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Preparation of Organocatalysts Derived from Monosaccharides

Příprava organických katalyzátorů odvozených z monosacharidů

Bachelor thesis

Supervisor: Jan Veselý, Ph.D.

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This bachelor thesis was in connection with research plan MSM0021620857.

PRONOUNCEMENT

I thereby declare that this thesis was written independently and under supervising by Jan Veselý, Ph.D. I cited all used information sources and literature. This thesis or its any part was not introduced to claim another or same academic title.

In Prague 31st May 2012

Jan Nekvinda

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ABSTRACT

This bachelor thesis is focused on the synthesis of organocatalysts derived from monosaccharides, in particular D-glucose and D-glucosamine, with various protecting groups. Synthesis of various thiourea catalysts and the attempt to prepare new squaramide catalysts is described.

CONTENT

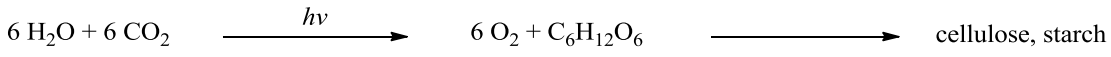
LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
COSY	correlation spectroscopy
DCM	dichloromethane
de	diastereomeric excess
DMF	*N*,*N*-dimethylformamide
DMAP	4-(*N*,*N*-dimethylamino)pyridine
dr	diastereomeric ratio
EtOAc	ethyl acetate
Et	ethyl
ESI	electrospray ionization
ee	enantiomeric excess
eq	equivalent
LUMO	lowest unoccupied molecular orbital
hex	*n*-hexane
HMBC	heteronuclear multiple bond correlation
HMDS	hexamthyldisilazane
HOMO	highest occupied molecular orbital
HSQC	heteronuclear single quantum coherence
*i*PrOH	isopropanol
Me	methyl
MeOH	methanol
MeONa	sodium methoxide
MS	mass spectroscopy
NaOAc	sodium acetate
NMR	nuclear magnetic resonance
Ph	phenyl
Piv	pivaloyl
pm	pico meter
*t*Bu	*tert*-butyl
TFAA	trifluoro acetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TES	triethylsily
TMS	trimethylsilyl
$TMSN_3$	trimethylsilyl azide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TMSSCN	trimethylsilyl isothiocyanate
TMSCN	trimethylsilyl cyanate

1. INTRODUCTION

1.1 SACCHARIDES

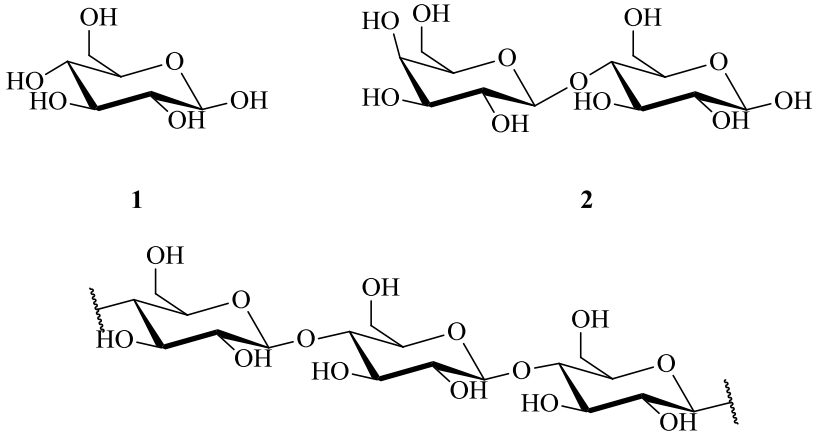
Saccharides are biomolecules and most common compounds in the living world. It is impossible to imagine the World without them. Fact, that every living organism contains saccharide scaffold, makes these chemical compounds very important to man.[1] Some of them are recruiting from the basic and crucial process known as photosynthesis (Scheme 1).[2]



Scheme 1: *Photosynthesis equation.*

An expression carbohydrate, against saccharide, is more commonly used name in English speaking countries. Carbohydrate is quite unlucky name, which has been developed with first discover of D-glucose and its summary formula $C_6H_{12}O_6$, respectively $C_6(H_2O)_6$, which indicates a carbon hydrate.[3] Following this definition formaldehyde was used to considered to be a simplest carbohydrate.[4]

Family of saccharides is divided, with making provision for its molecular weight, into three groups – mono-, oligo- and polysaccharides. Monosaccharides are elementary units and can't be split (by hydrolysis) into smaller saccharides units, for example D-glucose (**1**) (Figure 1). Oligosaccharides are compounds built by two to ten monosaccharides, for example saccharose, commonly known as table sugar, which is built by monosaccharides D-glucose and D-fructose. Other example could be lactose (**2**) (disaccharide consisting of D-glucose and D-galactose unit), which is present in human or cow milk. Last group – polysaccharides, built by tens to thousands of monosaccharides, could stand out as a structural element of plants (e.g. cellulose (**3**)) or energy storage (e.g. starch).[1,2]



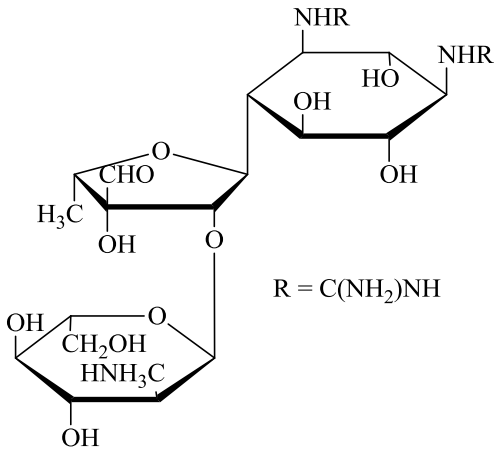
1 **2**

3

Figure 1: *The most common carbohydrates shown with pyranose form – β-D-glucopyranose (**1**), lactose (**2**) and cellulose (**3**).*

What else makes saccharides so important? Besides what was already mentioned (building material, energy storage), it is following:

a) they are involved in the biosynthesis of proteins and lipids;[1,2,5]
b) they are parts of glycoproteins, glycolipids and also nucleic acids (D-ribose, 2-deoxy-D-ribose);[1,2,5]
c) they are used for making drugs (e.g. streptomycin (**4**)) (Figure 2);[1]
d) many of industrial uses (including hardly believe gunpowder).[1]

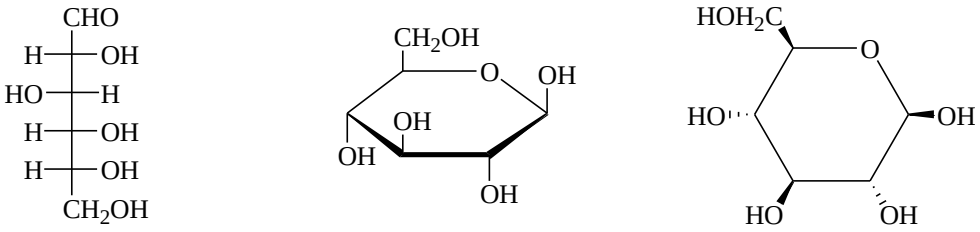


4

Figure 2: *Streptomycin (**4**) is an antibiotic drug and was the first drug remedy for tuberculosis.*

We can summarize basic physical properties of non-substituted saccharides. They are always chiral, mostly crystalline solids and solvable in water and other polar solvents. They are hardly solvable in non-polar solvents.[1]

To display carbohydrates four different formulas are used. Original formula by E. Fischer, next Haworth and Mills formula are shown in Figure 3. Advantage of Haworth projection is simply imagination in the space; on the other hand, Mills formula can help us with determining absolute stereochemistry.[1] In Figure 1 we presented another display type of carbohydrates formula – chair conformation.



5 **6** **7**

Figure 3: *D-glucose displayed by Fischer formula (**5**), β-D-glucopyranose by Haworth formula (**6**) and β-D-glucopyranose by Mills formula (**7**).*

Pioneering work[6] in the field of saccharides did German chemist Emil Fischer (1882-1919, Nobel Prize 1902). He was the first, who proved D-glucose scaffold and invented Fischer formula. His only clue was optical rotation and yet he successfully determine (+)-glucose as a D-form.

"With its oxygen-containing structure (pyranose) and five stereogenic centers (four controllable), glucose represented the state-of-the-art in terms of target molecules at the end of the nineteenth century." states K. C. Nicolaou in the review on the history of the total synthesis.[7]

1.2 ORGANOCATALYSIS

Modern asymmetric catalysis is built on biocatalysis, metal catalysis and organocatalysis.[9] Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom.[8] Organocatalysts can be classified into four groups – Lewis bases, Lewis acids, Brønsted bases and Brønsted acids[10] (Figure 4).

Nowadays, organocatalysis is widespread used, for example Diels-Alder reaction[11], Mannich reaction[12], Michael addition[13] or Aza-Henry reaction[14]. Not only natural compounds, but also synthetic catalysts, act as organocatalysts (e.g. prolin).[15]

Unlike metal-ligand complexes, organocatalysts generally tolerate aerobic conditions and do not require rigorous exclusion of water. They possess a wider substrate scope than enzymes and can be used in a variety of organic solvents. Organocatalysts can be synthesized or accessed from naturally chiral molecules and they can be used in solid phase synthesis. Moreover it is possible prepare both enantiomer modifications and therefore we can prepare different enantiomer products. Besides, there are already a number of organocatalytic reactions being used in the pharmaceutical and chemical industries.[8,9]

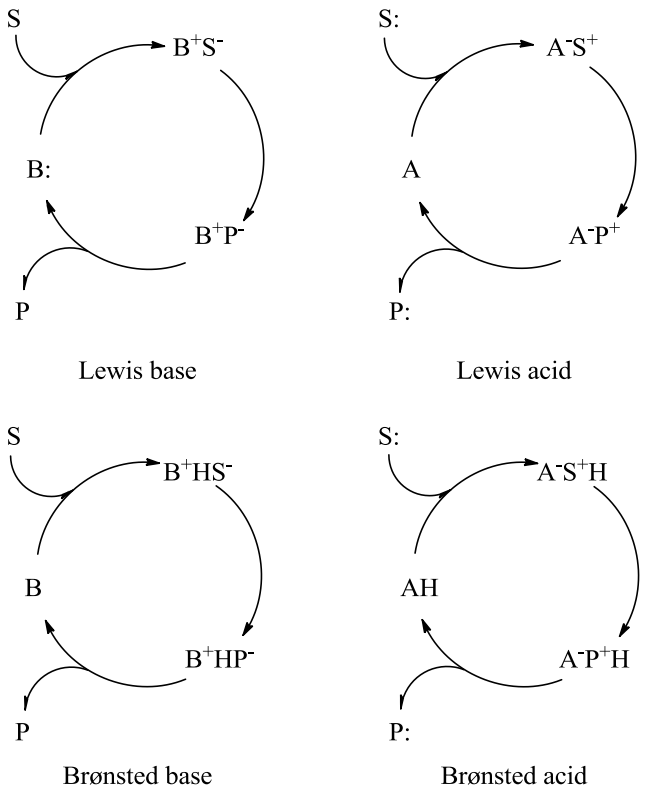
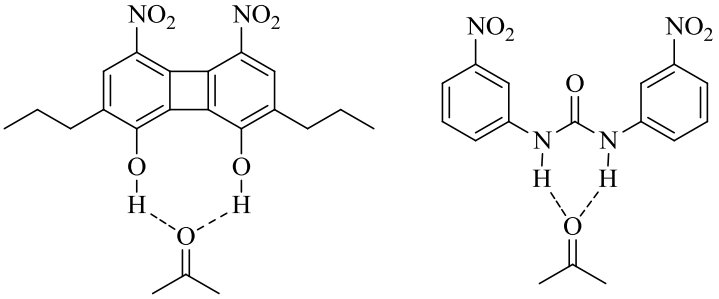


Figure 4: *Lewis and Brønsted acid/base catalysts.*

These catalysts (Figure 4) initiate their catalytic cycles by either providing or removing electrons or protons from a substrate or a transition state. The former class of organocatalysts includes compounds that act as covalently bonded reagents. However, latter class induces mainly such interactions as hydrogen bonding or ion bonding to provide high level of enantioselectivity. The huge potential of hydrogen bonding as an activating interaction has been recognized in recent decades. For example, (thio)urea catalyst can also act as a Brønsted acid.[9]

1.3 (THIO)UREA BASED ORGANOCATALYSTS

Various derivatives of urea and, preferably, thiourea were studied due to their hydrogen donor character.[16] Their catalytic effect was proven lately as acid catalysts. Success of (thio)urea based catalysts is its ability to form two H-bonds to a reactant. The second H-bond not only activates reactant but also constrains it to a well-defined orientation. Original concept of double H-bonding was represented in 1990. Diels-Alder reaction was catalyzed by biphenyl-diol **I**[17] and subsequently urea catalyst **II**[18] was presented. Both cases demonstrate coordination of two hydrogen atoms to the carbonyl group (Figure 5).



