, **2a–g**, **8** and **9** were synthesized as previously reported by our group.[22] Compound **4** was synthesized as previously reported by our group.[23] Compounds **5** and **6** were synthesized as previously reported by our group.[24]

General Procedure for the Anion Exchange with Silver Bis-Triflyl-Imide towards Organocatalysts 3a–g, 7, 10 and 15

The carbohydrate-based iodide salt **2a–g**, **6**, **9** or **14** and an equimolar amount of silver bis-trifyl-imide were dissolved in water (3.0 mL/mmol) and stirred at room temperature for 20 h under absence of light. The reaction was the filtered through celite and the aqueous filtrate containing the product was concentrated. The product was dissolved in MeOH (3.0 ml/mmol) and filtered through celite again to remove black silver particles. The product was achieved in full conversion after drying.

General Procedure for the Synthesis of Imines 17a–g

Adapting the procedure of Cimeralli *et al.*,[28] *(R)*-phenylethylamine and the corresponding aldehyde (1.2 eq) (**17a**: benzaldehyde, **17b**: butyraldehyde, **17c**: pivaldehyde, **17d**: *p*-fluorobenzaldehyde, **17e**: *p*-methoxybenzaldehyde, **17f**: *m*-methoxybenzaldehyde, **17g**: *o*-methoxybenzaldehyde) were stirred in dichloromethane (1.0 mL/mmol) with $MgSO_4$ (2.0 g/mmol) for 24 hours. After filtration, the product was obtained from the filtrate after drying. 79% yield was achieved for **17a**, 52% for **17b**, 81% for **17c**, 81% for **17d**, 82% for **17e**, 79% for **17f** and 87% for **17g**.

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General Procedure for the Aza-Diels-Alder Reaction towards Products 18a–g

Imine **17a-g** (1.0 mmol), Danishefsky's diene (1.5 mmol, 258 mg) and GMIM-NTf_2 **3a** (0.3 mmol, 162 mg) were added into a flask. After stirring for 18 hours, the reaction was dried under high vacuum. Then water (10 mL) was added and extracted with Et_2O (3x10 mL). The organic phase was collected and dried under high vacuum to achieve the crude product as a yellow oil. The purified product was obtained after column chromatography: heptane/ ethyl acetate 9:1→3:7→methanol for **18b**, heptane/ ethyl acetate 9:1→3:7 for **18d** and **18f–g**, heptane/ ethyl acetate 9:1→chloroform/ methanol 12:1 for **18e**.

Methyl α-L-Glucopyranoside 12

L-Glucose (10 mmol, 1.802 g) was suspended in MeOH (10 mL) and cooled to 0 °C. A methanolic HCl solution was prepared by adding acetyl chloride (0.6 mL) dropwise to MeOH (6 mL). This methanolic HCl solution was added slowly to the suspension containing L-glucose and the reaction was stirred at 0 °C for 30 min. Then, the reaction was refluxed at 70 °C for 20 h. The solvent of the clear solution was evaporated to achieve a crude alpha/beta mixture of methyl α-L-glucopyranoside. This was dissolved in pyridine (50 mL), benzoyl chloride (5 mL) was added slowly and the reaction was stirred at 70 °C for 20 h. Ethyl acetate (100 mL) was added and the organic phase was washed sequentially with 1M HCl (100 mL), 1M NaOH (100 mL) and water (100 mL) and finally dried with $NaSO_4$ and filtered. The solvent was removed and methyl 2,3,6-*O*-benzoyl-α-L-glucopyranoside **11** (952 mg, 46% after two steps) was obtained after column chromatography (heptane/ ethyl acetate 3:1). **11** (1.88 mmol, 952 mg) was then dissolved in MeOH (18 mL) and 1,4-dioxane (18 mL) and a 0.5M NaOMe in MeOH solution (1 mL) was added. The reaction was stirred at room temperature for 20 h. Amberlite IR-120 (pre-washed in MeOH) was added for neutralization and then filtered off. The solvents were removed and the crude product was dissolved in water (30 mL) and washed with diethyl ether (3x 30 mL). The product was obtained as a yellow oil (363 mg, 99%) after the removal of water.

Methyl 6-Iodo-α-L-Glucopyranoside 13

12 (320 mg, 1.65 mmol), triphenylphosphine (671 mg, 2.56 mmol), iodine (607 mg, 2.39 mmol) and imidazole (225 mg, 3.30 mmol) were refluxed in THF (10 mL) for 4 h. The resulting solid was filtered off, the solvent was removed and the product was obtained as an off-white solid (355 mg, 71%) after column chromatography (chloroform/methanol 12:1).

1-(Methyl-α-L-Glucopyranosid-6-yl)-3-Methylimidazolium Iodide (L-GMIM-I) 14

13 (350 mg, 1.15 mmol) and N-methylimidazole (157 mg, 1.92 mmol) were dissolved in DMF (5 mL) and stirred at 110 °C for 20 hours. After cooling down, ethyl acetate (30 mL) was added and the flask was stored in a fridge overnight. The solvent was decanted and the precipitated solid was washed with ethyl acetate (3x 10 mL) and dried under high vacuum to achieve the product as a light-brown solid (301 mg, 68%).

Methyl 2,3,4-O-Acetyl-6-Iodo-α-L-Glucopyranoside 16

13 (200 mg, 0.66 mmol) was dissolved in pyridine (5 mL) and acetic anhydride (2 mL) was added. The reaction was stirred at room temperature for 4 h. All volatiles were removed via co-distillation with toluene (3x 50 mL). The product was obtained as a white solid (250 mg, 88%) after column chromatography (heptane/ethyl acetate 1:1).

Supporting Information

Characterization data and ^{1}H-, ^{13}C- and ^{19}F-NMR spectra of all CHILS-organocatalysts **3a–g**, **7** and **10**, all L-glucose products **12–16** and all new aza-Diels-Alder products **18b–g** can be found in the supporting information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Ionic Liquid · Carbohydrate · Glucose · Organocatalysis · Aza-Diels Alder Reaction

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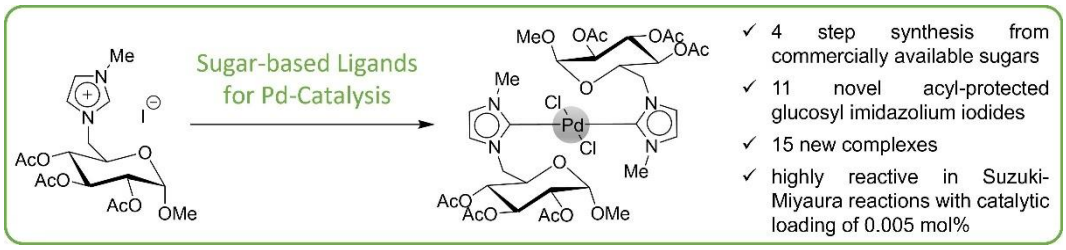
7. Publication II: Structure-Activity Relationships of Glucose-based Pd^{II}-Bis(NHC) Complexes in a Model Suzuki-Miyaura Reaction



H. Ziems, M. Komabayashi, P. Lehmann, A. Villinger, S. Jopp, *Eur. J. Org. Chem.* **2024**, *27*, e202400177. https://doi.org/10.1002/ejoc.202400177

Contribution statement:
Mirai Komabayashi contributed to the synthesis and analysis of the metal complexes together with Hannes Ziems. Paul Lehmann did the GC analysis. The publication was co-authored by Mirai Komabayashi after the initial draft by Hannes Ziems and Stefan Jopp.

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Structure-Activity Relationships of Glucose-based Pd^{II}-Bis(NHC) Complexes in a Model Suzuki-Miyaura Reaction

Hannes Ziems,[a] Mirai Komabayashi,[a] Paul Lehmann,[b] Alexander Villinger,[b] and Stefan Jopp*[a]

The authors of this work have optimized a novel synthetic route towards glucose-based Pd^{II}-bis(NHC) complexes in only 4 steps with total yields up to 73%. The synthesis route encompasses an Appel reaction towards 6-iodo-glucopyranosides, followed by acyl-protection, then quaternization with imidazoles and finally the conversion of these acyl-protected glucosyl imidazolium salts to their respective palladium(II)bis(NHC) complexes, via an intermediary silver(I) complex. Overall, 11 acyl-protected glucosyl imidazolium iodides as NHC-precursors and 15 complexes have been synthesized. The structure-activity relationships of different functionalizations in these complexes and their reactivity in a model Suzuki-Miyaura between bromobenzene and 4-tolueneboronic acid reaction has been investigated, and a highly reactive complex leading to >99% yield at 0.005 mol% catalytic loading has been found.

Introduction

N-heterocyclic carbenes (NHCs), also known as Arduengo carbenes, named after the discoverer of the first bench-stable NHC,[1] are a class of stable carbene molecules that are mainly used as ligands in transition metal or p-block element complexes.[2–5] NHCs can be prepared from many different heterocycles, however, the most commonly used structure are the imidazolylidene-NHCs, which are synthesized from imidazolium salts or ionic liquids as precursors. These imidazolylidene-NHCs can bear a wide array of substituents on the nitrogen atoms and the backbone of the heterocycle, from simple alkyl chains[6] to bulky aromatic rings.[7] Natural chiral pools such as amino acids have also been explored.[8] However, even though carbohydrates are the most ubiquitous class of biomolecules, they have only rarely been used in coordination chemistry, with only a few known examples of phosphine-[9] and NHC-ligands[10] incorporating a carbohydrate moiety. Besides the important factor of sustainability, carbohydrate-based NHC complexes have an increased water solubility[11] and are expected to exhibit a lower toxicity, since similar trends are found in biomolecule-bearing imidazolium based ionic liquids.[12–13]

The most notable examples of carbohydrate-based NHC complexes are the glucose-based bis(NHC) palladium bromide complexes of Lin *et al.* (Scheme 1A),[11] the glucose-based pincer complexes by Nishioka *et al.* (Scheme 1B)[14] and the glucose-based PEPPSI complexes by Zhou *et al.* (Scheme 1C).[15] All of these complexes have been reported as highly active catalysts for Suzuki-Miyaura reactions in aqueous or ethanolic media. However, due to the complexity of carbohydrate chemistry, including protecting groups and chemoselective reactions on either the anomeric center or other hydroxy groups, all of these catalysts are prepared in multistep syntheses of 4 to 8 steps with low to mediocre total yields (11 to 41%). Furthermore, only little investigation has been done on the structure-activity relationships so far, since all of the above complexes have only been prepared with small variations in alkyl-chain length on the imidazolylidene and have used only a single palladium salt (either palladium bromide or chloride) in the center of the complexes.