I **II**

Figure 5: *Coordination to the carbonyl group via hydrogen bonding.*

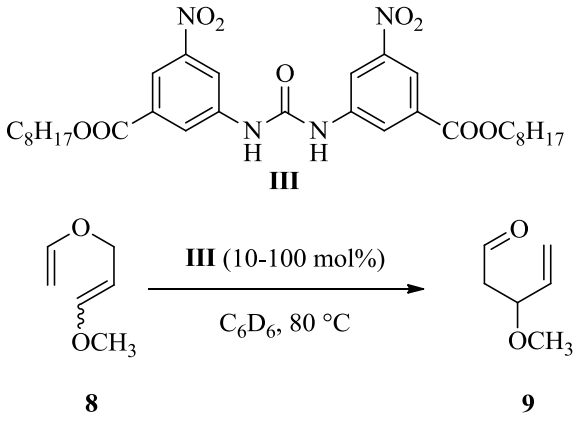
Double H-bonding is also used in catalysis of Lewis acids and central-coordinated metal atoms, but this could be limited to appropriate substrate structure. Against that, any Lewis base (aldehydes, ketones, esters, imine derivatives, etc.) could interact via two H-bonds with this organocatalysts.[19]

(Thio)urea's catalytic properties are given by their ability of decreasing LUMO energy of electrophile functional group present in the base. This is possible due to its double H-bond donating. Preference of thiourea functional group is due to its more acidic character (pK_a = 21.0 in comparison to pK_a = 26.9 of urea) and also much weaker H-bond acceptance.[20] It was proven that (thio)urea catalysts makes their H-bond with the functional group, which is also strongest Lewis bases and reduces difference in HOMO and LUMO energy in a similar way as Lewis acids does.[21]

1.3.1 ACHIRAL (THIO)UREA CATALYSTS

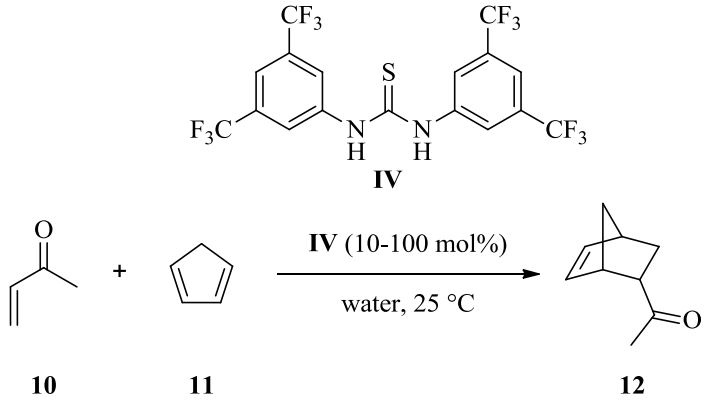
Development of (thio)urea catalysts begun in 90's, when Curran and his research group published application of electron-deficient derivatives of diarylurea **III** (Scheme 2).[22]

Those compounds were successfully employed for Claisen rearrangement and radical reaction.[23] Their preference is easy preparation and modifications.



Scheme 2: *Claisen rearrangement was promoted by Curran's urea catalyst **III**.*

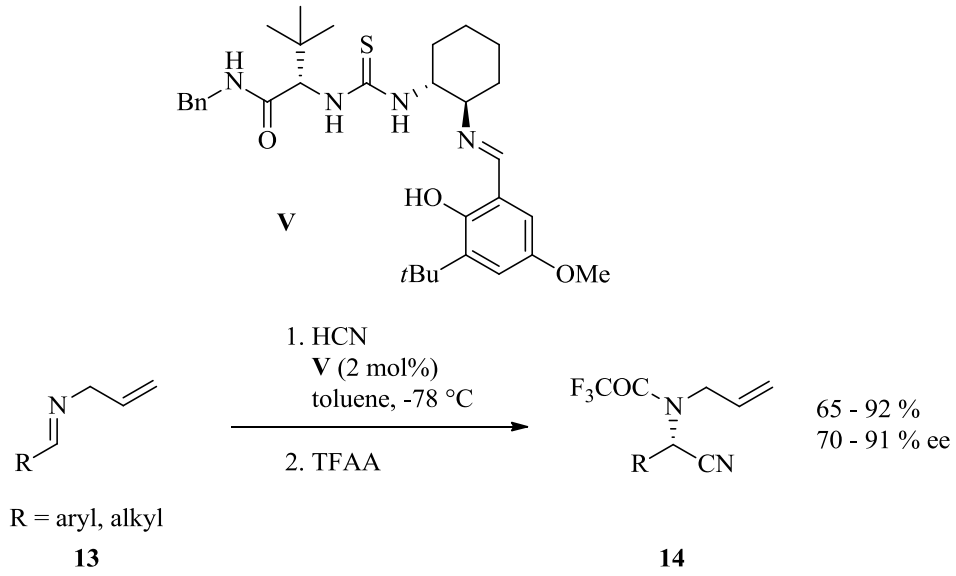
Thiourea derivative **IV** (Scheme 3) developed by Schreiner[24] and co-workers in 1998 was successfully used for Diels-Alder reaction and 1,3-dipolar cycloaddition of α,β-unsaturated carbonyl groups.



Scheme 3: *Schreiner's thiourea catalyst **IV** was used for Diels-Alder reaction.*

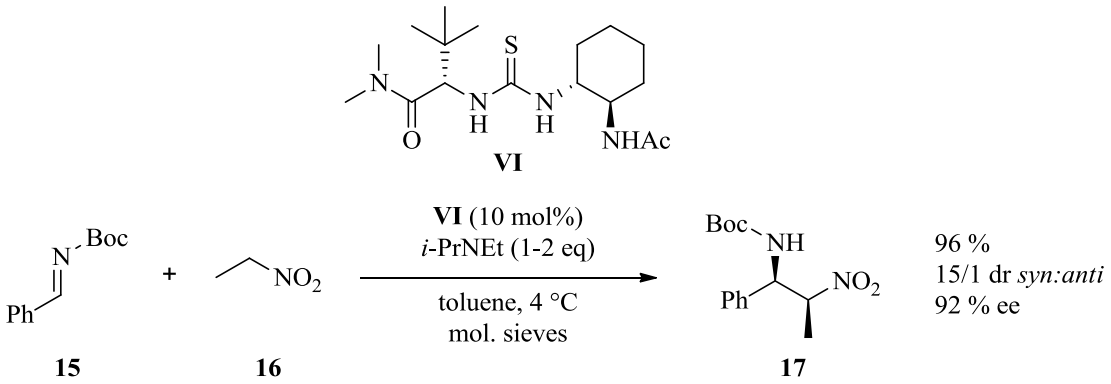
1.3.2 CHIRAL (THIO)UREA CATALYSTS

In 1998 Jacobsen[25] reported the first use of compounds containing thiourea moiety as catalysts for highly enantioselective Strecker reaction of imines (Scheme 4). Catalyst **V** was originally designed as a ligand for reactions of Lewis acids and metal-coordinated compounds



Scheme 4: *Strecker imine reaction was catalyzed by Schiff base containing thiourea moiety **V**.*

Later, in 2005, Jacobsen presented thiourea catalysts without Schiff base and applied it for aza-Henry reaction (Scheme 5).[26] In the presence of Hünig base and molecule sieves corresponding aza-Henry products were achieved excellent yields with excellent enantioselectivity. Those results led to conclusion that Schiff base isn't necessary in (thio)urea catalysts moiety.



Scheme 5: *Thiourea catalyst **VI** showed whitout Schiff base and its use in aza-Henry reaction of N-Boc imine **15** and nitroalkans **16**.*

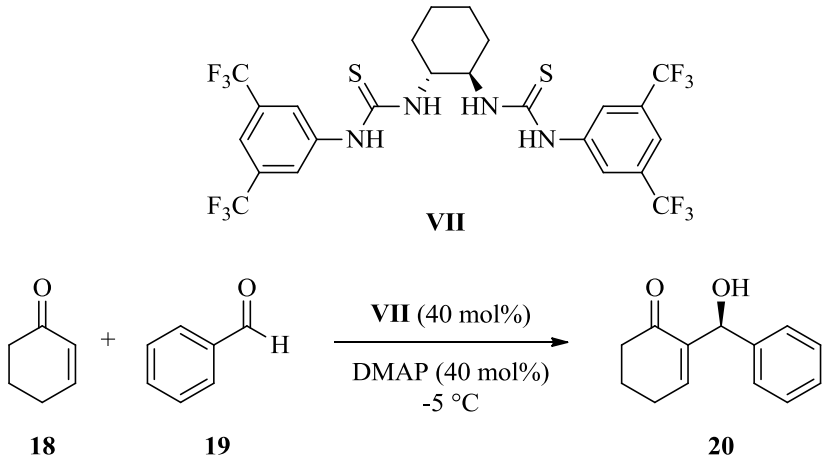
Use of those organocatalysts is unfortunately limited (to specific substrates), because their weaker acidity than Lewis acids containing metals.[27] Hence a class of bifunctional (thio)urea catalysts was developed.

1.3.3 BIFUNCTIONAL (THIO)UREA CATALYSTS

One of the most important aspects of organocatalysis is biomimetics, thus enzyme-behaviour imitation.[28] Enzymes form multiple weak interactions with substrates. On the other hand, Lewis bases in response to Lewis acids provide one strong interaction, which we know as monofunctional catalysts concept.

Bifunctional catalysts contain several functional groups. These groups interact with two components of chemical reaction at one time. This is commonly used in biocatalytic systems. It enables control of transition state development and therefore it increases the stereoselectivity of the particular reaction.[28]

(Thio)ureas were used for molecule recognizing at first and therefore their H-bond interaction with nitro group was known.[29] In 2004 Nagasawa presented bis-thiourea catalyst **VII** (Scheme 6).[30] This catalyst was successfully used for Baylis-Hillman reaction of cyclohexenones with aldehydes in the presence of DMAP including transition state (Figure 6), which describes coordination of **VII** via hydrogen bonds with enone **18** and aldehyde **19**.



Scheme 6: *Baylis-Hillman reaction of cyclohexenon (**18**) with benzaldehyde (**19**), which was catalyzed by bis-thiourea bifunctional catalyst **VII**, was presented.*

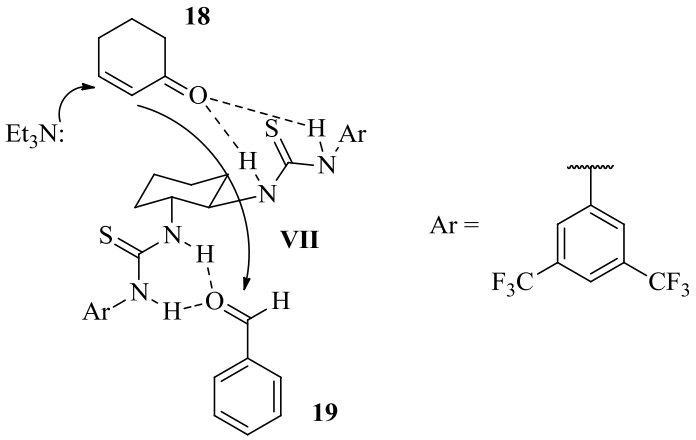
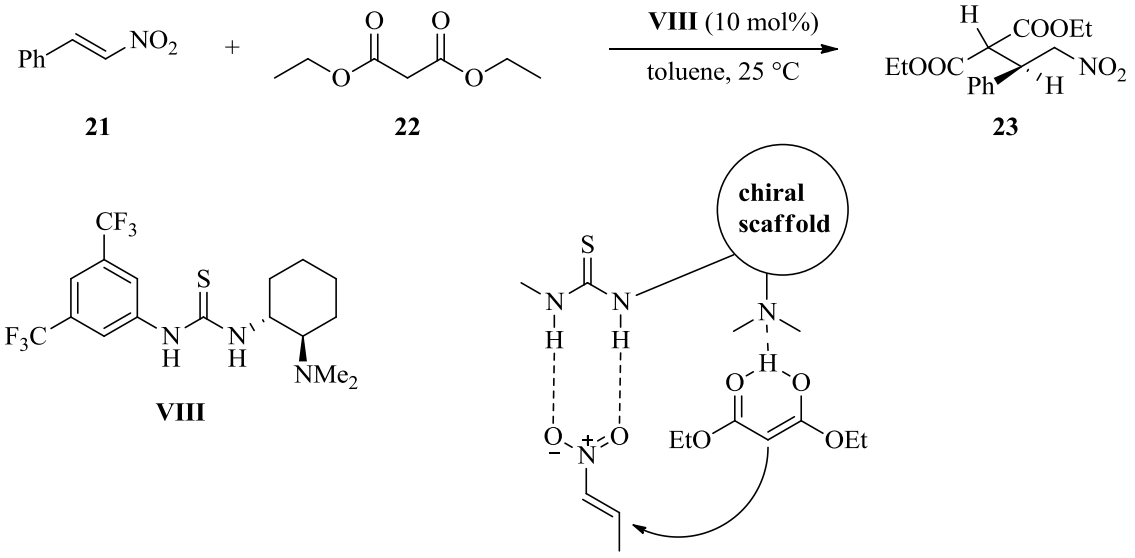


Figure 6: *Transition state of the bis-thiourea-catalyzed Baylis-Hillman reaction.*

In 2005, Takemoto developed chiral bifunctional thiourea organocatalyst **VIII** (Scheme 7) and demonstrated its application for Michael addition of diethyl malonate (**22**) to β-nitrostyrenes (**21**).[31] Necessity of thiourea moiety and tertiary amine (bifunctional character of organocatalyst) for the acceleration and high enantioselectivity of the reaction was proven by structural methods (X-ray). Particular orientations of N-H group and tertiary amine were also proven.[32] Nowadays Takemoto catalyst belongs to commonly used thiourea.[33]



Scheme 7: *Takemoto bifunctional catalyst **VIII** was used in Michael addition of β-nitrostyrene (**21**) to diethyl malonate (**21**), and activation via this catalyst was presented.*

1.4 SQUARAMIDE AS H-BOND DONORS

As we outlined above in 1.3, H-bonding promoted organocatalysis has grown explosively over the past decades.[34] Mainly, we discussed (thio)ureas as most used organocatalyst so far.[35] Let's introduced new family of H-bonding catalysts based on squaramide motive **25** (Figure 7) presented in 2008 by Rawal and his research group.[36]