Recently our working group has discovered a straightforward and high-yielding two-step synthesis of glucosyl imidazolium ionic liquids.[13] These ionic liquids have been proven to exert a remarkable biocompatibility[13] and have also been applied in biocatalysis[16] and for hydrogel synthesis.[17]

In this work we aim to use our established glucosyl imidazolium ionic liquids combined with the catalyst preparation route by Lin *et al.*[11] to achieve the synthesis of novel complexes with only 4 overall steps in high total yields. Furthermore, we aim to prepare these glucose-based Pd^{II}-bis(NHC) complexes with a high number of variations on the palladium, the imidazole and the carbohydrate itself, to study the influence of these variations on the catalytic activity in a Suzuki-Miyaura model reaction.

[a] *H. Ziems, M. Komabayashi, Dr. S. Jopp*
Department Life, Light & Matter
University of Rostock
Albert-Einstein-Str. 25, 18059 Rostock, Germany
E-mail: stefan.jopp@uni-rostock.de

[b] *P. Lehmann, Dr. A. Villinger*
Institute of Chemistry
University of Rostock
Albert-Einstein-Str. 3a, 18059 Rostock, Germany

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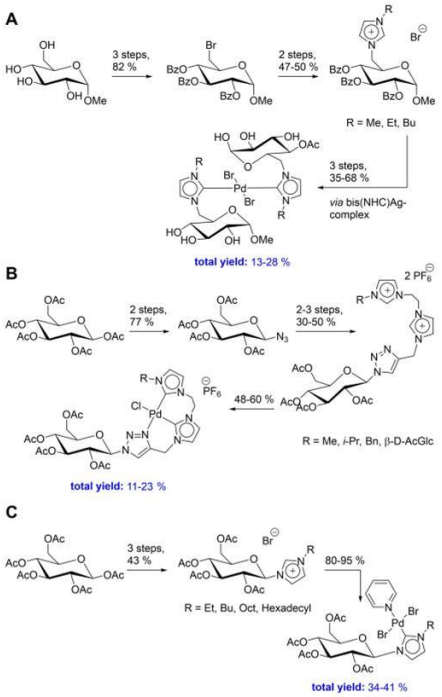
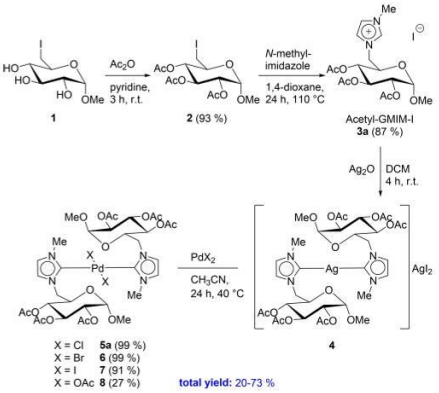


Scheme 1. Previous works on glucose-based Palladium NHC complexes by A) Lin *et al.*,[11] B) Nishioka *et al.*[14] and C) Zhou *et al.*[15]



Scheme 2. Synthesis of Pd^{II}-bis(NHC) complexes with different anions on the palladium.

Results and Discussion

The synthesis starts from methyl 6-iodo-α-D-glucopyranoside **1**, which can be prepared in one step from the commercially available methyl α-D-glucopyranoside in 91% yield via an Appel reaction.[13] **1** was then converted into the acetyl-protected product **2** in 93% yield with a simple work-up protocol of filtration and washing with ethanol (Scheme 2).[18] We decided to mainly work with acetyl protecting groups due to their widespread use in carbohydrate chemistry and due to the comparison of our complexes with the previous works of Nishioka *et al.*[14] and Zhou *et al.*,[15] though we also introduced other protecting groups later. As the next step, **2** was quarternized with *N*-methylimidazole to achieve Acetyl-GMIM–I **3a** (GMIM–I = glucosyl methyl imidazolium iodide). In our previous projects, where we worked with the analogue unprotected GMIM–I, we used DMF as a solvent for this step and precipitated the salt product by addition of ethyl acetate to the reaction mixture.[13] This procedure however does not work for the acetyl-protected **3a**, since this product does not precipitate from ethyl acetate. Changing the reaction solvent from DMF to 1,4-dioxane however leads to the direct precipitation of **3a** from the reaction mixture while still enabling high yields in this step.

With Acetyl-GMIM–I **3a** in hand we initially converted this with 0.5 equivalents of silver(I) oxide to the silver complex **4** (Scheme 2), using the procedure reported by Lin *et al.* for similar complexes.[11] Lin *et al.* reported the precipitation of the silver halogenide from this reaction, but we always observed clear solutions during this step. This can be explained by the formation of an iodoargentate anion.[19] The solvent of this solution was then removed and the resulting white solid was analyzed via ^{1}H- and ^{13}C-NMR (Figure 1) without any further work-up. This resulted in a clean spectrum of **4**, thus confirming the full conversion of **3a** to **4**. The carbon signal of the NCN-bridge shifted downfield from ~137 ppm in **3a** to ~186 ppm in **4**. This fits the expected range for a silver-NHC bond.[11]

The silver complex **4** was from then onwards always handled as an intermediate and was directly converted into the palladium complexes without further work-up or analysis. The new glucose-based Pd^{II}-bis(NHC) complexes **5a** and **6**–**8** were thus produced from **3a** in a one-pot two-step synthesis. Here we optimized the reaction conditions reported by Lin *et al.*[11] for similar complexes by slightly raising the reaction temperature from room temperature to 40 °C and by prolonging the reaction time from 4 hours to 24 hours, thus raising the reported 50% yield to up to 99% for our complexes (Scheme 2). Notably, all palladium halogenides (chloride, bromide and iodide) were converted into their respective complexes with over 91% yield under these conditions, while the palladium acetate complex **8** was achieved in a low yield of 27%, which can likely be attributed to higher stability of the usually trimeric palladium acetate complex as well as its sterical hindrance.[20] With this we were able to raise the total yields (calculated

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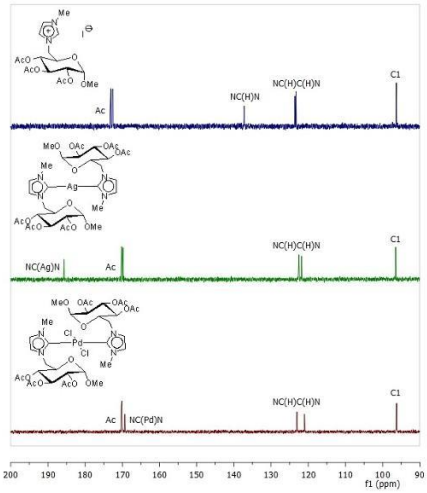


Figure 1. Exert of the ^{13}C-NMR spectra of **3a** in D_2O (blue), **4** in $CDCl_3$ (green) and **5a** in $CDCl_3$ (red).

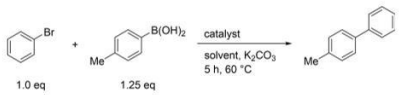
starting from the commercially available starting material methyl α-D-glucopyranoside) of the 4-step synthesis to 67–73% for the complexes **5a**, **6** and **7**, while the low reactivity of palladium acetate leads to low total yield of 20% for **8**.

NMR analysis of complex **5a** in comparison to **3a** and **4** showed the shift of the NCN-bridge to ~169 ppm (Figure 1), as expected for the palladium-NHC bond.[11] The signal at 169 ppm was identified as the NCN-bridge of the imidazolium ring through HSQC- and HMBC-2D-NMR experiments. A clear interaction of the signal at 169 ppm with the imidazole protons, the C-6 protons and the methyl group on the imidazole can be seen in the HMBC experiments (see supporting information). Interestingly, both **5a** and **7** feature only one isomer in the NMR spectrum in $CDCl_3$, while both **6** and **8** appear as a mixture of 4 isomers. This can be attributed to the *cis/trans*- as well as *syn/anti* isomers.[21] The *trans-anti*-isomer is generally expected to be the preferred isomer due to the lowest sterical hindrance, though an equilibrium between all isomers may appear in solution. Lastly, complex **8** uniquely confirms the formation of Pd^{II}-bis(NHC) complexes as opposed to mono(NHC) complexes, since **8** has overall 5 singlet-signals at 1.71, 2.03, 2.06, 2.07 and 2.14 ppm in the ^{1}H-NMR. Both the signals at 1.71 and 2.14 are integrated as 3 and are attributed to the acetate anions located at the palladium, while the signals at 2.03, 2.06 and 2.07 are integrated as 6 and are attributed to the three different acetyl groups at O-2, O-3 and O-4 of the glucose, which each exist two times in a Pd^{II}-bis(NHC) complex.

It should be noted that the acetyl-deprotection of the complexes is possible through Zemplen conditions.[11] This will lead to water-soluble complexes with free hydroxy groups, which have previously been investigated by Lin *et al.* (Scheme 1A)[11] and are thus not the focus of this work.

To determine which palladium salt at the center of the NHC-complexes will be used for further syntheses of the functionalized complexes, we first tested the reactivity of **5a** and **6**–**8** in a model Suzuki-Miyaura reaction between bromobenzene and 4-tolueneboronic acid to 4-methylbiphenyl (Scheme 3).

Entries 1–4 of Table 1 show the reactivity of the complexes under the chosen reaction conditions of 60 °C and 5 h reaction time. The product yield sinks from **5a** (40%) to **6** (25%) to **7** (4%), which may be explained by the rising atom sizes of the halogenide anions and thus the higher sterical hindrance surrounding the palladium. The palladium acetate complex **8** leads with 34% yield to only slightly lower results than the chloride complex **5a**. As solvent we initially chose chloroform due to the high solubility of the complexes in this solvent. A thorough optimization of the base and the solvent was performed (see supporting information for additional optimization tables) and overall ethanol (Table 1, entry 5) and potassium carbonate were found to be the best solvent and base for our complexes. Furthermore, 5 mol% of the complexes have initially



Scheme 3. Model Suzuki-Miyaura reaction between bromobenzene and 4-methylphenyl boronic acid.

Table 1. Influence of the catalysts **5a** and **6**–**8** on a Suzuki-Miyaura model reaction.[a]

Entry	Catalyst	Catalyst name	Solvent	Yield (%)[b]
1	**5a**	(Acetyl-GMIM)$_2$PdCl$_2$	$CHCl_3$	40
2	**6**	(Acetyl-GMIM)$_2$PdBr$_2$	$CHCl_3$	25
3	**7**	(Acetyl-GMIM)$_2$PdI$_2$	$CHCl_3$	4
4	**8**	(Acetyl-GMIM)$_2$Pd(OAc)$_2$	$CHCl_3$	34
5	**5a**	(Acetyl-GMIM)$_2$PdCl$_2$	EtOH	56

[a] Reaction conditions: bromobenzene (1.0 mmol), 4-tolueneboronic acid (1.25 mmol), K_2CO_3 (2.0 mmol), catalyst (0.05 mmol), solvent (3 mL), 60 °C, 5 h. [b] Yield of 4-methylbiphenyl determined by GC, using nitrobenzene as internal standard, with 3 individual samples taken from each reaction.

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been used for the model reaction, as these catalytic loadings are often employed for Suzuki-Miyaura reactions using various Pd-catalysts.[22–26]

After determining palladium chloride as the best salt for the complexes, we next synthesized 7 further acetyl-protected glucosyl imidazolium salts from **2** by varying the imidazole used for the quarternization, and subsequently converted these salts **3b–h** into their respective Pd^{II}-bis(NHC) complexes **5b–h** (Scheme 4).

The synthesis of the salts was performed as described before for Acetyl-GMIM–I **3a** and similar yields in the region of 70 to 84% were achieved for all alkyl-substituted products, while the two aryl-substituted products had slightly lower yields of around 58%. However, only the phenyl-substituted **3f** precipitated from the reaction as **3a** did, while all the other products had to be purified via a filtration-like column chromatography, where first ethyl acetate was used to remove all remaining starting material **2** and *N*-substituted imidazole, while the product was collected from methanol afterwards.

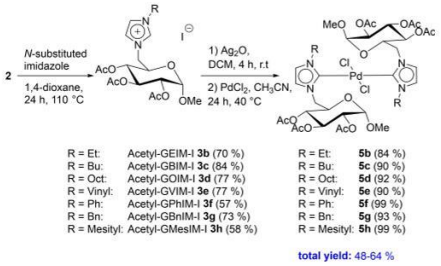
As mentioned before, the complexes **5b–h** were produced in a one-pot two-step synthesis, where the intermediate silver complex was not collected. Generally, very good yields between 84 and 99% were achieved for all complexes in this step. The total yields of all complexes with different alkyl- and aryl-groups at the imidazolylidene (**5a–h**) vary between 48 and 73% and all exceed the known literature (Scheme 1).

After the successful synthesis of the complexes **5a–h**, which all differ in the substituent located at the imidazolylidene, we next aimed to prepare 3 further complexes with structural variations on the glucose.

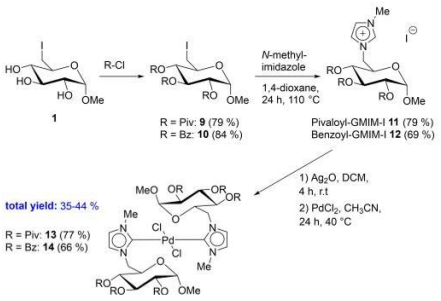
In an analogue pathway as performed for the acetyl-protected products, both pivaloyl- and benzoyl-protected starting materials (**9** and **10**), glucosyl methyl imidazolium salts (**11** and **12**) and Pd^{II}-bis(NHC) complexes (**13** and **14**) were synthesized (Scheme 5). The reaction procedures for the introduction of the pivaloyl[27] and benzoyl[28] protecting groups were adapted from known procedures for similar sugars. In general, all yields were in the same regions as for the acetylated products, with the exception of the complexes, whose yields dropped from 96% (**5a**) to 77% for the pivaloylated complex **13** and to 66% for the benzoylated complex **14**, which is likely explained by the rising steric demand of these groups.

Lastly, we also converted phenyl 6-iodo-ß-D-glucopyranoside **15**, which has been previously synthesized by our group from the commercially available phenyl ß-D-glucopyranoside in 51% yield,[13] into the acetyl-protected **16** in 88% yield, followed by its quarternization with *N*-methylimidazole to Acetyl-PhO-GMIM–I **17** in 76% yield and finally the formation of the complex **18** in 61% yield (Scheme 6). This complex differs from **5a** in its glycosidic group. The yield of the complex formation step is comparatively lower, likely due to the bigger phenyl ring in **18** in comparison to the smaller methyl group in **5a**.

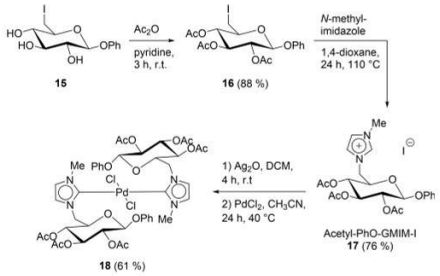
Overall five x-ray crystal structures were obtained of the compounds described in this work. These are the acyl-protected starting materials **2**, **9** and **10** as well as the salts Acetyl-GMIM–I **3a** and Acetyl-GEIM–I **3b**. The ORTEP plots of **3a** and **9** are given in figures 2 and 3, while the ORTEP plots of the other similar compounds can be found in the supporting information. The crystal structures of **3a** and **9** prove the expected stereochemistry (α-OMe, chair conformation) as well as the correct positioning of all groups, like the imidazolium ring/iodine bound to C-6 of the glucose. All compounds have been



Scheme 4. Synthesis of Pd^{II}-bis(NHC) complexes with different alkyl- and aryl-groups at the imidazolylidene.



Scheme 5. Synthesis of Pd^{II}-bis(NHC) complexes with different acyl-protecting groups on the glucose.



Scheme 6. Synthesis of a Pd^{II}-bis(NHC) complex with a different glycosidic group.

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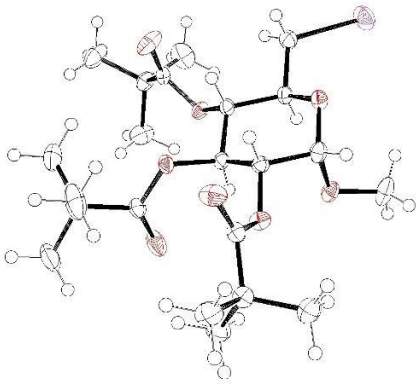

Figure 2. ORTEP plot of **9**.[29]

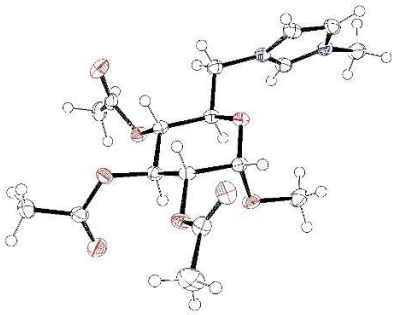

Figure 3. ORTEP plot of Acetyl-GMIM–I **3a**.[29]

crystallized by slow crystallization from chloroform. In case of the benzoylated starting material **7**, twelve sugar molecules crystallized together with sixteen chloroform molecules in a cell, leading to a proportion of 1.33 solvate molecules. Interestingly, the salt **3b** crystallized with one water solvate molecule, even though water has not been used in any step of the synthesis or work-up. This proves the hygroscopy observed for some of the salts, though that effect was visibly strongest for **3d** and **3g**. All further supplementary crystallographic data can be accessed under their respective CCDC numbers.[29]

Crystallization (either by slow evaporation or by precipitation) of the complexes was attempted from several solvents and solvent mixtures of chloroform, ethyl acetate, THF, methanol, ethanol, heptane and toluene and always lead to amorphous solids.

With all differently functionalized dichlorobis(glucose-based-NHC)Pd^{II} complexes in hand, we performed the final investigation of their reactivity in the aforementioned model Suzuki-Miyaura reaction (Table 2).

Entries 1–8 of table 2 allow thorough comparison of the effect of different alkyl- and aryl-substitutions on the imidazoylidene of our complexes. All alkyl-substituted complexes, namely the methyl- (**5a**), ethyl- (**5b**), butyl- (**5c**), octyl- (**5d**) and benzyl-groups (**5g**), all lead to the same catalytic activity in the chosen model reaction, with GC yields of 4-methylbiphenyl of 52 to 56%. This was an unexpected result, as the previous works of Lin *et al.*[11] and Zhou *et al.*[15] always observed rising catalytic activities with rising alkyl chain length. The vinyl-substituted complex **5e** shows no catalytic activity, which might stem from additional coordination bonds between the palladium and the vinyl-group, thus deactivating the palladium. The aryl-substituted complexes **5f** (phenyl) and **5h** (mesityl) lead to a strong rise of catalytic activity, leading to 80 and >99% product yield, respectively. The +M effect of the aryl-substituents, which is even stronger in the electron-richer mesityl-group, thus takes an important role in these complexes.

The change of the acyl-protecting group from acetyl (**5a**) to the similar yet sterically more demanding pivaloyl (**13**) leads to a decrease of catalytic activity with only 19% product yield (Table 2, entry 9). Interestingly, the also sterically more demanding benzoyl protecting group (**14**) leads a slight increase of the activity to 63% yield (Table 2, entry 10). Similarly, replacing the glycosidic group of the carbohydrate from methyl (**5a**) to phenyl (**18**) also leads to a small increase in catalytic activity from 56 to 60% (Table 2, entry 11).

It can thus be concluded that the functional variations on the imidazoylidene have the highest influence on the catalytic activity, followed by the variation of the *O*-protection on the carbohydrate, while the variation of the glycosidic group seems to influence the overall activity of the complex only slightly. In all cases, aromatic groups had a positive effect.

The catalytic loading of the best catalyst, (Acetyl-GMeslM)$_2$PdCl$_2$ **5h**, was then decreased bit by bit from 5 mol% to 0.5, 0.05, 0.005 and 0.0005 mol% (Table 2, entries 8 and 12–16). The product yield remains at >99% until 0.005 mol% catalytic loading is reached and drops only slightly to 81% at 0.001 mol% of **5h**. At 0.0005 mol%, however, the catalytic activity completely drops to only 8% yield.

Furthermore, to test our catalyst for a less reactive substrate, the reaction was performed with the electron-withdrawing 4-fluorophenyl boronic acid instead of the electron-donating 4-toluneboronic acid while using 0.005 mol% of **5h** (Table 2, entry 17). The catalyst remains reactive and the product was isolated in 90% yield.