It was proved by examination of crystallographic and computational data that two hydrogen atoms of thiourea **24** are positioned ~213 pm apart, each canted by ~0.6°. The distance between two hydrogens is determined by the fact that the accompanying N atoms are connected by a one-carbon link. Than was postulated that bisamide derivatives of squaric acid **25**, which position the hydrogen 60 pm further apart, could serve as a versatile core activation unit for dual H-bonding catalysts.[37]

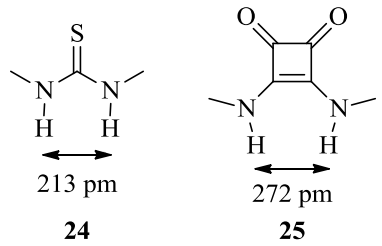
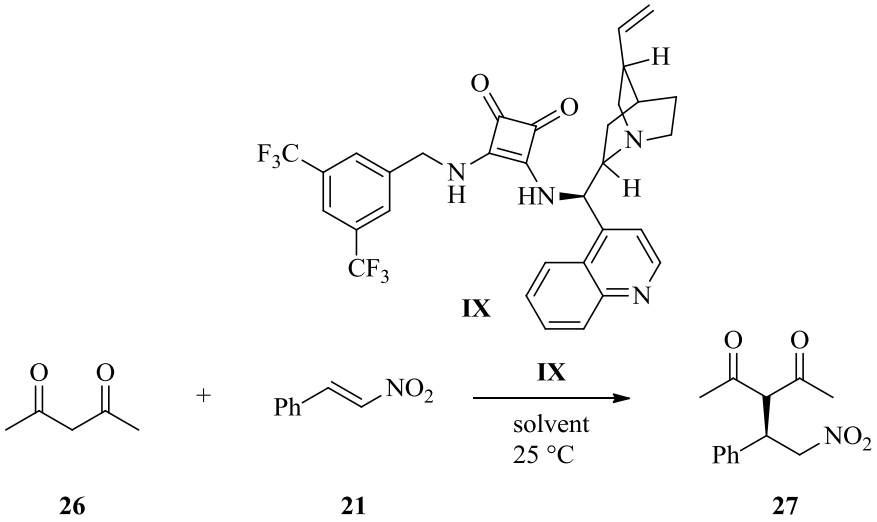


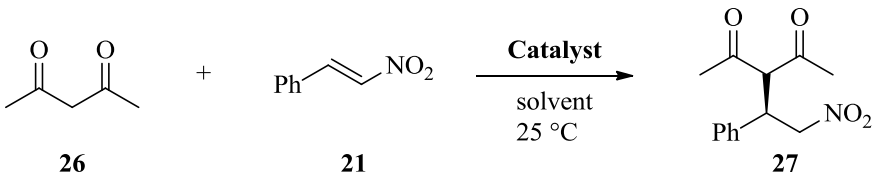
Figure 7: *Calculated distances in N,N'-dimethylthiourea (**24**) and N,N'-dimethylsquaramide (**25**).*

Squaramid derivative **IX** was firstly used as catalyst for the conjugate addition of 2,4-pentanedione **26** to nitrostyrene **21** (Scheme 8). This reaction had showed excellent yield and enantiomeric excess.[36] Now we are able to compare thiourea and squaramide based catalysts (see Table 1).[30,36]



Scheme 8: *Conjugate addition of 2,4-pentanedione (**26**) to β-nitrostyrene (**21**) promoted by squaramide catalyst **IX**.*

Table 1: *Comparison of thiourea catalyst **VIII** and squaramide catalyst **IX** using the same reactions.*



Catalyst	mol %	Solvent	Time (h)	Yield (%)	ee (%)
VIII	0.1	DCM	24	53	90
VIII	0.1	toluene	24	**60**	**92**
VIII	0.1	MeOH	24	33	29
IX	0.1	DCM	20	97	96
IX	2.0	DCM	7	**98**	**99**
IX	2.0	toluene	24	94	98

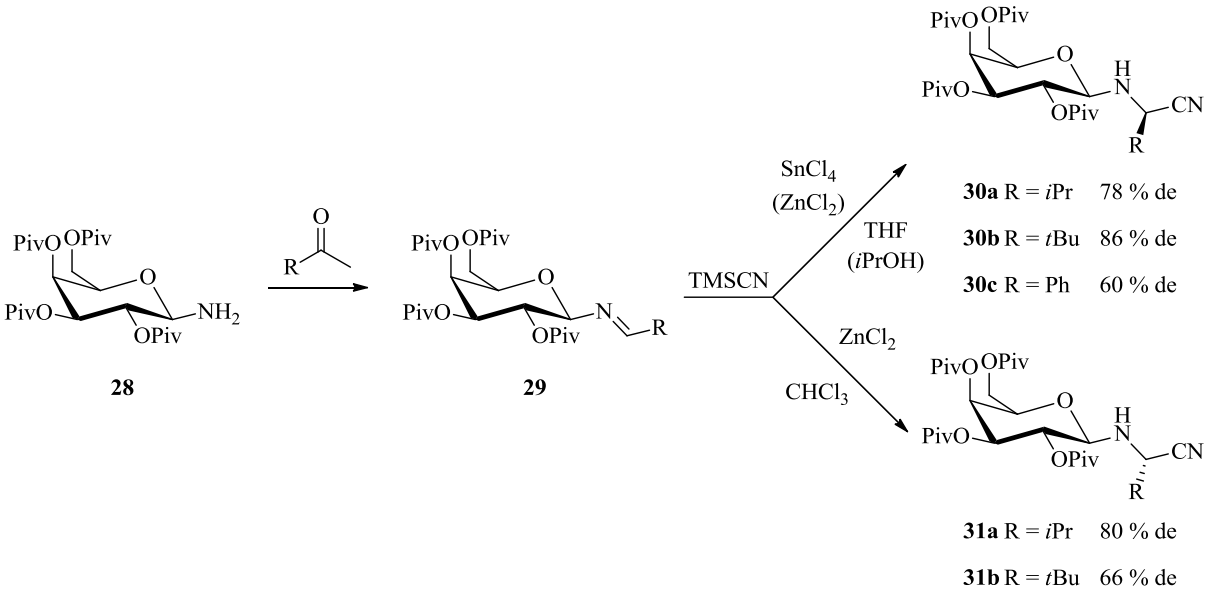
Results summarised in Table 1 by Rawal show the squaramide unit to be an effective scaffold. For this conjugate addition it was remarkably active catalyst and it deserves our attention.

1.5 CARBOHYDRATES IN ORGANIC SYNTHESIS

As it was told above, carbohydrates are chiral and natural compounds.[1] They are readily available in a variety of diastereometric forms, chiral and conformationally rigid molecules providing a various multi-configured hydroxyl groups for chemical modifications.[38] Carbohydrates can stand out as an auxiliaries, reactants, ligands or organocatalysts.[39]

1.5.1 CARBOHYDRATE AUXILIARIES

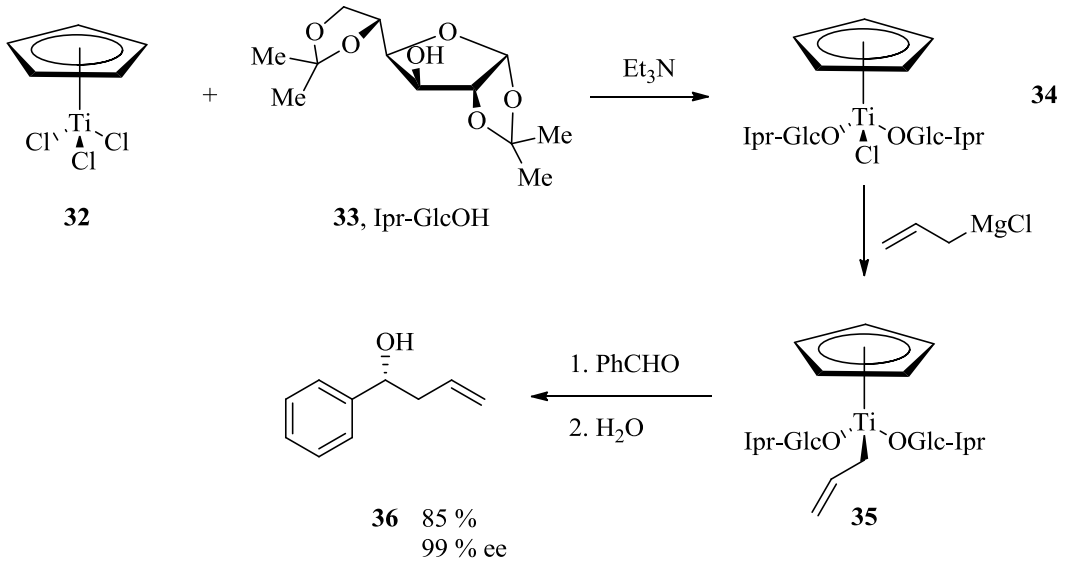
Almost 40 years ago carbohydrates were reported as an auxiliary tool. Broader investigation started only 25 years ago. Since then a multitude of structures were developed and applied to various reactions.[40] Kunz and co-workers reported a very versatile tool in a pivaloyl protected D-galactosyl amine **28**.[41] Condensation with aldehydes yielded galactosyl aldimines **29** which underwent highly diastereoselective Strecker reactions with trimethylsilyl cyanide in the presence of Lewis acids (Scheme 9).[41] The solvent had a crucial influence on the stereoselectivity, $SnCl_4$ in tetrahydrofuran (affording *R* configuration) or $ZnCl_2$ (*S*) in isopropanol yielding α-aminonitriles[40,41] while Strecker products with opposite configuration at the new stereocenter were obtained with $ZnCl_2$ in the less polar chloroform.[40,42]



Scheme 9: *Strecker diastereoselective reaction uses a D-galactose as an auxiliary group.*

1.5.2 CARBOHYDRATE REAGENTS

Duthaler and his research group successfully prepared half-sandwich titanium compound **34**.[43] When compound **34** was treated with an allyl magnesium chloride, compound **35** was formed, which transferred the allyl residue to aldehydes with good to excellent enantiomeric excess (Scheme 11).[44] Reagent **35** has proved valuable in aldol reactions.

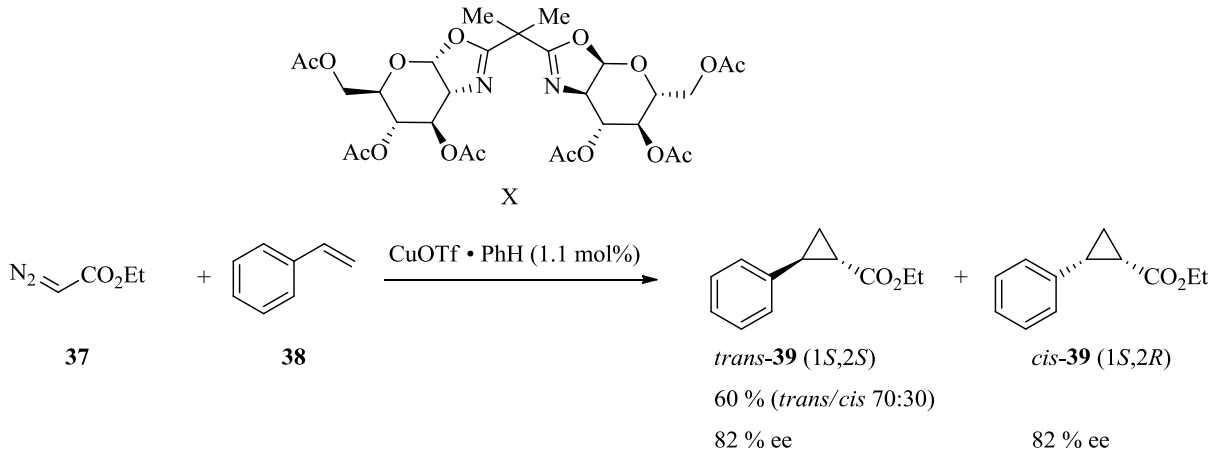


Scheme 10: *Titanium half-sandwich compound **32** treated with diisopropylidene glucose **33** to afford carbohydrate reagent **34**.*

1.5.3 CARBOHYDRATE LIGANDS

Carbohydrates have been increasingly used as chiral ligands in the last two decades. Carbohydrates generally contain several weak donor sites. Since then, many of the catalytic precursors in homogenous coordination complexes of the platinum-group metals have been presented. The required ligands should contain such donor atoms such as N, S and P which can form stable complexes with practically all transition metals.[45]

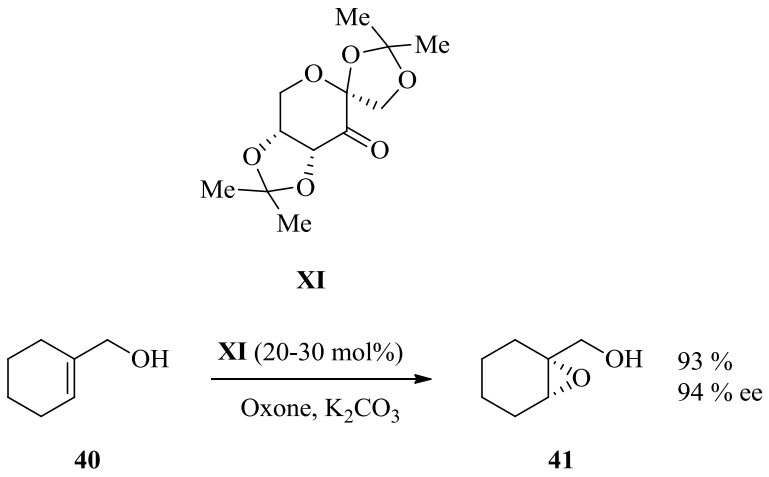
Recently, Boysen and co-workers presented a new carbohydrate bis(oxazoline) ligand **X** with a dimethylmethylene bridge (''*gluco*Box'') derived from D-glucosamine hydrochloride. This ligand was used to catalyze cyclopropanation of olefins with diazoacetates promoted by copper(I) (Scheme 11).[46]