A direct comparison of the catalytic activity of our complexes to the other carbohydrate-based NHC complexes referenced in this work remains difficult, since other model substrates and other reaction conditions (like higher temperatures of 100 °C and longer reaction times in case of Lin *et al.* and Nishioka *et al.*) were used. The glucose-based PEPPSI

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Table 2. Influence of the catalysts **5a–h** and **13**, **14** and **18** on a Suzuki-Miyaura model reaction.[a]

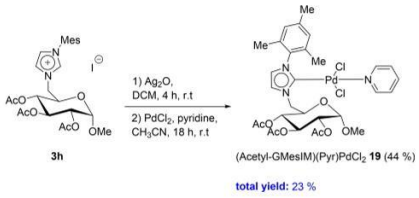
Entry	Catalyst	Catalyst name	mol% of Catalyst	Yield (%)[b]
1	**5a**	(Acetyl-GMIM)$_2$PdCl$_2$	5	56
2	**5b**	(Acetyl-GEIM)$_2$PdCl$_2$	5	52
3	**5c**	(Acetyl-GBIM)$_2$PdCl$_2$	5	52
4	**5d**	(Acetyl-GOIM)$_2$PdCl$_2$	5	53
5	**5e**	(Acetyl-GVIM)$_2$PdCl$_2$	5	traces
6	**5f**	(Acetyl-GPhIM)$_2$PdCl$_2$	5	80
7	**5g**	(Acetyl-GBnIM)$_2$PdCl$_2$	5	56
8	**5h**	(Acetyl-GMesIM)$_2$PdCl$_2$	5	>99
9	**13**	(Pivaloyl-GMIM)$_2$PdCl$_2$	5	19
10	**14**	(Benzoyl-GMIM)$_2$PdCl$_2$	5	63
11	**18**	(Acetyl-PhO-GMIM)$_2$PdCl$_2$	5	60
12	**5h**	(Acetyl-GMesIM)$_2$PdCl$_2$	0.5	>99
13	**5h**	(Acetyl-GMesIM)$_2$PdCl$_2$	0.05	>99
14	**5h**	(Acetyl-GMesIM)$_2$PdCl$_2$	0.005	>99 (99)[d]
15	**5h**	(Acetyl-GMesIM)$_2$PdCl$_2$	0.001	81
16	**5h**	(Acetyl-GMesIM)$_2$PdCl$_2$	0.0005	8
17[c]	**5h**	(Acetyl-GMesIM)$_2$PdCl$_2$	0.005	90[d]
18	/	(PPh$_3$)$_2$PdCl$_2$	0.005	74
19	**19**	(Acetyl-GMesIM)(Pyr)PdCl$_2$	0.005	>99
20	**19**	(Acetyl-GMesIM)(Pyr)PdCl$_2$	0.001	76

[a] Reaction conditions: bromobenzene (1.0 mmol), 4-toluneboronic acid (1.25 mmol), K_2CO_3 (2.0 mmol), catalyst, abs. EtOH (3 mL), 60 °C, 5 h. [b] Yield of 4-methylbiphenyl determined by GC, using nitrobenzene as internal standard, with 3 individual samples taken from each reaction. [c] 4-Fluorophenyl boronic acid was used. [d] Isolated yield.

complexes by Zhou *et al.* however where also evaluated in the same model reaction between bromobenzene and 4-toluneboronic acid (Scheme 3) under very similar reactions conditions and in their case 0.05 mol% of their best catalyst was determined as the best activity.[15] As a further comparison we also used the commercially available catalyst (PPh$_3$)$_2$PdCl$_2$ under our optimized reaction conditions at 0.005 mol% catalytic loading, which achieved 74% yield (Table 2, entry 18). Thus, our complexes are comparatively more reactive than the complexes of Zhou *et al.* and the tested commercial catalyst.

To get a full understanding of the structure-activity relationships, we finally synthesized the glucopyranoside-based PEPPSI complex **19** from **3h** (Scheme 7). The synthesis of **19** was adapted from a recent work by Fiego and Silbestri *et al.*, who investigated galactopyranoside-based PEPPSI complexes.[30] The synthetic strategy is similar to the one employed by us for Pd^{II}-bis(NHC) complexes in this work, whereas firstly a silver complex is formed, which is then transformed into the PEPPSI complex by addition of palladium chloride and pyridine in equimolar amounts to **3h**. This procedure is, however, less selective than the formation of Pd^{II}-bis(NHC) complexes and leads to bis(pyridine)PdCl$_2$ as side product, while also some starting material **3h** was not converted. Thus, an lower yield of only 44% was achieved. The structure of the PEPPSI complex **19** was confirmed via NMR, which shows all expected pyridine signals and the palladium-NHC bond at ~152 ppm, as expected for such a PEPPSI complex.[15,30]

The PEPPSI complex **19** was then used in our model Suzuki-Miyaura reaction (Table 2, entries 19–20). Similar to **5h**, the best Pd^{II}-bis(NHC) complex of this work, **19** leads to >99% yield at 0.005 mol%, further proving the generally high activity of the mesitylene- and glucopyranoside-substituted imidazoylidene ligand. At 0.001 mol% **19** also performs similar to **5h**, with 76% yield in comparison to 81% yield. This comparison shows that, at least in case of the activity in Suzuki-Miyaura reactions, one or two bulky mesitylene- and glucopyranoside-substituted NHC ligands make only a small difference. However, due to the higher total yields in catalyst preparation, **5h** is preferable over **19**.



Scheme 7. Synthesis of a PEPPSI complex from **3h**.

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Conclusions

A novel synthetic pathway leading from commercially available glucopyranosides to glucose-based Pd^{II}-Bis(NHC) complexes in only 4 steps was established. In this work overall 11 new acyl-protected glucosyl imidazolium salts were synthesized, which were used as precursors for overall 15 novel complexes. These palladium complexes have been synthesized in total yields up to 73%, highly advancing the previously known synthetic protocols. The NHC-complexes have been designed with a high number of possible functionalizations in mind, ranging from different alkyl- and aryl-groups on the imidazoylidene, over different acyl-protecting groups and varying glycosidic groups on the carbohydrate to different palladium(II) salts at the complex center. The structure-activity relationship of all these functionalized Pd-complexes in a model Suzuki-Miyaura reaction has been studied. The investigation showed that both the palladium salt at the center of the complex as well the imidazoylidene functionalizations have a strong influence on the catalytic activity, while the influence of the functional variations on the carbohydrate is smaller. Overall, palladium chloride was found to be preferable over other palladium salts and aryl-groups were found to positively influence the catalytic activity. The mesityl-substituted complex $(Acetyl\text{-}GMesIM)_2PdCl_2$ was found to be the most reactive complex in the model Suzuki-Miyaura reaction, leading to $>99\%$ product yield with very low catalyst loadings of 0.005 mol% and to 81% yield at 0.001 mol%, surpassing other comparable catalysts.

Experimental Section

The NMR spectra were recorded on a Bruker AVANCE 300 III or 500. $CDCl_3$ was calibrated as 7.27 (^1H) and 77.00 (^{13}C). DMSO-d_6 was calibrated as 2.49 (^1H) and 39.50 (^{13}C). D_2O was calibrated as 4.80 (^1H). ESI-MS was measured in an Agilent 1200/6210 Time-of-Flight LC–MS or a Thermo Scientific Exactive ESI/DART FTMS. The specific rotations were measured with a Dr. Kernchen Gyromat-HP Digital Automatic Polarimeter with concentrations given in mg per mL. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) measurements were performed on a Setaram Labsys TGA-DSC 1600 with a heating program from 25 to 500 °C and a heating rate of 10 °C/min under an argon flow of 100 mL/min.

Methyl 6-iodo-α-D-glucopyranoside **1** and *phenyl 6-iodo-ß-D-glucopyranoside* **15** have been synthesized as previously published by our group.[10]

Methyl 2,3,4-O-acetyl-6-iodo-α-D-glucopyranoside 2

The procedure was adapted from Vasella *et al.*[15] **1** (3.041 g, 10 mmol) was dissolved in pyridine (25 mL) and acetic anhydride (15 mL) was added. The reaction was stirred at room temperature for 3 h. All volatiles were removed via co-distillation with toluene (3x). Ethanol (10 mL) was added and the resulting suspension was filtered and the solid was washed with ethanol (2x 10 mL) to obtain the product as a white solid (4.013 g, 93%).

General Procedure for the Synthesis of the Acetylated Glucosyl Imidazolium Iodides 3 a–h

2 (1.290 g, 3.0 mmol) and the *N*-substituted imidazole of choice (5.0 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 110 °C for 24 hours. In case of **3 a** and **3 f**, the resulting precipitate was collected by filtration and was washed with ethyl acetate to achieve the product. For **3 b–e** and **3 g–h** all volatiles were removed and the product was obtained after column chromatography (first ethyl acetate to remove remaining *N*-substituted imidazole and starting material, then methanol to collect the product).

General Procedure for the Synthesis of the Pd^{II}-bis(NHC) Complexes 5 a–h and 6–8

The acetylated glucosyl imidazolium iodide **3 a–h** (1.0 mmol) and silver(I) oxide (116 mg, 0.5 mmol) were stirred in dichloromethane (5 mL) at room temperature for 4 hours under absence of light. The solvent was removed and palladium(II) chloride (89 mg, 0.5 mmol) and acetonitrile (10 mL) were added. The reaction was stirred at 40 °C for 24 hours under absence of light. The product was obtained after column chromatography (chloroform/methanol 24:1). In case of **6**–**8**, **3 a** and palladium(II) bromide (for **6**, 133 mg, 0.5 mmol), palladium(II) iodide (for **7**, 180 mg, 0.5 mmol) or palladium(II) acetate (for **8**, 112 mg, 0.5 mmol) were used.

Methyl 2,3,4-O-pivaloyl-6-iodo-α-D-glucopyranoside 9

The procedure was adapted from Hollingsworth *et al.*[24] **1** (1.216 g, 4.0 mmol) was dissolved in pyridine (12 mL) and pivaloyl chloride (6 mL) was added. The reaction was stirred at room temperature for overall 3 days and more pivaloyl chloride (3 mL) and pyridine (6 mL) were added after 24 h and again after 48 h of reaction time. All volatiles were removed via co-distillation with toluene (3x). The product was obtained as a white solid (1.752 g, 79%) after column chromatography (heptane/ethyl acetate 9:1).