Scheme 11: *Asymmetric cyclopropanation promoted with copper(I)-glucoBox **X**.*

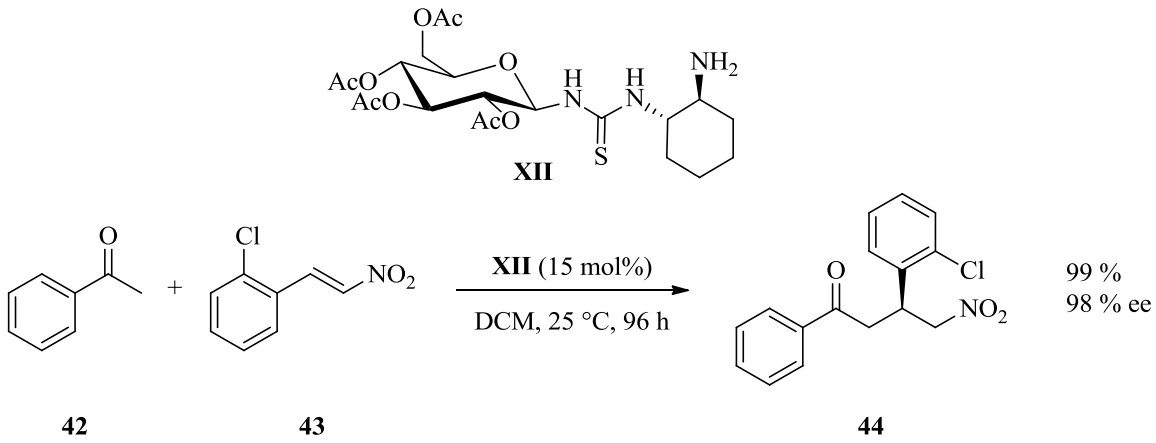
1.5.4 CARBOHYDRATE ORGANOCATALYSTS

One of the first example of use of carbohydrate derivative as catalyst is the D-fructose-based ketone **XI** applied in Shi epoxidation (Scheme 12).[47] Dioxirane is generated *in situ* from **XI** and Oxone (Potassium peroxysulfate) which epoxidized 1,2-*trans* di- and trisubstituted alkenes in good to excellent enantiomeric excess.[48]



Scheme 12: *Epoxidation of alkens with D-fructose based ketone **XI** catalyst.*

Typical example of carbohydrate catalysts containing thiourea moiety is Ma's bifunctional catalyst **XII** (Scheme 13).[49] Catalysts developed by Ma has proved valuable in Michael addition of aromatic ketones to a range of nitroolefins with excellent enantiomeric excess.



Scheme 13: *Direct enantioselective Michael addition promoted by carbohydrate catalyst **XII**.*

A bifunctional catalytic mechanism was suggested in which a thiourea moiety interacts through H-bonding with a nitro group of the nitroolefines and enhances their electrophility while the neighbouring primary amine activates ketones involving an enamine intermediate. The observed absolute configuration (*S*) of the conjugate adduct was explained by the transition state model (Figure 8).[49]

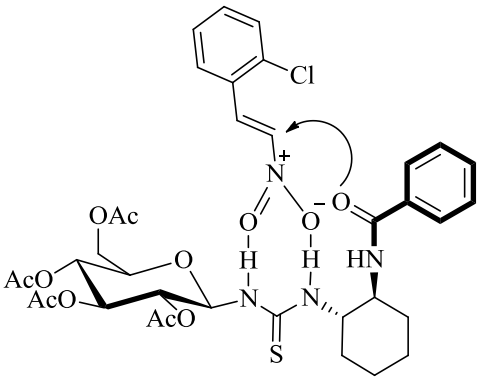
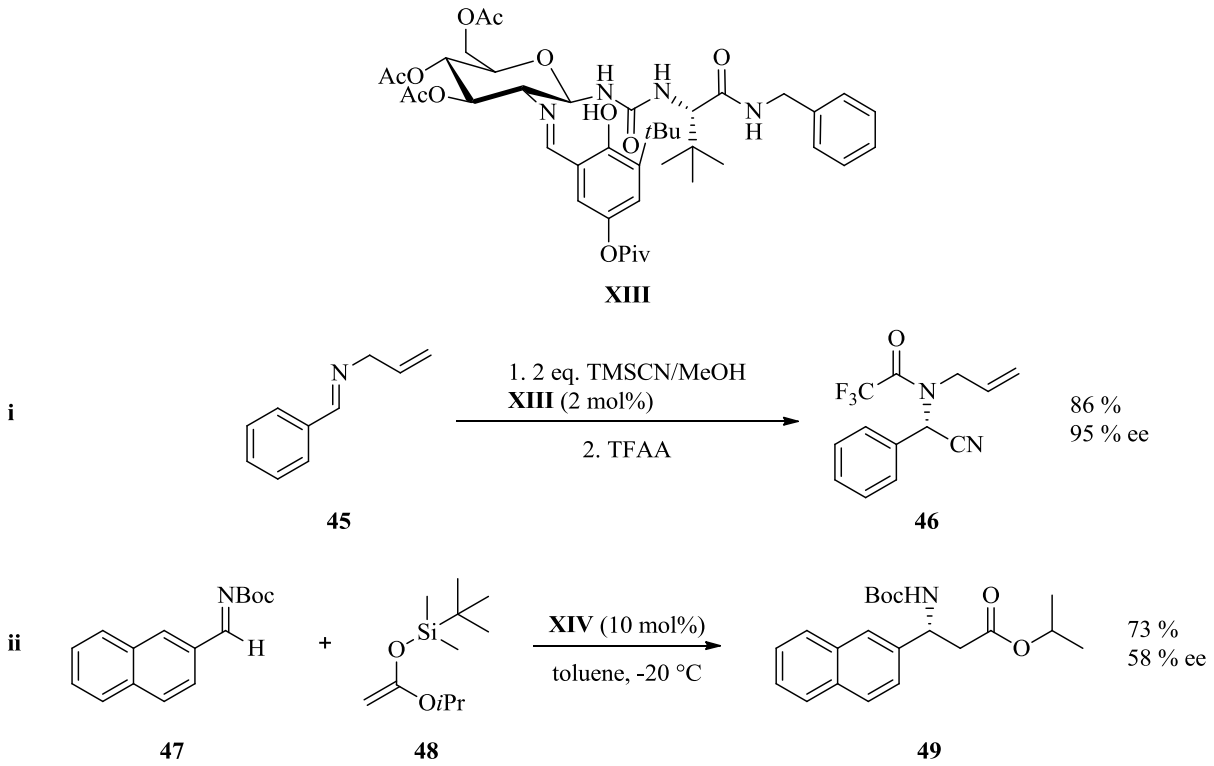


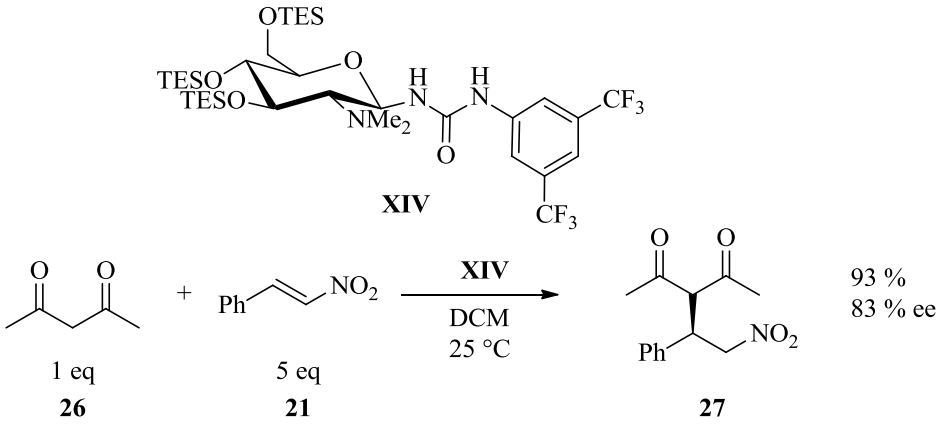
Figure 8: *Transition state model.*

Efficient organocatalysts for enantioselective Strecker[24] and Mannich[50] reactions can be constructed from D-glucosamine as a component of the natural chiral pool. With catalyst **XIII**, high yields and enantioselectivity were accomplished in hydrocyanation reactions of aromatic aldimines (Scheme 14, **i**). It has also proven to be able to enantioselectively catalyze the Mannich reaction of *N*-Boc-aldimine **47** with silyl ester enolate **48** to produce β-amino acid ester **49** (Scheme 14, **ii**).[51]



Scheme 14: *Strecker synthesis **(i)** and Mannich reaction **(ii)** catalyzed by glucosamine derived catalyst **XIII**.*

From research of Kunz and his group[51], novel bifunctional catalyst **XIV** has recruited.[52] Then urea catalyst was applied to nucleophilic addition to nitroolefines. Best results were achieved by using silyl ethers protecting groups (Scheme 15). The level of stereoselectivity was comparable to Takemoto catalyst **VIII** and also the urea derivative was shown to behave better than corresponding thiourea catalyst, where 70:30 α/β-anomers were achieved.



Scheme 15: *Addition of acetylacetone **(26)** to β-nitrostyrene **(21)** performed by urea catalyst **XIV** containing carbohydrate scaffold.*

2. GOALS OF THIS THESIS

With the respect to the general needs to improve accessibility of H-bonding organocatalysts, the aim of this work is the preparation of a set of various sugar-derived organocatalysts containing thiourea and squaramide moiety from the most easily available monosaccharides, D-glucose and D-glucosamine. This general aim includes several goals, as follows:

1. Preparation of acyl-, alkyl- and silyl-protected saccharide units suitable for the construction of thiourea and squaramide organocatalysts.

2. Synthesis of new thiourea catalysts derived from D-glucose and D-glucosamine.

3. Synthesis of new squaramide catalysts derived from D-glucose.

3. RESULTS AND DISCUSSION

As was told above (Page 19), carbohydrates are natural, cheap and readily available compounds. They provide multi-configured hydroxyl groups for chemical modifications.[38] Hence they are very good participants to organocatalytic chemistry. D-Glucose and D-glucosamine hydrochloride, respectively, were used as starting material. Variously modified catalysts **XVI** – **XX** were prepared by altering protecting groups of hydroxyls on D-glucose or by altering position of thiourea linkage itself (Figure 9).

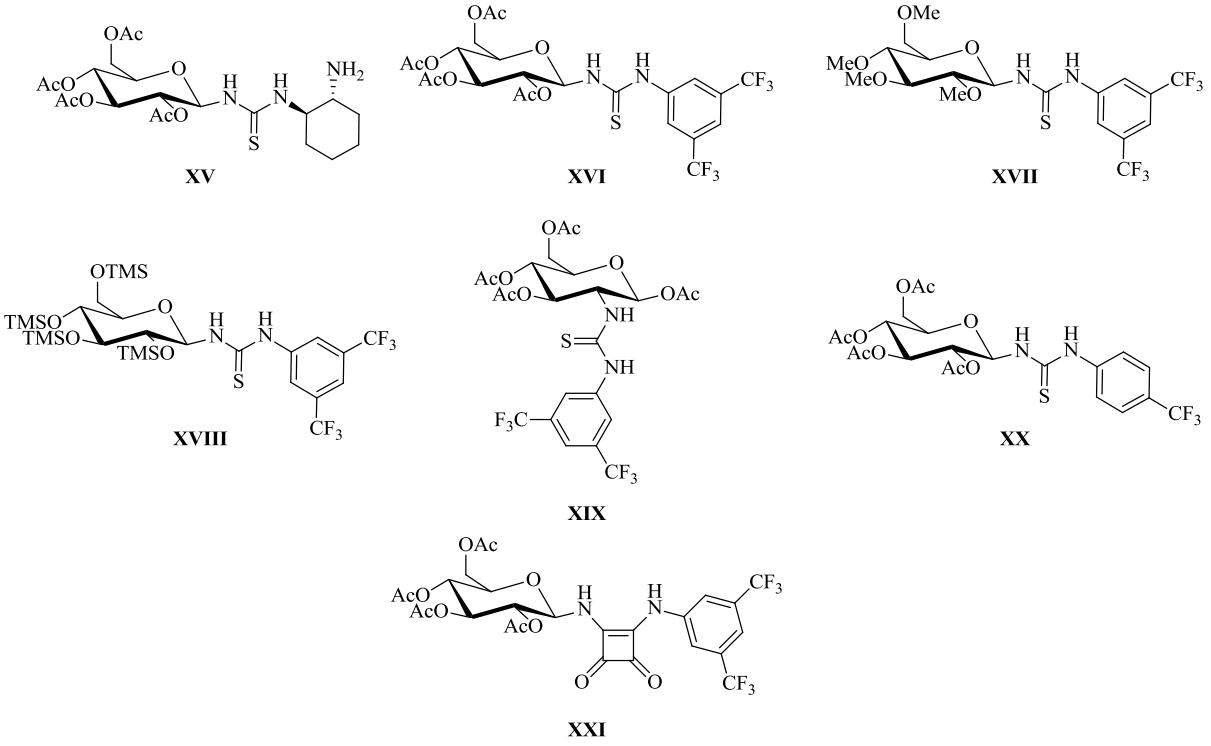


Figure 9: *Catalysts prepared during completing this thesis.*

Acetyl was selected as acyl group. Reasons comprised its easy preparation and ability to modify as well as its stability in various conditions. Methyl ether was used as alkyl protecting group, because small size of alkyl chain and stability in majority of conditions. Finally we prepared silyl protected derivative, namely trimethylsilyl derivative. It is stable and large protecting group, which can be easily installed and removed.

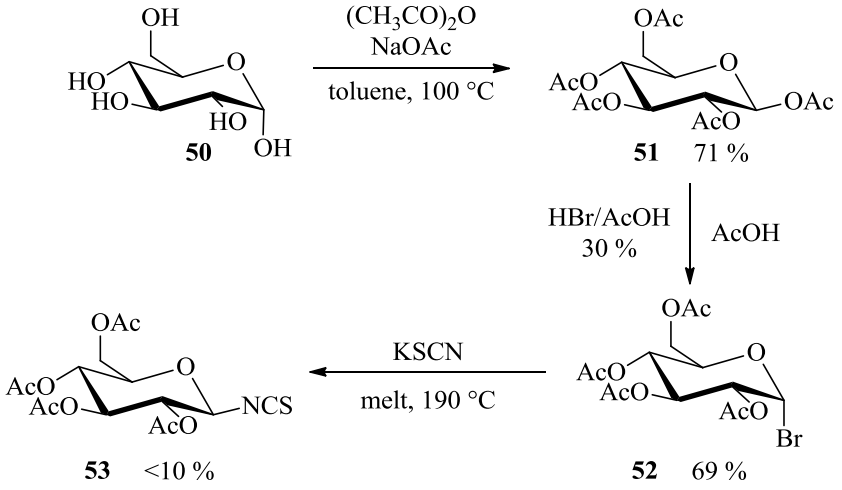
Catalyst **XV** was prepared in cooperation with Tereza Řehůřková and it was not object of this thesis.[53] This catalyst is modification of Ma's catalyst. Primary amine group of cyclohexane could be transformed to tertiary amine or to another modification.

Squaramide catalyst **XXI**, which was subject of this thesis, was not prepared yet successfully neither with changing reaction conditions and this area of research is still in progress.

3.1 SACCHARIDE DERIVATIVES

3.1.1 PREPARATION OF ISOTHIOCYANATE AND AZIDE

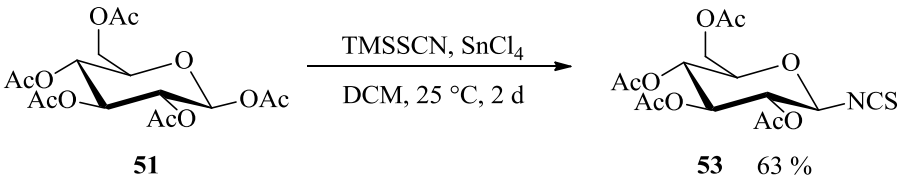
α-D-Glucopyranose (**50**) was used as the starting compound **51**. After completing acetylation we obtained much more reactive β-anomer of D-glucopyranose.[54] From this derivative **51** was subsequently prepared isothiocyanate **53**, which was synthesized by two different methods (**A** and **B**). In Scheme 16 is shown Method A.



Scheme 16: *Preparation of fully acetylated glucose **51** and glycosyl isothiocyanate **53** using KSCN.*

Method A: After obtaining fully acetylated glucose **51**, glycosyl bromide **52** was prepared by dissolving **51** in glacial acetic acid and addition to 30 % solution of HBr in acetic acid was performed. Next, glycosyl bromide **52** was melted with KSCN to afford glycosyl isothiocyanate **53**.[55] Unfortunately, this reaction afforded less than 10 % yield. Moreover, it takes 2 steps to isothiocyanate product and reaction was not so comfortable to perform, because of high temperature needed for melting and solution of HBr in acetic acid.

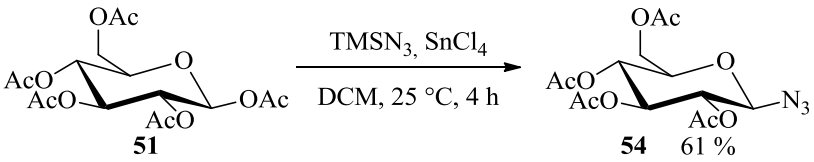
Method B: As is shown in Scheme 17, simple one-step preparation of isothiocyanate **53** was performed.[56] Trimethylsilyl isothiocyanate was added and tin(IV) chloride was used as a Lewis acid. This reaction was providing good yields even in larger amounts.



Scheme 17: *One-step preparation of glycosyl isothiocyanate **53**.*

It is clear now that we prefer Method B because it provides better yields and the synthesis is quicker.

As is shown in Scheme 18, glycosyl azide[51] **54** was prepared from starting material **51** with very similar conditions as glycosyl isothiocyanate **53**. In this case we did not use trimethylsilyl isothiocyanate, but trimethylsilyl azide instead and tin(IV) chloride as well. We achieved 100 % conversion with good to excellent yields. This reaction was modified, from that given in literature (increase of $TMSN_3$, longer reaction time). Using this modification we avoid purifying on silica gel.

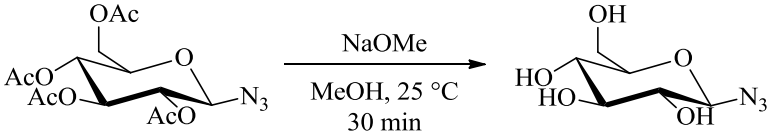


51 **54** 61 %

Scheme 18: *Preparation of glycosyl azide **54**.*

3.1.2 *ALTERATION OF PROTECTING GROUPS*

Starting material **54** was deacetylated and subsequently protected by methyl and silyl ethers. Deacetylation was performed by the classical Zemplén method.[58] We used 1 M solution of sodium methoxide in methanol, which was used also as solvent (Scheme 19).

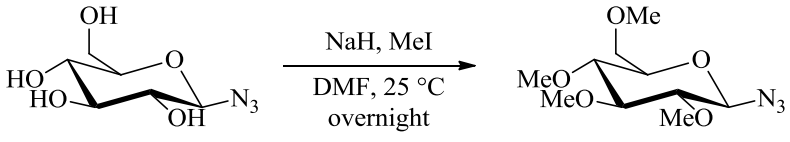


54 **55** 99 %

Scheme 19: *Zemplén O-deacetylation.*

Zemplén method was very satisfying, providing excellent yields in short reaction time. Compound **55** were immediately used for next reactions.

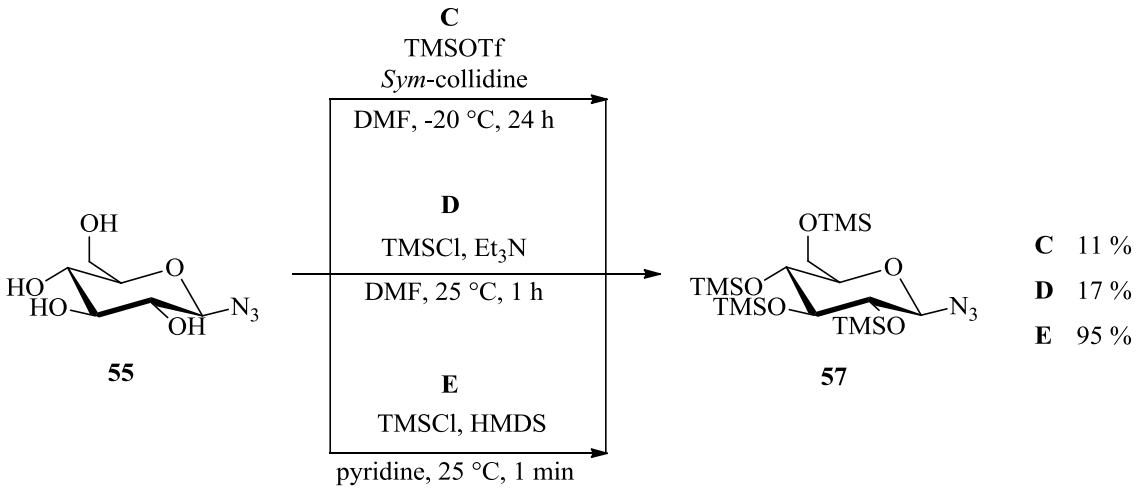
As the first, we prepared *O*-methylated glycosyl azide **56** (Scheme 20). The product **55** was functionalized under classical Williamson conditions.[59]



55 **56** 76 %

Scheme 20: *Williamson ether synthesis.*

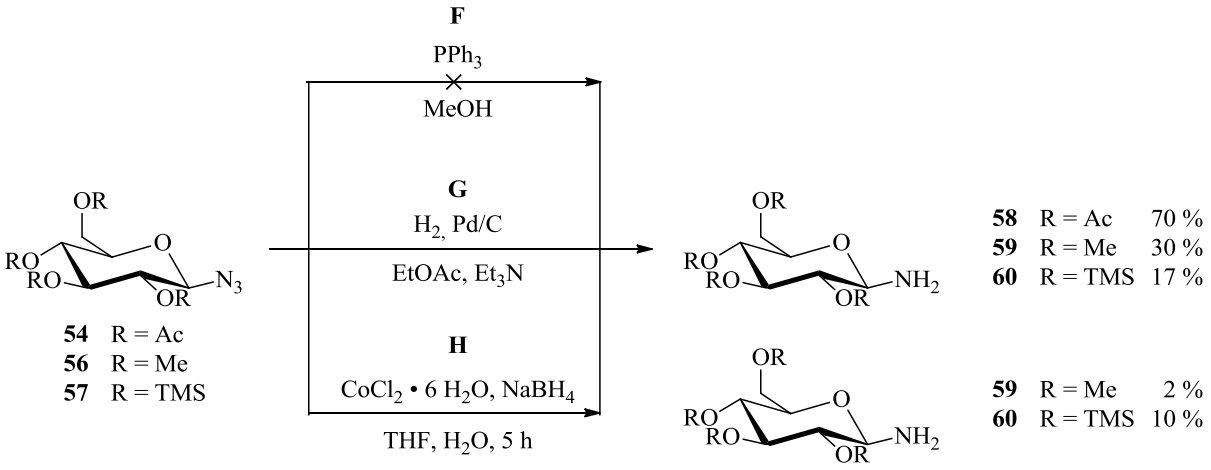
Then we focused on the preparation of *O*-silylated azide **57**. To achieve satisfactory results in the preparation of this substance, we had to try three different procedures – **C**[52], **D** and **E**[60] (Scheme 21). Methods **C** and **D** provided very low yields of **57**, moreover, method **C** was practically uncomfortable, due to its reaction conditions (-20 °C for 24 hours). On the other hand, method **E** afforded compound **57** in excellent yields. Performing Method **E** is also very effective and quick, because reaction time is only 1 minute and it gives very good yields (95 % in small amount, about 70 % in larger amounts).



Scheme 21: *Preparation of a silylated glycosyl azide **57**.*

3.1.3 REDUCTION OF AZIDES TO AMINES

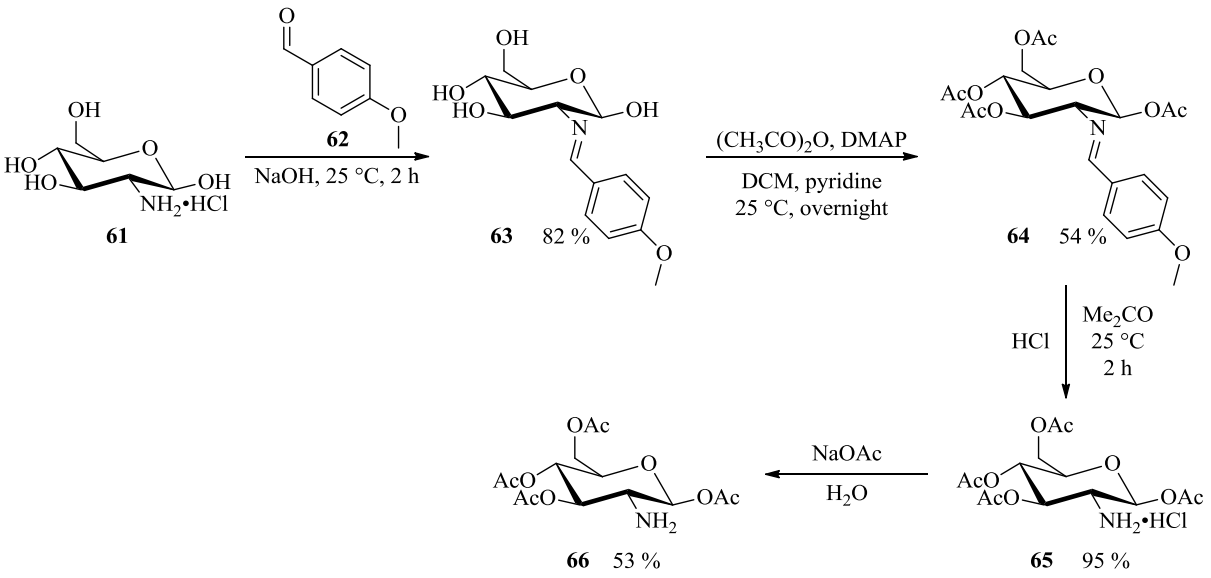
Next, we needed to reduce the azide to amine. To obtain the amine three different methods – **F**[61], **G**[62] and **H**[63] were tested (Scheme 22). Method **F**, which is Staudinger reduction, was not successful at all, even when we changed reaction conditions (temperature, solvents and reaction time). Method **H**, where $NaBH_4$ was used to generate H_2 *in situ*, did not afford satisfying conversion. The isolation of resulting product was the major problem. Best results were achieved using method **G** – classical method of hydrogenation using Pd/C. Sometimes 100 % conversion was achieved (mostly with smaller amounts). Reaction mixture was purified on silica gel with 1 % of triethylamine. We successfully produced glycosyl amine in various, poor to good, yields. This could be caused by saturating the palladium with other elements besides the hydrogen molecule.