Methyl 2,3,4-O-benzoyl-6-iodo-α-D-glucopyranoside 10

The procedure was adapted from Hanna *et al.*[25] **1** (1.216 g, 4.0 mmol) was dissolved in pyridine (12 mL) and benzoyl chloride (6 mL) was added. The reaction was stirred at room temperature for 3 h. All volatiles were removed via co-distillation with toluene (3x). The product was obtained as a white solid (2.079 g, 84%) after column chromatography (heptane/ethyl acetate 15:1).

1-(Methyl-2,3,4-O-pivaloyl-α-D-glucopyranosid-6-yl)-3-methylimidazolium Iodide (Pivaloyl-GMIM-I) 11

11 was synthesized following the general procedure for the synthesis of the acetylated glucosyl imidazolium iodides **3 a–h**, using **9** (1.669 g, 3.0 mmol) and *N*-methylimidazole (411 mg, 5.0 mmol). Yellow solid (1.512 g, 79%).

1-(Methyl-2,3,4-O-benzoyl-α-D-glucopyranosid-6-yl)-3-methylimidazolium Iodide (Benzoyl-GMIM-I) 12

12 was synthesized following the general procedure for the synthesis of the acetylated glucosyl imidazolium iodides **3 a–h**, using **10** (1.849 g, 3.0 mmol) and *N*-methylimidazole (411 mg, 5.0 mmol). Yellow solid (1.453 g, 69%).

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Dichlorobis[1-(methyl-2,3,4-O-pivaloyl-α-D-glucopyranosid-6-yl)-3-methylimidazol-2-ylidene]palladium(II) 13

13 was synthesized following the general procedure for the synthesis of the Pd^{II}-bis(NHC) complexes **5a–h**, using **11** (638 mg, 1.0 mmol). Yellow solid (463 mg, 77%).

Dichlorobis[1-(methyl-2,3,4-O-benzoyl-α-D-glucopyranosid-6-yl)-3-methylimidazol-2-ylidene]palladium(II) 14

14 was synthesized following the general procedure for the synthesis of the Pd^{II}-bis(NHC) complexes **5a–h**, using **12** (699 mg, 1.0 mmol). Yellow solid (432 mg, 66%).

Phenyl 2,3,4-O-acetyl-6-iodo-ß-D-glucopyranoside 16

15 (1.292 g, 3.0 mmol) was dissolved in pyridine (7.5 mL) and acetic anhydride (4.5 mL) was added. The reaction was stirred at room temperature for 3 h. All volatiles were removed via co-distillation with toluene (3x). The product was obtained as a white solid (1.292 g, 88%) after column chromatography (heptane/ethyl acetate 4:1).

1-(Phenyl-2,3,4-O-acetyl-ß-D-glucopyranosid-6-yl)-3-methylimidazolium iodide (Acetyl-PhO-GMIM-I) 17

17 was synthesized following the general procedure for the synthesis of the acetylated glucosyl imidazolium iodides **3a–h**, using **16** (1.477 g, 3.0 mmol) and *N*-methylimidazole (411 mg, 5.0 mmol). Yellow solid (1.307 g, 76%).

Dichlorobis[1-(phenyl-2,3,4-O-acetyl-ß-D-glucopyranosid-6-yl)-3-methylimidazol-2-ylidene]palladium(II) 18

18 was synthesized following the general procedure for the synthesis of the Pd^{II}-bis(NHC) complexes **5a–h**, using **17** (574 mg, 1.0 mmol). Yellow solid (324 mg, 61%).

Dichloro[1-(methyl-2,3,4-O-acetyl-α-D-glucopyranosid-6-yl)-3-mesitylimidazol-2-ylidene](pyridyl)palladium(II) 19

3h (163 mg, 0.264 mmol) and silver(I) oxide (30.6 mg, 0.132 mmol) were stirred in dichloromethane (3 mL) at room temperature for 4 hours under absence of light. The solvent was removed and palladium(II) chloride (46.8 mg, 0.264 mmol), pyridine (22 μL, 0.264 mmol) and acetonitrile (1 mL) were added. The reaction was stirred at room temperature for 18 hours under absence of light. The product was obtained as a yellow solid (87 mg, 44%) after column chromatography (heptane/ethyl acetate 1:1).

General Procedure for the Model Suzuki-Miyaura Reaction

Bromobenzene (157 mg, 1.0 mmol), 4-tolueneboronic acid (170 mg, 1.25 mmol), K_2CO_3 (276 mg, 2.0 mmol) and the appropriate amount of catalyst were weighted into a Schlenk tube under air. EtOH (3 mL) was added and the reaction was stirred at 60 °C for 5 h. In case of very low catalyst loadings, like 0.05 mol%, a solution of 0.005 mmol (equals 0.5 mol%) catalyst in 1 mL of EtOH was prepared and 100 μL of this solution was given into the Schlenk tube. In this case 2.9 mL of EtOH were added. Product yield of 4-methylbiphenyl was controlled by GC analysis. A 200 μL sample was withdrawn from the reaction and further diluted with 1 mL THF and 200 μL internal standard (a 40 mM mixture of nitrobenzene in THF). Temperature program for GC started at 75 °C, followed by a heating rate of 5 K/min to 110 °C and 30 K/min to 140 °C which was hold for 12 minutes. The final ramp included a heating rate of 30 K/min to 200 °C which was hold for 5 minutes.

Supporting Information

Characterization data and ^{1}H- and ^{13}C-NMR spectra of all compounds as well as HSQC- and HMBC-2D-NMR spectra of all palladium complexes, additional optimization tables for the Suzuki-Miyaura model reaction as well as additional ORTEP plots of the x-ray crystal structures can be found in the supporting information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carbohydrate · *N*-heterocyclic carbene · palladium · cross coupling · ionic liquid

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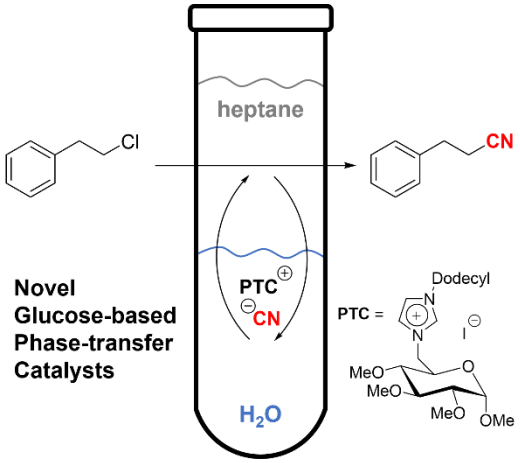
8. Publication III: Developing a Biphasic Kolbe Nitrile Synthesis using Glucose-based Ionic Liquids as Phase-transfer Catalysts



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Contribution statement:
Mirai Komabayashi did all experiments and analysis in this work. The publication was written by Mirai Komabayashi as first author.

RESEARCH ARTICLE

Developing a Biphasic Kolbe Nitrile Synthesis using Glucose-based Ionic Liquids as Phase-transfer Catalysts

Mirai Komabayashi[a] and Stefan Jopp*[a]

[a] M. Komabayashi, Dr. S. Jopp
Department Life, Light & Matter
University of Rostock
Albert-Einstein-Str. 25, 18059 Rostock, Germany
E-mail: stefan.jopp@uni-rostock.de

Supporting information for this article is given via a link at the end of the document.

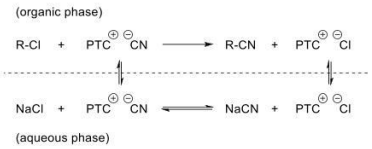
Abstract: In this work, glucose-based phase-transfer catalysts with several functionalizations (different alkyl substitutions, different cationic head-groups, different *O*-protecting groups on the glucose) have been synthesized and employed in a model liquid-liquid Kolbe nitrile synthesis with water and *n*-heptane. The influences of the different catalyst functionalizations on its activity have been studied thoroughly and an optimal glucose-based PTC, leading to 99 % yield of the nitrile product, was found. The new PTCs were designed to remain in the water phase after the end of the reaction, leading to a simplified purification of the nitrile product and less handling of toxic NaCN-containing mixtures. The catalyst recycling has also been studied in this work.

Introduction

Nitriles are a highly important molecule class in organic chemistry. They are commonly found in pharmaceuticals,[1] natural products[2] and materials like co-polymers made from acrylonitrile.[3-4] Nitriles are furthermore commonly used as synthetic intermediates, since their cyano group can be converted to amides, carboxylic acids, imines, aldehydes/ ketones, amines, or into heterocycles using cycloaddition reactions.[5]

Some typical preparation methods of nitriles are the Kolbe nitrile synthesis, the Rosenmund-von Braun reaction and the hydrocyanation reaction. In case of the Kolbe nitrile synthesis, alkyl nitriles are synthesized through a nucleophilic substitution reaction between alkyl halides and metal cyanides.[6] The Rosenmund-von Braun reaction employs aryl halides and cuprous cyanide for the synthesis of aryl nitriles.[7] The hydrocyanation, which is the addition of HCN to alkenes or alkynes, is a method also used on industrial scale.[8] The major problem of these and similar preparation methods is the high toxicity of cyanide salts and hydrogen cyanide.[9] Other methods for the synthesis of nitriles, which circumvent the usage of cyanides, are also known. Some examples include the desulfonylative Smiles rearrangement,[10] the oxidative synthesis of nitriles from alcohols, aldehydes and amines,[11-12] or the nitrile synthesis via nitration of double bonds.[13] These methods are however often more limited in their substrates than the aforementioned Kolbe nitrile synthesis, Rosenmund-von Braun reaction or hydrocyanation.

The Kolbe nitrile synthesis is usually performed in DMSO,[14] which means that a separation of the nitrile product from the sodium cyanide and the removal of the high boiling DMSO from this mixture have to considered. This translates to extended handling of highly toxic NaCN-containing mixtures. As a variation of the Kolbe reaction, Starks has previously investigated the liquid-liquid phase transfer reaction between 1-chlorooctane and sodium cyanide in water and decane, using hexadecyltributylphosphonium bromide or tricaprylylmethylammonium chloride as phase-transfer catalysts.[15] In this system, the phase-transfer catalyst (PTC) forms a cyanide salt *in situ* and moves between both phases, thus enabling the substitution reaction in the organic phase (Scheme 1). While this system leads to less handling of NaCN-containing mixtures, since the NaCN stays in the aqueous phase, the PTC itself is also toxic and soluble in the organic phase and thus still needs to be removed from the organic phase.