Scheme 22: *Different ways to prepare an amine from azide.*

3.1.4 PREPARATION OF O-ACETYLATED D-GLUCOSAMINE

Finally, we prepared acetylated glucosamine derivative **66** (Scheme 23) based on the procedure described in literature[57]. D-Glucosamine hydrochloride (**61**) was used as the starting material. The Schiff base **63** was prepared by using anisaldehyde (**62**) in 1 M aqueous solution of sodium hydroxide. Product **63** was *O*-acetylated with acetic anhydride in the mixture of dichloromethane and pyridine. This transformation was promoted by DMAP. Subsequently, Schiff base was removed by treatment of compound **64** with 5 M HCl. To the resulting *O*-acetylated glucosamine hydrochloride **65**, sodium bicarbonate was added, affording corresponding derivative **66**.

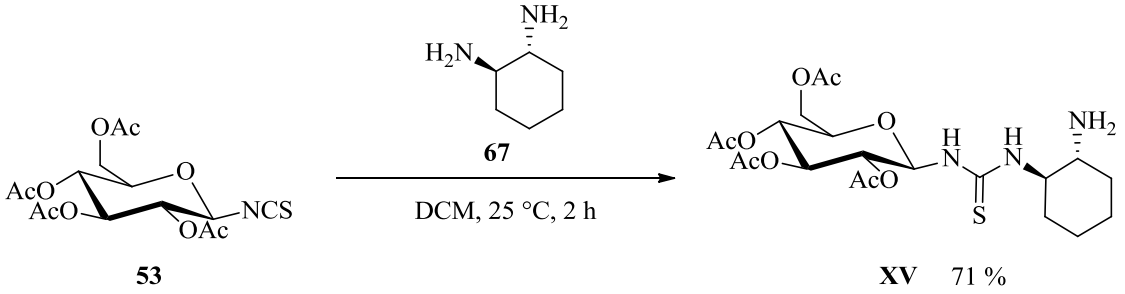


Scheme 23: *Preparation of acetylated glucosamine.*

3.2 THIOUREA CATALYSTS

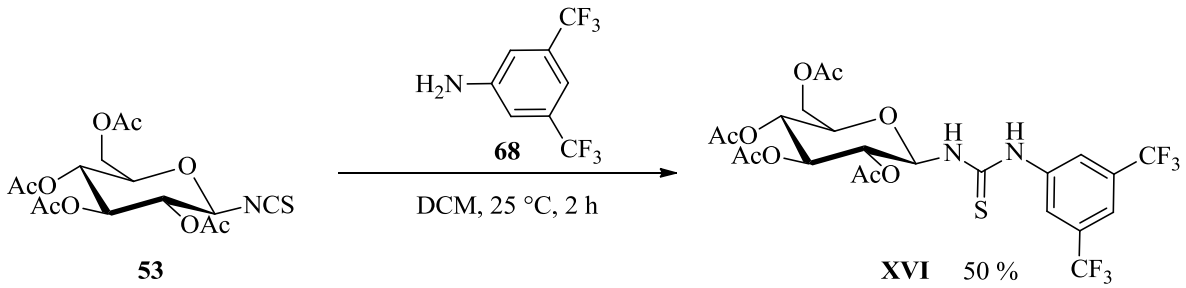
In general, nucleophile attack to carbonyl group of isothiocyanate was performed. Isothiocyanate derivatives were 3,5-bis-trifluoromethylphenyl or 4-trifluoromethylphenyl. Individual reactions were performed in very similar conditions, thus at room temperature (approx. 25 °C) and as preferred solvent dichloromethane was selected. Conversion of the reaction was monitored on TLC. Thiourea linkage was defined by NMR measurements (corresponding chemical shifts to thiourea link), MS (ESI source) and IR.

The fact that glycosyl isothiocyanates and primary amines interact and provide good yields was reported in Ma's research[49]. We also tried this reaction type. Reaction between compound **53** and **67** was performed as in Scheme 24.[53]



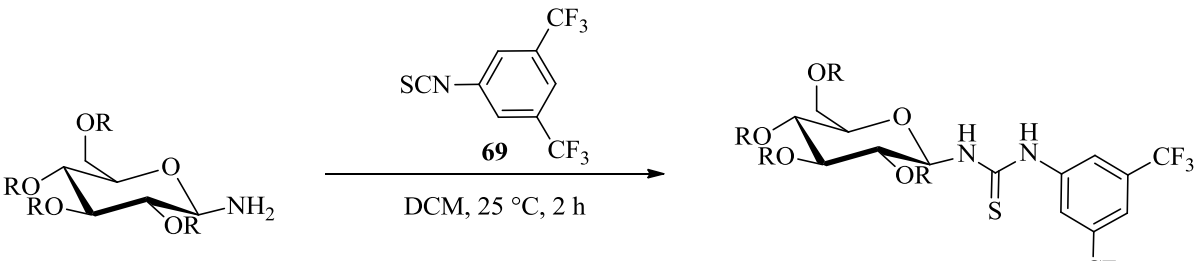
Scheme 24: *Preparation of Ma catalyst.*

Next, the reaction between compound **53** and 3,5-bis-trifluoromethylphenyl aniline (**68**) was performed. Reaction conditions used previously were successfully adopted to this transformation, and maximum conversion of **53** to **XVI** was obtained after 2 hours (Scheme 25).



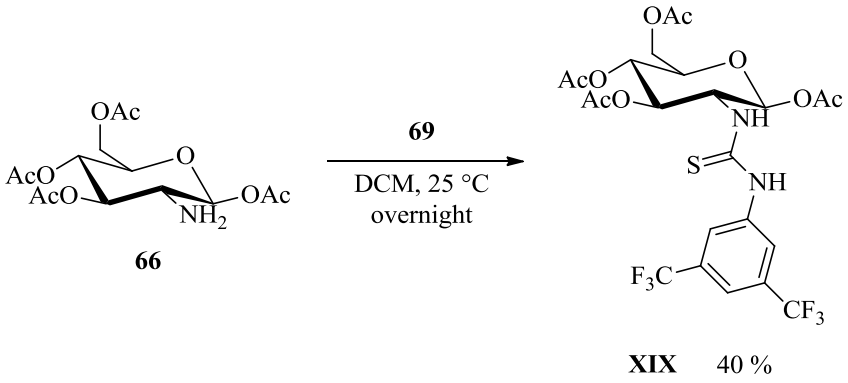
Scheme 25: *Preparation of new thiourea catalyst.*

Further, we had to perform reaction between glycosyl amine derivatives **58**, **59**, **60, 66** and aryl isothiocyanate (**69**). All these reactions afford very similar yields as compared to that shown in Scheme 25. In this way we prepared catalysts **XVII** and **XVIII** (Scheme 26).



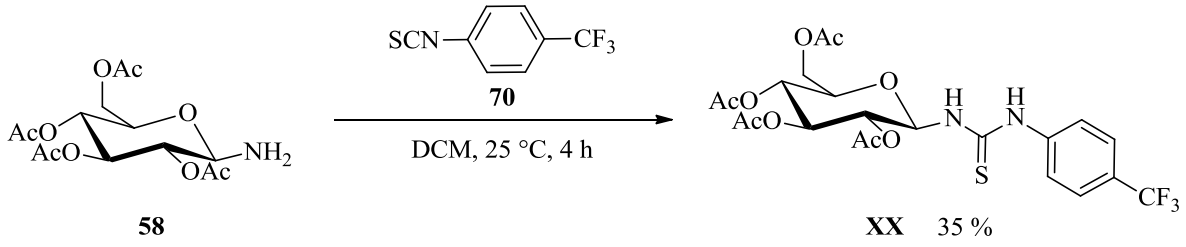
Scheme 26: *Catalysts **XVII** and **XVIII** were prepared.*

We also decided to examine effect of thiourea linkage located to C_2 carbon of D-glucose. Catalyst **XIX** (Scheme 27) was prepared under the same conditions as other catalysts, but reaction time was increased up to 12 hours.



Scheme 27: *Reaction between glucosamine and isothiocyanate **69** was affording catalyst **XIX**.*

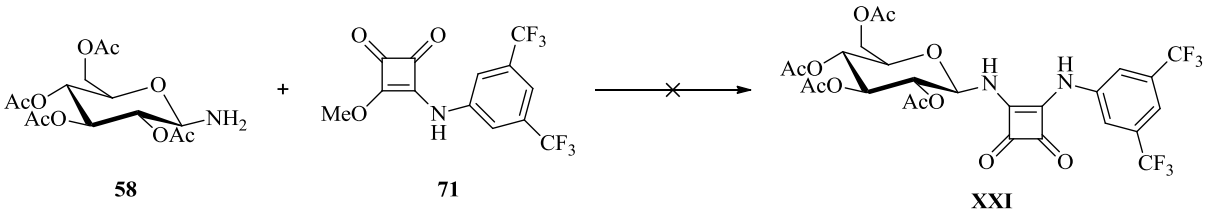
Another catalyst was prepared (Scheme 28). This time we used 4-trimethylphenyl isothiocyanate (**70**). Catalyst **XX** was prepared in view of the catalytic effect of different aryl group.



Scheme 28: *Preparation of catalyst **XX** using glycosyl amine **58** and aryl isothiocyanate **70**.*

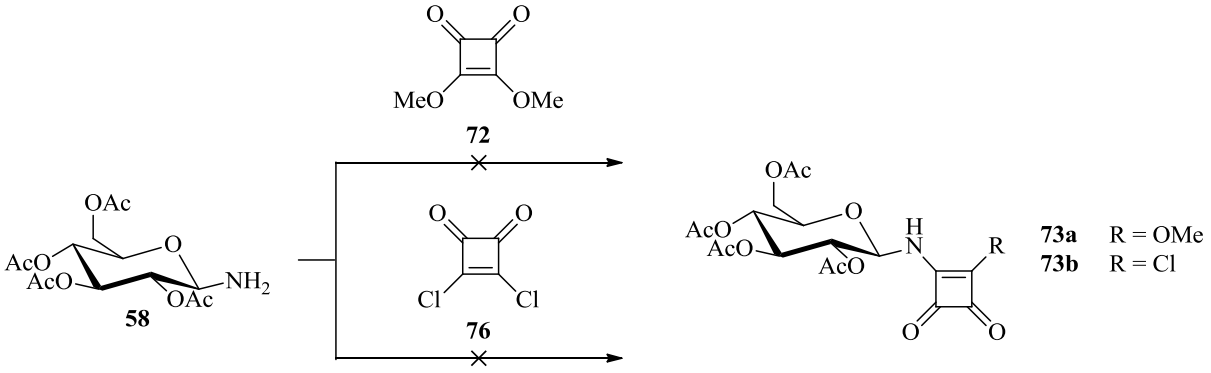
3.3 SQUARAMIDE CATALYSTS

We decided to prepare new carbohydrate catalyst that would include squaramide scaffold. As starting materiel we used glycosyl amine **58** and various derivatives with squaramide motive (**71**, **72** and **73**, Scheme 29 and 30).



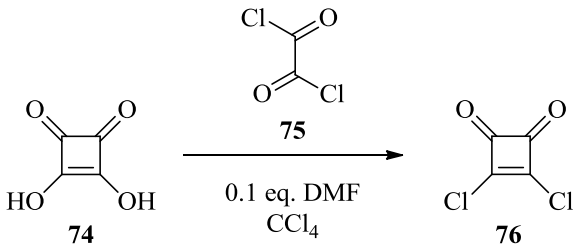
Scheme 29: *Unsuccessful preparation of new squaramide catalyst **XXI**.*

To perform this reaction we followed literature[64], which described also the preparation of compound **71**. Unfortunately, these conditions did not led to satisfactory conversion, so we tried different solvents, namely methanol, tetrahydrofuran and toluene. Hence, we decided to try reaction between amine **58** and non-substituted squaric acid derivative **72**, and also to change methoxy group for some more reactive group or element (compound **76**) (Scheme 30).



Scheme 30: *Different experiments of preparation compound **73**, which could serve as a starting material for preparation catalyst **XXI**.*

Reaction using compound **72** was performed as described above, thus using toluene as solvent and reflux. In the same scheme, we described reaction performed with dichloride derivative of squaric acid **73** dissolved in THF at 0 °C and continuous stirring for 2 hours – 2 days at room temperature. As it turned out from MS and NMR, resulting product was not compound **73a** or **73b**. Compound **76** was prepared from squaric acid (**74**) and oxalyl chloride (**75**) (Scheme 31).[65]



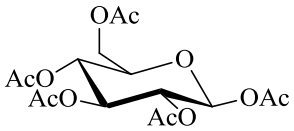
Scheme 31: *Preparation of dichloride derivative **76** of squaric acid.*

After obtaining these results, we left this topic and focused on thioureas. Nevertheless, squaramide derivatives remain our aim for the future.

4. EXPERIMENTAL PART

Chemicals and solvents were either purchased p.a. from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F_{254} were used, and compounds were visualized with UV light and/or by treatment with a solution of sulphuric acid (5% solution in water), followed by heating. Flash chromatography was performed by using silica gel Merck 60 (particle size 0.063–0.200 mm). ^{1}H and ^{13}C NMR spectra were recorded with a Varian ^{UNITY}INOVA-300 and Brucker AVANCE III 600. Chemical shifts for protons are given in δ relative to tetramethylsilane (TMS) and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ = 7.26 ppm). Chemical shifts for carbon are given in δ relative to tetramethylsilane (TMS) and are referenced to the carbon resonances in the solvent ($CDCl_3$: δ = 77.0 ppm). Peaks of ^{19}F NMR spectra were referenced to the standards peak of trifluoacetic acid (0 ppm). Interact constant *J* is reported in Hz units. 2D NMR spectra (HMBC, COSY and HSQC) were measured for accurate peaks defining. MS ESI spectra were measured by using Bruker Esquire 3000.

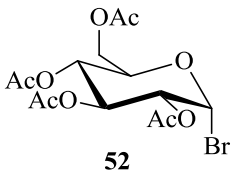
1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (**51**)



51

To the suspension of D-glucose (**50**) (10.0 g, 55.6 mmol) in toluene (83 ml), acetic anhydride (33.0 ml, 356.0 mmol) and sodium acetate (1.7 g, 20.7 mmol) were added under stirring. The reaction mixture was refluxed at 110 °C for 4 hours. Water (30 ml) was added and the mixture was neutralized with 3% NaOH aq. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to halves. The obtained crystals were filtered and recrystallized from ethanol. It was obtained 15.5 g of pure colourless crystalline solid (**51**) (yield 71 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73 d (1H, *J* = 8.4 Hz, C_1H), 5.25 t (1H, *J* = 9.3 Hz, C_2H), 5.17-5.10 m (2H, C_3H, C_4H), 4.32 dd (1H, J_{13} = 12.6 Hz, J_{23} = 8.1 Hz, C_6Ha), 4.14 dd (1H, J_{13} = 12.3 Hz, J_{23} = 10.2 Hz, C_6Hb), 3.87-3.81 m (1H, C_5H), 2.12 s (3H, CH_3CO), 2.09 s (3H, CH_3CO), 2.03 s (6H, CH_3CO), 2.01 s (3H, CH_3CO).

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**52**)

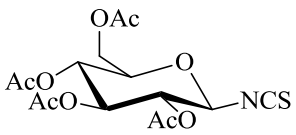


52

1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (**51**) (1.0 g, 2.6 mmol) was dissolved in glacial acetic acid (3.0 ml) and 33% solution of HBr in acetic acid was added drop wise. The reaction mixture was stirred for 24 h in

the dark. Reaction was monitored by TLC and after disappearance of starting compounds ice water was added (10 ml). The reaction mixture was extracted with DCM (3x 4 ml) and the organic layers were separated, neutralized with water and $NaHCO_3$ sat. aq. was added. The organic layer was finally washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. It was obtained 0.7 g of brown oil (**52**) (yield 69 %); R_f = 0.73 (H/EA 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60 d (1H, *J* = 3.9 Hz, C_1H), 5.54 t (1H, *J* = 9.6 Hz, C_4H), 5.14 t (1H, *J* = 9.6 Hz, C_3H), 4.84 dd (1H, J_{13} = 10.2 Hz, J_{23} = 6.0 Hz, C_2H), 4.34-4.25 m (2H, C_5H, C_6Hb), 4.13 dd (1H, J_{13} = 12.3 Hz, J_{23} = 10.5 Hz, C_6Hb), 2.08 s (3H, CH_3CO), 2.07 s (3H, CH_3CO), 2.03 s (3H, CH_3CO), 2.01 s (3H, CH_3CO).

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl isothicyanate (**53**)

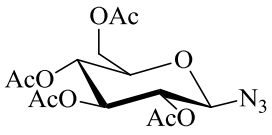


53

Method A: To the solution of compound **52** (0.7g, 1.8 mmol), potassium isothiocyanate (1.8 g, 18.5 mmol) was added and the mixture was dissolved in the minimum volume of EtOAc (ca 2.0 ml). Solvent was evaporated under reduced pressure after homogenization and mixture was degassed and carried with inert atmosphere (Ar). The flask was moved to the pre-warmed (190 °C) sand for 1 h. The reaction mixture was cooled down and dissolved in a mixture of water and DCM (5 + 5 ml). The organic phase was separated, dried over $MgSO_4$ and evaporated under reduced pressure. Suspension was purified by flash chromatography on silica gel; R_f = 0.3 (toluene/EtOAc 1:1). Reaction was given product in minimum yield of **53**.

Method B: 1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (**51**) (4.0 g, 10.3 mmol) and $SnCl_4$ (10.6 ml, 1 M solution in DCM) were dissolved in DCM (60 ml). After 5 minutes TMSSCN (1.6 ml, 11.6 mmol) was added and the reaction mixture was stirred at25 °C for 2 days. Then $NaHCO_3$ sat. aq. (60 ml) was added and the aqueous phase was extracted with DCM (40 ml). The combined organic phases were washed with water (3x 30 ml) and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel; R_f = 0.7 (DCM/EtOAc 1:1). Solvent was evaporated to obtain 2.5 g of pure crystalline solid (**53**) (yield 63 %). ^{1}H NMR spectrum corresponds to the literature.[56]

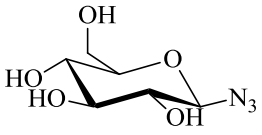
2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (**54**)



54

Compound **51** (8.0 g, 20.5 mmol) was dissolved in dry DCM (130.0 ml). To the solution $TMSN_3$ (3.7 ml, 30.5 mmol) and $SnCl_4$ (0.5 ml, 3.3 mmol) were added at 25 °C and the reaction mixture was stirred for 4 h. The solution was poured into a saturated $NaHCO_3$ solution (130 ml) and extracted with a separator funnel until evolution of CO_2 was ceased. The organic layer was separated, washed with brine (80 ml) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the resulting viscous oil was dissolved in DCM and concentrated under reduced pressure to give pure monocrystaline product; R_f = 0.7 (DCM/EtOAc 5:1). It was obtained 4.6 g of **54** (yield 61 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.20 t (1H, *J* = 9.3 Hz, C_2H), 5.09 t (1H, *J* = 8.1 Hz, C_3H), 4.94 t (1H, *J* = 9.0 Hz, C_4H), 4.64 d (1H, *J* = 9.0 Hz, C_1H), 4.29 dd (1H, J_{13} = 12.6 Hz, J_{23} = 7.8 Hz, C_6Ha), 4.18 dd (1H, J_{13} = 10.2 Hz, J_{23} = 2.4 Hz, C_6Hb), 3.80-3.75 m (1H, C_5H), 2.10 s (3H, CH_3CO), 2.07 s (3H, CH_3CO), 2.01 s (3H, CH_3CO), 1.99 s (3H, CH_3CO).

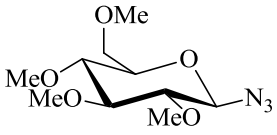
β-D-glucopyranosyl azide (**55**)



55

Compound **54** (4.0 g, 10.7 mmol) was dissolved in dry methanol (80 ml) and solution of 1 M MeONa (0.2 eq), which was prepared by dissolving sodium in methanol. After disappearance of starting material (TLC analysis, EtOAc), the reaction was quenched with DOWEX® 50W resin (H^+ form), filtered and concentrated under reduced pressure, affording 2.2 g (yield 99 %) of compound **55** as a yellow glass. Compound was used for another reaction without further characterization.

2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl azide (**56**)

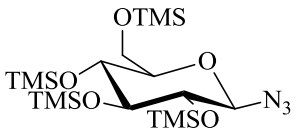


56

NaH (60% dispersion in mineral oil, 1.8 g, 55.0 mmol) was added under stirring to a cooled (0 °C) solution of β-D-glucopyranosyl azide (**55**) (2.2 g, 10.5 mmol) in dry DMF (66 ml). After stirring for 1 h at 25 °C, the solution was cooled down to 0 °C before dropwise addition in 2 portions of MeI (4.4 ml, 77.4 mmol) at this temperature. The reaction mixture was stirred overnight at 25 °C before second portion was added and then was stirring continued for 3 h. Methanol (4 ml) was added. The residue obtained after solvent removal under reduced pressure was taken up in DCM (130 ml). After washing with water and brine, the organic

phase was concentrated and the residue applied to a column chromatography on silica gel; R_f = 0.6 (hex/EtOAc 1:1). It was obtained 2.1 g (yield 76 %) of brown oil **56**. ^{1}H NMR (300 MHz, C_6D_6): δ 4.13 d (1H, *J* = 8.4 Hz, C_1H), 3.48 s (3H, CH_3), 3.43-3.41 m (2H, C_6Ha, C_6Hb), 3.94 s (3H, CH_3), 3.38 s (3H, CH_3), 3.22 t (1H, *J* = 9.6 Hz, C_4H), 3.14 s (3H, CH_3), 3.10-3.03 m (2H, C_3H, C_5H), 2.91 t (1H, *J* = 8.4 Hz, C_2H).

2,3,4,6-Tetra-*O*-trimethylsilyl-β-D-glucopyranosyl azide (**57**)



57

Method A: Compound **55** (0.12 g, 0.6 mmol) was dissolved in dry DMF (2.5 ml) under an inert atmosphere (Ar) and cooled to -20 °C. *Sym*-collidine (9.2 ml, 6.7 mmol) and TMSOTf (0.2 ml, 0.8 mmol) were slowly dropped into the solution. After 24 h the reaction was quenched by pouring it into a $NaHCO_3$ sat. aq. (10.0 ml) and extracted with EtOAc (10.0 ml). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated under a reduced pressure. The crude product was purified by flash chromatography on silica gel; R_f = 0.6 (hex/EtOAc 10:1). It was obtained 33 mg (yield 11 %) of pure compound **57**. ^{1}H NMR spectrum corresponds to the literature.[52]

Method B: Compound **55** (60 mg, 0.3 mmol) was dissolved in dry DMF (2 ml). TMSCl (0.15 ml, 1.2 mmol) and triethylamine (0.4 ml, 3 mmol) were slowly dropped into the solution. After 1 h the reaction was quenched by pouring it into a $NaHCO_3$ sat. aq. (5.0 ml) and extracted with EtOAc (5.0 ml). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated under a reduced pressure. The crude product was purified by flash chromatography on silica gel; R_f = 0.6 (hex/EtOAc 10:1). It was obtained 25 mg (yield 17 %) of pure compound **57**. ^{1}H NMR spectrum corresponds to the literature.[60]

Method C: Compound **55** (64.5 mg, 0.3 mmol) was dissolved in pyridine (8 ml). HMDS (0.2 ml, 0.8 mmol) and TMSCl (0.1 ml, 0.6 mmol) were added into the solution. The solution was shaken for 30 s and stored at 25 °C for 10 min. The solvent was removed under reduced pressure. The crude product was dissolved in EtOAc and concentrated under reduced pressure again. It was obtained 149.9 mg (yield 95 %) of pure crystalline solid **57**. $\alpha]_D$: -17.7 (*c* 0.5, $CHCl_3$); IR (KBr) ν = 2953, 2905, 2875, 2489, 2241, 2110, 1455, 1437, 1413, 1383, 1353, 1287, 1251, 1180, 1159, 1090, 1039, 994, 875, 845, 755, 686 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.44 d (1H, *J* = 8.1 Hz, C_1H), 3.85 dd (1H, J_{13} = 11.7 Hz, J_{23} = 9.6 Hz, C_6Ha), 3.73 dd (1H, J_{13} = 11.4 Hz, J_{23} = 6.9 Hz, C_6Hb) 3.49-3.37 m (2H, C_3H, C_4H), 3.30-3.25 m (1H, C_5H), 3.20 t (1H, *J* = 8.1 Hz, C_2H), 0.14 s (36H, -Si(CH_3)$_3$); ^{13}C NMR (600 MHz, $CDCl_3$): δ

90.7, 78.9, 78.4, 75.5, 70.9, 61.9, 1.3 (3C), 1.1 (3C), 0.8 (3C), -0.2 (3C); m/z: ($C_{18}H_{43}N_3O_5Si_4$, M = 493.2), 516.3 $(M + Na)^+$.

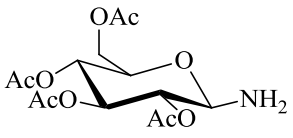
General procedure (**G**) of reduction using H_2 and Pd/C

Azide (1 eq.) was dissolved in EtOAc (15 ml per 1 mmol) and Et_3N (0.1 eq.) was added. The reaction mixture was degassed and the Pd/C (0.0035 eq.) dissolved in EtOAc (40 µl per 10 mg) was added *via* syringe. The reaction mixture was degassed again and the H_2 (g) was set into the reaction. The reaction mixture was stirred at 25 °C for 24 h and filtered through Na_2SO_4 pad (ca 1 cm) after disappearance of starting material (TLC analysis). Solvent was evaporated under reduced pressure and product was applied to column chromatography (hex/EtOAc 1:2 + 1 % Et_3N).

General procedure (**H**) of reduction using H_2 generated *in situ* from $NaBH_4$

Azide (1 eq.) was dissolved in water (10 ml per 0.3 mmol) and THF (20 per 0.3 mmol) and $CoCl_2 \cdot 6\ H_2O$ (0.8 eq.) was added. To this stirred mixture $NaBH_4$ (7.4 eq.) was added at 0 °C and mixture was continued to stirring for another 5 hours. After reaching maximum conversion (TLC analysis), the reaction mixture was transferred into the DCM and shaken with water. Organic layer was dried over $MgSO_4$ and solvent was evaporated under the reduced pressure and product was applied to column chromatography (hex/EtOAc 1:2 + 1 % Et_3N).