Scheme 1. General mechanism of a liquid-liquid phase-transfer Kolbe nitrile synthesis as published by Starks.[15]

As a new approach, our goal was to apply glucose-based ionic liquids as PTCs for a liquid-liquid Kolbe nitrile synthesis in this work.

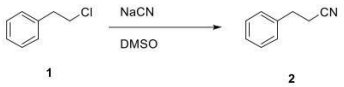
Carbohydrate-based ionic liquids and salts (CHILS)[16-19] have long been applied in organocatalysis, usually as solvents or co-solvents. Some notable examples are Diels–Alder reactions catalyzed by glucose-based ammonium ionic liquids,[20] the aza-Diels-Alder reactions catalyzed by isosorbide-based ammonium ionic liquids[21] or glucose-based imidazolium ionic liquids[22] and the synthesis of dihydropyrano coumarins catalyzed by ribose-based imidazolium ionic liquids.[23] Glucose-based ammonium ionic liquids have also once been used as phase-transfer catalysts, in the dehydrochlorination of 3,4-dichloro-1-butene to chloroprene.[24]

The usage of CHILS as phase-transfer catalysts is preferable over common PTCs like tetrabutylammonium bromide (TBAB), due to their higher biocompatibility and biodegradability.[24-25] Furthermore, due the existence of a hydrophilic part (the carbohydrate and the cationic group directly bound to it) and a lipophilic part (long alkyl chains), the CHILS-PTCs in this work will be designed to stay in the aqueous phase after the reaction, thus leading to new possibilities in recycling processes.

Results and discussion

Classical Kolbe nitrile synthesis

In this work, the conversion of 2-chloroethyl benzene **1** to 3-phenylpropionitrile **2** (Scheme 2) was chosen as the model Kolbe nitrile synthesis. The first reason for this choice of substrates is their reactivity. The aryl-substituted chloroalkane **1** is less reactive than its respective bromo- or iodo-counterparts,[14] which sets this substrate in field of moderate reactivity. The second reason is the easy differentiation of **1** and **2** in ^{1}H-NMR (see supporting information figure S1-S3), which allows us to calculate the yield of **2** from ^{1}H-NMR.



Scheme 2. Model Kolbe nitrile synthesis between 2-chloroethyl benzene **1** and sodium cyanide to 3-phenylpropionitrile **2**.

Before investigating the biphasic Kolbe nitrile synthesis, we first had to establish the reaction conditions of the classical Kolbe nitrile synthesis for our model reaction (Table 1). The optimization of different parameters, like temperature (Table 1, entries 1-3), amount of sodium cyanide (Table 1, entries 4-7) and reaction time (Table 1, entries 8-10) showed that the classical Kolbe nitrile synthesis for our model reaction leads to >99% yield of **2** with two equivalents of sodium cyanide at 40 °C after 24 hours of reaction time. These conditions were used as a comparison for the biphasic Kolbe nitrile synthesis.

Table 1. Optimization of the classical Kolbe nitrile synthesis of **1** and sodium cyanide to **2**.[a]

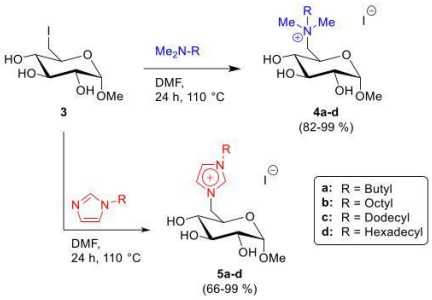
Entry	T (°C)	NaCN amount	t (h)	Yield (%)[b]
1	r.t.	5.0 eq	24	74
2	40	5.0 eq	24	>99
3	70	5.0 eq	24	>99
4	40	3.0 eq	24	>99
5	40	2.0 eq	24	>99
6	40	1.5 eq	24	79
7	40	1.1 eq	24	80
8	40	2.0 eq	4	73
9	40	2.0 eq	8	90
10	40	2.0 eq	16	98

[a] Reaction conditions: **1** (1.0 mmol) and the given amount of NaCN in DMSO (3.0 mL) at the given time and temperature. [b] Yield of **2** as determined by NMR from the raw reaction mixture (see supporting information figure S4-S13).

Organocatalytic biphasic Kolbe nitrile synthesis

Before investigating the biphasic Kolbe nitrile synthesis that we aimed for in this work, we first had to prepare our novel glucose-based phase-transfer catalysts. For this, we used our established 2-step synthesis route for the preparation of glucose-based ionic liquids and salts.[25]

First, commercially available methyl α-D-glucopyranoside was transformed to the 6-iodo-substituted glucopyranoside **3** via an Appel reaction with 91 % yield.[25] The iodine leaving group of starting material **3** was then used to introduce either dimethyl-alkyl-ammonium groups (**4a-d**) or alkyl-imidazolium groups (**5a-d**), which carry butyl-, octyl, dodecyl- or hexadecyl-chains, into the organocatalyst (Scheme 3). Previously, our group had focused solely on glucosyl imidazolium ionic liquids, due to their variety of applications,[22, 26-28] and we had reported the products **5a-b** before.[25] In this work, inspired by the usage of glucose-based ammonium ionic liquids as phase-transfer catalysts by the group of Chrobok *et al.*,[24] we decided to also introduce ammonium groups and directly compare them to imidazolium groups. All products **4a-d** and **5a-d** were synthesized in good to high yields between 66 and 99 %. The ammonium products **4a-d** led to comparatively higher yields due to a combination of higher conversion and easier removal of remaining amine excess from the products than the analogue imidazoles.



Scheme 3. Synthesis of the ammonium- and imidazolium-organocatalysts **4a-d** and **5a-d**, with varying alkyl chain lengths.

Next, we started with the optimization of the reaction parameters of the biphasic Kolbe nitrile synthesis (Table 2). We decided to use the dodecylammonium catalyst **4c** as the first catalyst, due its structural similarity to the best phase-transfer catalyst from the work of Chrobok *et al.*,[24] and we decided to start with 0.25 equivalents.

Table 2. First optimization of reaction parameters, using **4c** as model catalyst.[a]

Entry	T (°C)	Solvent	NaCN amount	Catalyst amount	Yield (%)[b]
1	70	*n*-heptane	2.0 eq	0.25 eq	8
2	100	*n*-heptane	2.0 eq	0.25 eq	39
3	100	cyclohexane	2.0 eq	0.25 eq	28
4	100	toluene	2.0 eq	0.25 eq	15
5	100	ethyl acetate	2.0 eq	0.25 eq	-
6	100	diethyl ether	2.0 eq	0.25 eq	22
7	100	chloroform	2.0 eq	0.25 eq	10
8	100	*n*-heptane	3.0 eq	0.25 eq	42
9	100	*n*-heptane	5.0 eq	0.25 eq	52
10	100	*n*-heptane	5.0 eq	0.5 eq	72
11	100	*n*-heptane	5.0 eq	1.0 eq	93
12[c]	100	*n*-heptane	5.0 eq	-	4
13[d]	100	*n*-heptane	5.0 eq	0.25 eq	27
14[e]	100	*n*-heptane	5.0 eq	0.25 eq	42

[a] Reaction conditions: **1** (1.0 mmol) and the given amounts of NaCN and organocatalyst **4c** in an organic solvent (1.5 mL) and water (1.5 mL) at the given temperature for 24 h. [b] Yield of **2** as determined by NMR from the raw reaction mixture (see supporting information figure S14-S27). [c] The reaction was performed without catalyst. [d] Tetrabutylammonium iodide was used as organocatalyst. [e] Organocatalyst **4c-Br** was used.

For this biphasic Kolbe nitrile synthesis, water and an organic solvent were used in a 1:1 ratio. Initial tests at 40 °C, which was the best temperature found for the classical Kolbe nitrile synthesis (Table 1, entry 5), led to no product formation. Even at 70 °C, only 9 % yield of **2** were calculated from NMR (Table 2, entry 1). The rise of the temperature to 100 °C led to the rise of the product yield to 39 % (Table 2, entry 2).

The comparison of different organic solvents (Table 2, entries 2-7) shows that *n*-heptane leads to the best results, but cyclohexane, toluene and diethyl ether are also viable options for this reaction. More polar solvents, like ethyl acetate and chloroform, lead to low or no product formation.

Rising the amount of sodium cyanide in the water phase from 2.0 to 5.0 equivalents rises the yield up to 52 % (Table 2, entries 8-9). Heightening the amount of the phase-transfer catalyst to 0.5 or 1.0 equivalents shows a strong effect, leading to 72 and 93 % yield, respectively (Table 2, entries 10-11). On the other hand, performing the biphasic Kolbe nitrile synthesis without the presence of a phase-transfer catalyst leads to close to no product formation (Table 2, entry 12). Additionally, tetrabutylammonium iodide was chosen as a commercially available phase-transfer catalyst for comparison (Table 2, entry 13). This catalyst led to a low yield of 27 %.

To investigate the influence of the anion, we also prepared the starting material **3** as the analogue bromo-compound **3-Br** and chloro-compound **3-Cl**, using bromine or *N*-chlorosuccinimide as halogen source, respectively.[27] However, only the catalyst **4c-Br** was successfully synthesized from **3-Br**. **3-Cl** proved to be too unreactive for the quarternization with dimethyldocecylamine towards **4c-Cl**, even at higher reaction temperatures of 130 or 150 °C. The result of the biphasic Kolbe nitrile synthesis (Table 2, entry 14) with **4c-Br** as catalyst shows that the anion has a notable influence on the performance of the catalyst, leading to 10 % lower yield than **4c** with its iodide anion.

According to the widely accepted reaction mechanism of a liquid-liquid phase transfer catalysis as published by Starks (Scheme 1),[15] the following four steps control the reaction: (1) the formation of an intermediate reactant containing the PTC cation and a cyanide anion in the water phase, (2) the transfer of this intermediate reactant to the organic phase, (3) the Kolbe nitrile synthesis performed in the organic phase and (4) the transfer of the PTC back to the water phase.[29] Our experimental data shows that many different parameters influence the speed of these steps. For example, a higher amount of sodium cyanide most likely leads to a faster step (1), while a higher amount of catalyst likely positively influences the reaction speed of all four steps. On the other hand, a PTC bearing a bromide anion seems to lead to a slower step (1) in comparison to a PTC with an iodide anion.

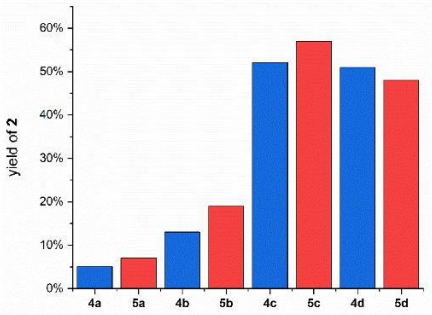
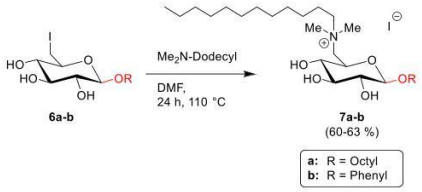


Figure 1. Performance of the ammonium catalysts **4a-d** and the imidazolium catalysts **5a-d** (a = butyl, b = octyl, c = dodecyl, d = hexadecyl).

Our next goal after optimizing the reaction conditions was to investigate the influence of different structural variations on the phase-transfer catalysts on their performance (Table 3).

For this we initially used the CHILS-PTCs **4a-d** and **5a-d**, which gave us insight into the influence of alkyl chain length from butyl to hexadecyl and the type of cationic head-group between ammonium or imidazolium (Table 3, entries 1-8). The data points have also been visualized in figure 1. The experimental results show a very clear trend that the catalyst performance rises from butyl to dodecyl and then drops very slightly at an alkyl chain length of hexadecyl. It can also be seen in figure 1 that the imidazolium catalysts **5a-c** always perform slightly better than the

ammonium catalysts **4a-c**. Notably, the hexadecyl catalysts **4d** and **5d** lead to an increased amount of water in the organic phase, as seen in the NMR, likely due to a stronger mixing of the two phases.

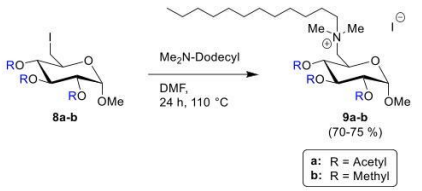


Scheme 4. Synthesis of organocatalysts **7a-b** with varying glycosidic groups.

Next, we continued with the synthesis of the catalysts **7a-b**, which bear octyl- and phenyl-glycosidic groups at position 1, instead of the previously used methyl group (Scheme 4). Due to easier handling and lower costs, we continued our investigation with dimethyldocecylamine instead of dodecylimidazole.

The starting materials **6a-b** were synthesized from commercially available octyl β-D-glucopyranoside and phenyl β-D-glucopyranoside via an Appel reaction with 40-50 % yield, as previously reported.[25] The new PTCs **7a-b** were synthesized with yields around 60 %. Their purification proved to be more difficult than **4c**, since **7a-b** act notably as surfactants, thus hindering the washing process for purification. A column chromatography had to used instead for the purification of **7a-b**.

The results of the tests of **7a-b** in the biphasic Kolbe nitrile synthesis can be found in table 3, entries 9-10. The octyl-glucoside catalyst **7a** leads to a 10 % higher yield than **4c** in comparison, however, the catalyst **7a** can be detected strongly in the organic phase in the NMR. This does not comply with our goal, as we want the catalysts to stay in aqueous phase after the reaction, for easy purification of the product in the organic phase. The phenyl-glucoside catalyst **7b** on the other hand is less reactive, leading to only 39 % yield, 13 % less than catalyst **4c** achieves.



Scheme 5. Synthesis of the ester- and ether-protected organocatalysts **9a-c**.

Lastly, we synthesized the *O*-protected PTCs **9a-b** (Scheme 5). The acetyl-protected starting material **8a** was synthesized by acetylation of **3** with yield, as previously published by our group.[28] The methyl-protected starting material **8b** has to be prepared in 4-step synthesis with a total yield of 62 %. The synthesis starts with 6-tritylation of methyl α-D-glucopyranoside, followed by the permethylation of the hydroxy groups using sodium hydride and methyl iodide, followed by the removal of the trityl protecting group using acetic acid and finally introduction of the iodine in 6-position using an Appel reaction.[26] The new CHILS-PTCs **9a-b** were synthesized from these *O*-protected starting materials in good yields of 70 to 75 %.

As catalyst, the acetyl-protected PTC **9a** (Table 3, entry 11) had a lower reactivity than **4c** (Table 3, entry 3), leading to 40 % yield in the biphasic Kolbe nitrile synthesis. Interestingly, methyl protecting groups, as used in catalyst **9b**, were found to be the optimal functionalization, leading to a high yield of 71 %.

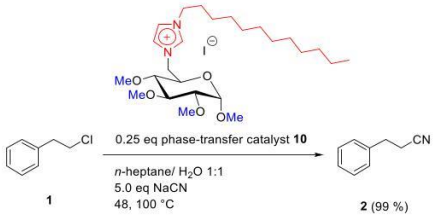
Table 3. Comparison of different organocatalysts.[a]

Entry	Catalyst	Catalyst name	Yield (%)[b]
1	**4a**	MeGlu(OH)-NMe_2Bu-I	5
2	**4b**	MeGlu(OH)-NMe_2Oct-I	13
3	**4c**	MeGlu(OH)-NMe_2Dodec-I	52
4	**4d**	MeGlu(OH)-NMe_2Hexadec-I	51
5	**5a**	MeGlu(OH)-ImBu-I	7
6	**5b**	MeGlu(OH)-ImOct-I	19
7	**5c**	MeGlu(OH)-ImDodec-I	57
8	**5d**	MeGlu(OH)-ImHexadec-I	48
9	**7a**	OctGlu(OH)-NMe_2Dodec-I	62
10	**7b**	PhGlu(OH)-NMe_2Dodec-I	39
11	**9a**	MeGlu(OAc)-NMe_2Dodec-I	40
12	**9b**	MeGlu(OMe)-NMe_2Dodec-I	71

[a] Reaction conditions: **1** (1.0 mmol), NaCN (5.0 eq), organocatalyst (0.25 eq), *n*-heptane (1.5 mL), water (1.5 mL), 100 °C, 24 h. [b] Yield of **2** as determined by NMR from the raw reaction mixture (see supporting information figure S28-S49).

The comparison of all PTCs with different alkyl-substituted cationic head-groups (Table 3, entries 1-8), different glycosdic groups (Table 3, entries 9-10) and different protecting groups on the sugar (Table 3, entries 11-12) resulted in two major findings: First, dodecyl-substituted imidazolium is the best cationic head-group and second, permethylation is the best functionalization of the sugar.

As such, our last synthesized PTC was **10** (Scheme 6), produced from **8b** and dodecyl imidazole in 77 % yield. PTC **10** led to 78 % yield in the biphasic Kolbe nitrile synthesis under the previously optimized conditions (**1** (1.0 mmol), NaCN (5.0 eq), organocatalyst (0.25 eq), *n*-heptane (1.5 mL), water (1.5 mL), 100 °C, 24 h), and an extension of the reaction time to 48 h led to 99 % yield of **2** (Scheme 6). From this reaction, the organic phase was collected and clean product **2** was achieved after removal of the solvent, without the necessity of any further purification method.



Scheme 6. Optimized model biphasic Kolbe nitrile synthesis using phase-transfer catalyst **10** (yield of **2** as determined by NMR from the raw reaction mixture, see supporting information figure S40-S41).

Recycling studies

Our novel phase-transfer catalyst **10**, which leads to 99 % of nitrile product **2** (Scheme 6), cannot be detected in the organic phase after the end of the reaction, as we aimed for in this work. Thus, PTC **10** was used for the investigation of catalyst recycling. In our reaction setup, the biphasic reaction was performed in a sealed glass pressure tube. After the reaction at 100 °C for 48h, the reaction was cooled to room temperature and the NMR sample was taken from the organic phase. For the recycling setup, all of the organic phase was removed and new starting material **1**, new organic phase and an additional 1.0 eq of NaCN (due to its consumption in the reaction) were added to the remaining aqueous phase for each cycle. The results are visualized in figure 2.

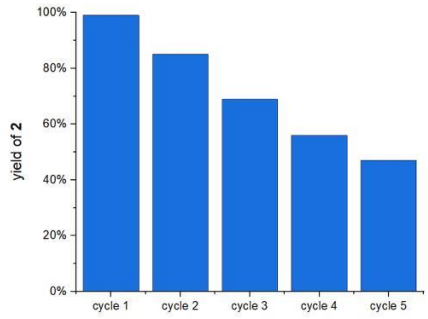


Figure 2. Recycling studies part 1. The first cycle starts with **1** (1.0 mmol), NaCN (5.0 mmol), PTC **10** (0.25 mmol), *n*-heptane (1.5 mL) and water (1.5 mL) at 100 °C for 48 h. After each cycle, the organic phase was removed and **1** (1.0 mmol), NaCN (1.0 mmol) and *n*-heptane (1.5 mL) were added to the remaining aqueous phase. Yield of **2** as determined by NMR from the raw reaction mixture, see supporting information figure S42-S46.

Unfortunately, the results of the recycling process show that the yield of **2** drops continuously with each cycle, starting at 99 %, then 85 %, 69 %, 56 % and finally 47 %. While it cannot be dismissed that our glucose-based PTC **10** may be instable under prolonged heating, we also observed another factor that heavily influences these recycling results: The formation of a dark-colored mix-phase between the water phase and the organic phase (Figure 3B). A small part of this mix-phase was unavoidably always removed together with the organic phase after each cycle. In another recycling study, in which this mix-phase was fully removed after the first cycle, led to drastic drop to only 10 % yield in the second cycle (Figure 3A). This proves that a high amount of the catalyst is situated in this mix-phase, and that the yield loss previously seen in figure 2 is, at least partly, associated with the loss of catalyst during the recycling process.

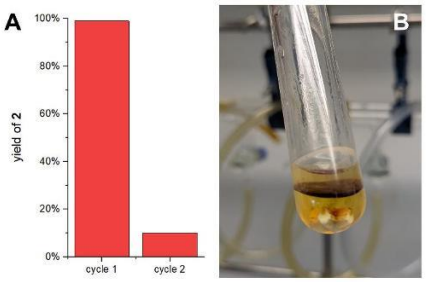


Figure 3. A) Recycling studies part 2. The first cycle starts with **1** (1.0 mmol), NaCN (5.0 mmol), PTC **10** (0.25 mmol), *n*-heptane (1.5 mL) and water (1.5 mL) at 100 °C for 48 h. After the first cycle, the organic phase and the yellow-colored mix-phase were removed and **1** (1.0 mmol), NaCN (1.0 mmol) and *n*-heptane (1.5 mL) were added to the remaining aqueous phase. Yield of **2** as determined by NMR from the raw reaction mixture, see supporting information figure S47-S48. B) Representative photo of a reaction after cycle 1.

Conclusion

In this work, overall 13 novel glucose-based phase-transfer catalysts, from the class of CHILS (carbohydrate-based ionic liquids and salts), have been synthesized and employed a model biphasic Kolbe nitrile synthesis between 2-chloroethyl benzene and sodium cyanide.

The structure-activity relationships of the CHILS-PTCs have been studied. Different alkyl chain lengths on the PTCs were compared and C12-chains were found to be the optimum. Cationic imidazolium head-groups led to slightly higher activities than ammonium head-groups. Despite the necessity of the catalyst to move between organic phase and aqueous phase, a property facilitated by both the lipophilic alkyl chains and the hydrophilic glucose, permethylation of the glucose led to the overall highest catalytic activity, while acetyl-protecting groups or varying glycosidic groups were unfavorable.

Both the classic and the biphasic Kolbe nitrile synthesis have been investigated, and both reactions can reach 99 % yield of the organic nitrile product under optimized reaction conditions. The comparison shows that the classic reaction in DMSO can be performed under milder reaction conditions (40 °C), but extended handling of NaCN-containing mixtures for product purification cannot be avoided. The biphasic Kolbe nitrile synthesis in water

and *n*-heptane on the other hand needs higher temperatures (100 °C), but the purification is simplified by just removing the organic phase containing the product, while the NaCN and the PTC remain in the aqueous phase. The recycling of this aqueous phase was studied, but the recycling possibilities remain limited, likely due to a loss of the catalyst during the recycling process.

Experimental section

The NMR spectra were recorded on a Bruker AVANCE 500 NEO or JEOL ECZL 400. $CDCl_3$ was calibrated as 7.27 (^{1}H) and 77.00 (^{13}C). DMSO-d_6 was calibrated as 2.49 (^{1}H) and 39.50 (^{13}C). D_2O was calibrated as 4.80 (^{1}H). MeOH-d_4 was calibrated as 3.31 (^{1}H) and 49.00 (^{13}C).
ESI-MS was measured in an Agilent 1200/6210 Time-of-Flight LC-MS or a Thermo Scientific Exactive ESI/DART FTMS. The specific rotations were measured with a Dr. Kernchen Gyromat-HP Digital Automatic Polarimeter with concentrations given in mg per mL.

General procedure for the Appel reaction

Methyl α-D-glucopyranoside, octyl β-D-glucopyranoside, phenyl β-D-glucopyranoside or methyl 2,3,4-*O*-methyl-α-D-glucopyranoside (10 mmol), triphenylphosphine (15.5 mmol), iodine (14.5 mmol) and imidazole (20 mmol) were refluxed in THF (60 mL) for 4 h. The resulting solid was filtered off, the solution was collected and evaporated and the product was obtained after column chromatography.
In case of product **3-Br**, bromine was used instead of iodine. The bromine has to be added slowly to the THF solution before heating. In case of product **3-Cl**, *N*-chlorosuccinimide was used instead of iodine.
Methyl 6-iodo-α-D-glucopyranoside **3** (91 %).[25] Eluent for column chromatography: $CHCl_3$/MeOH 12:1.
Methyl 6-bromo-α-D-glucopyranoside **3-Br** (70 %).[27] Eluent for column chromatography: $CHCl_3$/MeOH 12:1.
Methyl 6-chloro-α-D-glucopyranoside **3-Cl** (31 %).[27] Eluent for column chromatography: $CHCl_3$/MeOH 12:1.
Octyl 6-iodo-β-D-glucopyranoside **6a** (41 %).[25] Eluent for column chromatography: $CHCl_3$/MeOH 20:1 to 15:1.
Phenyl 6-iodo-β-D-glucopyranoside **6b** (51 %).[25] Eluent for column chromatography: $CHCl_3$/MeOH 15:1.
Methyl 6-iodo-2,3,4-*O*-methyl-α-D-glucopyranoside **8b** (89 %).[26] Eluent for column chromatography: heptane/ethyl acetate 7:1 to 4:1.

General procedure for the acetylation of 3

3 (10 mmol) was dissolved in pyridine (25 mL) and acetic anhydride (15 mL) was added. The reaction was stirred at room temperature for 3 h. All volatiles were removed via co-distillation with toluene (3x 30 mL). Ethanol (10 mL) was added and the resulting suspension was filtered and the solid was washed with ethanol (2x 10 mL) to obtain methyl 6-iodo-2,3,4-*O*-acetyl-α-D-glucopyranoside **8a** as a white solid (93%).[28]

General procedure for the synthesis of the CHILS-PTCs

The starting material **3**, **3-Br**, **6a-b**, or **8a-b** (1.0 equivalents) and the respective amine or imidazole (1.667 equivalents) were dissolved in DMF (1.667 mL per equivalent starting material) and stirred at 110 °C for 24 h. The purification varies between products. Please refer to the supporting information.
MeGlu(OH)-NMe_2Bu-I **4a** (82 %).
MeGlu(OH)-NMe_2Oct-I **4b** (86 %).
MeGlu(OH)-NMe_2Dodec-I **4c** (83 %).
MeGlu(OH)-NMe_2Dodec-Br **4c-Br** (>99 %).
MeGlu(OH)-NMe_2Hexadec-I **4d** (>99 %).
MeGlu(OH)-ImBu-I **5a** (94 %).[25]
MeGlu(OH)-ImOct-I **5b** (71 %).[25]
MeGlu(OH)-ImDodec-I **5c** (66 %).
MeGlu(OH)-ImHexadec-I **5d** (>99 %).
OctGlu(OH)-NMe_2Dodec-I **7a** (63 %).
PhGlu(OH)-NMe_2Dodec-I **7b** (60 %).
MeGlu(OAc)-NMe_2Dodec-I **9a** (70 %).
MeGlu(OMe)-NMe_2Dodec-I **9b** (75 %).
MeGlu(OMe)-ImDodec-I **10** (77 %).

Supporting Information

Characterization data and ^{1}H- and ^{13}C-NMR spectra of all CHILS-PTCs and ^{1}H-NMR spectra supporting the yield calculation of all classical and biphasic Kolbe nitrile syntheses, as seen in tables 1-3 and figures 1-3, can be found in the supporting information.

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Keywords: Phase Transfer Catalysis • Ionic Liquid • Carbohydrate • Kolbe Nitrile Synthesis • Recycling

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9. Curriculum Vitae

Personal data

Name: Mirai Komabayashi

E-mail: mirai.komabayashi@uni-rostock.de

Date/place of birth: 17.08.1997, Yamagata

Academic Background

12/2022-11/2025 (expected)	PhD Candidate in Technical Chemistry, University of Rostock
9/2022-4/2021	Master of Engineering in Chemistry, Tottori University
3/2021-4/2017	Bachelor of Engineering in Chemistry, Tottori University
3/2016-4/2013	Yamagata Minami Senior Highschool, Yamagata

Languages and Other Job-Related Skills

Languages: Japanese (native)
English
German (A1.2)

Job-Related skills

Microsoft Office programs: Word, Excel, PowerPoint

Other specialized software: MestReNova, TopSpin, Delta, ChemDraw, Mendeley, eLab FTW, Amsterdam Modeling Suite, Origin.

Analytical experience:

NMR (Nuclear Magnetic Resonance Spectroscopy)

ESI-/ MALDI-TOF-/ GC-MS, TG-DTA, DSC, GPC, IR Spectroscopy, Optical rotation measurement

10. Scientific Contributions

Publications

1) **M. Komabayashi**, T. Nokami, S. Jopp
   From Chitin to CHILs: First Glucosamine based Ionic Liquids
   Asian J. Org. Chem. 2020, *9*, 2092–2094.
   https://doi.org/10.1002/ajoc.202000569
2) **M. Komabayashi**, T. Stiller, S. Jopp
   Structure-property relationships of ribose based ionic liquids
   J. Mol. Liq. 2021, 325, 115167.
   https://doi.org/10.1016/j.molliq.2020.115167
3) **M. Komabayashi**, S. Okushiba, T. Nokami, S. Jopp
   Scope and Limitations in the Synthesis of Glucosamine-based Ionic Liquids
   Asian J. Org. Chem. 2023, *12*, e202300093.
   https://doi.org/10.1002/ajoc.202300093
4) H. Ziems, **M. Komabayashi**, P. Lehmann, A. Villinger, S. Jopp
   Structure-Activity Relationships of Glucose-based Pd^{II}-Bis(NHC) Complexes in a Model Suzuki-Miyaura Reaction
   Eur. J. Org. Chem. 2024, *27*, e202400177.
   https://doi.org/10.1002/ejoc.202400177
5) **M. Komabayashi**, S. Jopp
   Glucose-based Ionic Liquid Organocatalysts for Asymmetric aza-Diels-Alder Reactions
   ChemistryEurope 2024, *2*, e202400052.
   https://doi.org/10.1002/ceur.202400052

Participation of conference

1) The 101st CSJ Annual Meeting, online, 19.03 –22.03.2021
2) The 35th annual meeting of Japanese Society for Chitin and Chitosan, online, 26.08 –27.08.2021
3) The 11th Symposium of the Ionic Liquid Research Association, online, 18.11 –19.11.2021
4) RoHan DAAD SDG Summer School 2023, Rostock, 12.06. – 16.06.2023

5) Wissenschaftsforum (WiFo)2023, Leipzig, 04.09. – 06.09.2023

Oral Presentation

1) Synthesis of Glucosamine based chiral ionic liquid
   M. Komabayashi, T. Nokami, S. Jopp
   The 101st CSJ Annual Meeting, Japan (online)

Poster Presentation

1) Short-step Synthesis and Thermal Property Research of Glucosamine-Based Ionic Liquids
   M. Komabayashi, T. Nokami, S. Jopp
   the 35th annual meeting of Japanese Society for Chitin and Chitosan, Japan (online)
2) Synthesis of Glucosamine-Based ionic liquids
   M. Komabayashi, T. Nokami, S. Jopp
   the 11th Symposium of the Ionic Liquid Research Association, Japan (online)
3) Glucosamine-based Ionic Liquids for Asymmetric Catalysis
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