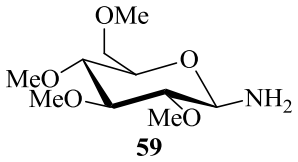
2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl amine (**58**)



58

By following method **G** was obtained 1.6 g of yellow crystalline solid **58** (yield 70 %). ^{1}H NMR (300 MHz, DMSO): δ 5.76 d (1H, *J* = 0.6 Hz, C_1H), 5.23 t (1H, *J* = 9.6 Hz, C_2H), 4.86 t (1H, *J* = 9.6 Hz, C_3H), 4.66 t (1H, *J* = 9.3 Hz, C_4H), 4.31 d (2H, *J* = 8.4 Hz, NH_2), 4.13 dd (1H, J_{13} = 12.0 Hz, J_{23} = 6.9 Hz, C_6Ha), 3.99 dd (1H, J_{13} = 12.0 Hz, J_{23} = 9.9 Hz, C_6Hb), 3.91 m (1H, C_5H), 2.00 s (3H, CH_3CO), 1.99 s (3H, CH_3CO), 1.97 s (3H, CH_3CO), 1.93 s (3H, CH_3CO).

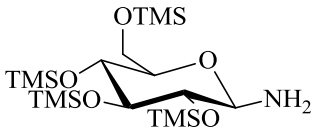
2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl amine (**59**)



59

By following method **G** was obtained 0.7 g of pure crystalline solid **59** (yield 30 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.98 d (1H, *J* = 8.4 Hz, C_1H), 3.64 s (3H, CH_3), 3.62 s (3H, CH_3), 3.60-3.55 m (2H, C_6Ha, C_6Hb) 3.53 s (3H, CH_3), 3.40 s (3H, CH_3), 3.33-3.27 m (1H, C_5H) 3.23-3.09 m (2H, C_3H, C_4H), 2.77 t (1H, *J* = 9.0 Hz, C_2H), 1.82 br s (2H, NH_2).

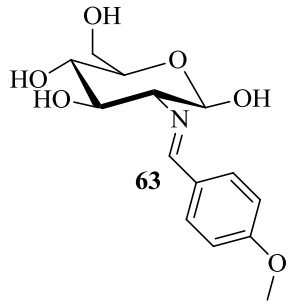
2,3,4,6-Tetra-*O*-trimethylsilyl-β-D-glucopyranosyl amine (**60**)



60

By following method **G** was obtained 81 mg of yellow oil **60** (yield 17 %). α]$_D$: 28.2 (*c* 0.4, $CHCl_3$); IR (KBr) ν = 3374, 2959, 2929, 2896, 2854, 1676, 1550, 1456, 1401, 1377, 1251, 1162, 1075, 872, 848, 752 cm^{-1} ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.86 d (1H, *J* = 4.5 Hz, C_1H), 3.91 dd (1H, J_{13} = 12.3 Hz, J_{23} = 9.2 Hz, C_6Ha), 3.78 dd (1H, J_{13} = 11.6 Hz, J_{23} = 6.7 Hz, C_6Hb) 3.51-3.37 m (2H, C_3H, C_4H), 3.33-3.26 m (1H, C_5H), 3.22 t (1H, *J* = 8.1 Hz, C_2H), 1.86 br s (2H, NH_2) 0.15 s (36H, -Si(CH_3)$_3$). ^{13}C NMR (600 MHz, $CDCl_3$): δ 93.2, 88.4, 86.4, 78.9, 71.9, 52.4, 1.3 (3C), 1.1 (3C), 0.8 (3C), 0.2 (3C); m/z: ($C_{18}H_{45}NO_5Si_4$, M = 467.2), 490.4 (M + Na)$^+$.

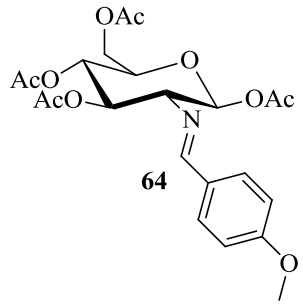
2-deoxy-2-[[(4-methoxyphenyl)methylene]amino]-β-D-glucopyranose (**63**)



63

Glucosamine hydrochloride **61** (15.0 g, 70.0 mmol) was dissolved in 1 M NaOH (aq. 84 ml) and Anisaldehyde (**62**) (15.0 ml, 714.6 mmol) was added to this vigorously stirred mixture. After solidifying, the mixture was placed to the refrigerator for 2 h and then mixed with ice-water (90 ml). Obtained solid was filtered and washed with Et_2O. After 2-days long dry over KOH and vacuum affording 17.4 g of **63** (yield 82 %). Compound was used for another reaction without further characterization.

1,3,4,6-Tetraacetate-2-deoxy-2-[[(4methoxyphenyl)methylene]amino]-β-D-glucopyranose (**64**)

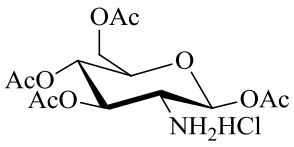


64

To the stirred mixture of **63** (17.4 g, 57.0 mmol) in DCM (73 ml) and pyridine (45 ml), acetic anhydride (33.0 ml, 369.0 mmol) and DMAP (0.4 g, 1.2 mmol) was added at 0 °C. The reaction mixture was stirred at 25 °C overnight. After disappearance of starting

material (TLC analysis; DCM/MeOH 7:1), The mixture was cooled down, ethanol (20 ml) was added and the mixture was stirred for another 3 h. The mixture was concentrated, co-distilled with toluene (5 x 50 ml) and concentrated. Obtained solid was mixed with Et_2O (30 ml) and placed to the refrigerator overnight. Product was filtered and recrystallized from ethanol affording 14.2 g of pure crystalline solid **64** (yield 54 %). Compound was used for another reaction without further characterization.

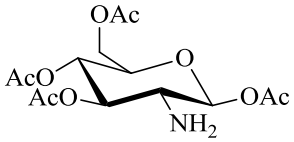
1,3,4,6-Tetra-*O*-acetatyl-β-D-glucosamine hydrochloride (**65**)



65

Compound **64** (5.0 g, 10.7 mmol) was dissolved in acetone (50 ml) and 5 M HCl was added dropwise. Solid product was placed to the refrigerator for 2 h and then mixed with acetone and filtered. Solid product was mixed with Et_2O, filtered and dried over KOH in vacuo. It was obtained 4.2 g of **65** (yield 95 %). Compound was used for another reaction without further characterization.

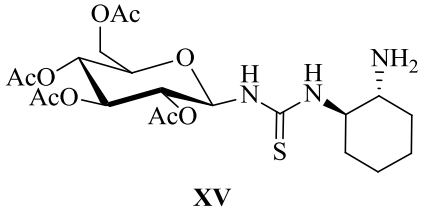
1,3,4,6-Tetra-*O*-acetatyl-β-D-glucosamine (**66**)



66

Glucosamine hydrochloride **65** (1.1 g, 2.9 mmol) was dissolved in water (6.3 ml) and DCM (7.5 ml) and NaOAc (0.8 g, 9.2 mmol, sat. aq.) was added. Mixture was stirred at 25 °C for 0.5 h and water phase was extracted with DCM (3 x 15 ml) and collected organic layers were dried over $MgSO_4$ and concentrated. After mixing with Et_2O, pure compound **66** was obtained (0.5 g, yield 53 %). ^{1}H NMR (300 MHz, DMSO): δ 5.55 d (1H, *J* = 8.4 Hz, C_1H), 5.08 t (1H, *J* = 9.6 Hz, C_3H), 4.83 t (1H, *J* = 9.9 Hz, C_4H), 4.19 dd (1H, J_{13} = 8.4 Hz, J_{23} = 7.8 Hz, C_6Ha), 3.96-3.92 m (2H, C_6Hb, C_5H), 2.77-2.71 m (1H, C_2H), 2.11 s (3H, CH_3CO), 1.99 s (3H, CH_3CO), 1.97 s (3H, CH_3CO), 1.96 s (3H, CH_3CO), 1.68 br s (2H, NH_2).

N-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-((1'*R*,2'*R*)-diaminocyclohex-2-yl) thiourea (**XV**)

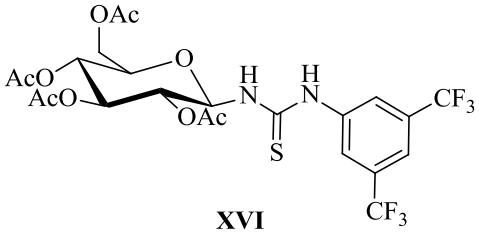


XV

Preparation of compound **XV** corresponds to literature.[53] It was obtained 89.5 mg (yield 71 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83-5.75 m (1H, C_1H), 5.16-4.99 m (3H, C_2H, C_3H, C_4H), 4.34 dd (1H, J_{13} = 12.3 Hz, J_{23} = 7.5 Hz,

C_6Ha), 4.16-4.09 m (1H, C_6Hb), 3.87-3.83 m (1H, C_5H), 3.69-3.52 m (1H, cyclohexyl-*H*), 2.58-2.31 m (3H, N*H*C(S)N*H*, cyclohexyl-*H*), 2.18-1.94 m (14H, 4x CH_3CO, 2x cyclohexyl-*H*), 1.74 br s (2H, NH_2), 1.24-1.11 m (6H, cyclohexyl-*H*).

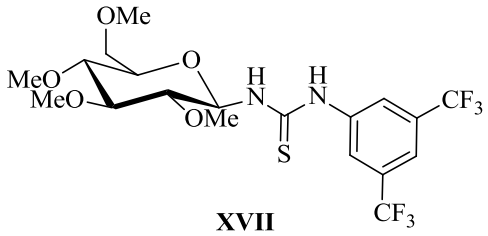
N-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-(3,5-bis-trifluoromethyl)phenyl thiourea (**XVI**)



XVI

To the mixture of **53** (0.8 g, 2.1 mmol) in DCM (15.0 ml) 3,5-bis-trifluoromethylphenyl aniline (**68**) (0.3 ml, 2.1 mmol) was added. The mixture was stirred at 25 °C for 2 h. The crude product was purified by flash chromatography on silica gel; R_f = 0.7 (hex/EtOAc 1:2). It was obtained 0.6 g of **XVI** (yield 50 %). $\alpha]_D$: 25.7 (*c* 0.5, $CHCl_3$); IR (KBr) ν = 3321, 3037, 2956, 2938, 1751, 1529, 1470, 1377, 1281, 1230, 1135, 1036, 955, 905 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 s (1H, ArN*H*), 7.88 s (2H, Ar), 7.73 s (1H, Ar), 7.22 d (1H, *J* = 4.2 Hz, C_1NH), 6.30 d (1H, *J* = 4.2 Hz, C_1H), 5.23 t (1H, *J* = 9.3 Hz, C_3H), 5.11 t (1H, *J* = 9.3 Hz, C_4H), 4.99 br s (1H, C_1NH), 4.32 dd (1H, J_{13} = 12.6 Hz, J_{23} = 7.8 Hz, C_6Ha), 4.19-4.09 m (1H, C_6Hb) 3.84-3.79 m (1H, C_5H), 2.17 s (1H, CH_3CO), 2.11 s (1H, CH_3CO), 2.10 s (1H, CH_3CO), 2.05 s (1H, CH_3CO); ^{13}C (600 MHz, $CDCl_3$): δ 182.5, 170.8, 170.7, 169.7, 169.6, 144.1, 139.7, 132.0, 131.8, 123.8, 123.7 (2C), 118.8, 90.0, 82.2, 72.9, 70.5, 69.3, 61.4, 20.7, 20.6, 20.5, 20.4; ^{19}F NMR (300 MHz, $CDCl_3$): δ -63.0; m/z: ($C_{23}H_{24}F_6N_2O_9S$, M = 618.5), 641.1 $(M + Na)^+$.

N-(2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl)-*N'*-(3,5-bis-trifluoromethylphenyl thiourea (**XVII**)

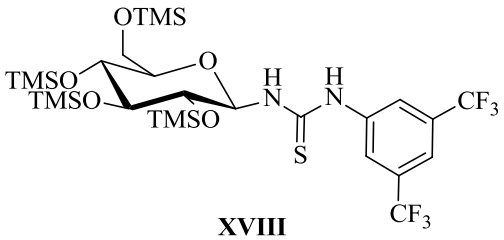


XVII

To the dissolved compound **59** (50.0 mg, 0.2 mmol) in DCM (1.0 ml) 3,5-bis-triflouromethylphenyl isothiocyanate (**69**) (0.04 ml, 0.2 mmol) was added and the mixture was stirred at 25 °C overnight. After solvent removal under reduced pressure the residue was applied to a column chromatography; R_f = 0.65 (hex/EtOAc 1:2). It was obtained 48.6 mg of **XVII** (yield 50 %). $\alpha]_D$: -8.6 (*c* 0.4, $CHCl_3$); IR (KBr) ν = 3434, 3252 3066 2989, 2941, 2902, 2836, 1628, 1556, 1497, 1470, 1389, 1287, 1251, 1186, 1123, 1087, 958, 896 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.43 s (1H, ArN*H*), 8.51 s (2H, Ar), 7.66 s (1H, Ar), 6.72 s (1H, C_1NH), 3.93 m (1H, C_5H), 3.72 dd (1H, J_{13} = 9.8 Hz, J_{23} = 2.0 Hz, C_6Ha), 3.63 s (3H, CH_3),

3.53 s (3H, CH_3), 3.52 s (3H, CH_3), 3.51 dd (1H, J_{13} = 9.8 Hz, J_{23} = 8.8 Hz, C_6Hb), 3.42 s (3H, CH_3) 3.37 m (1H, C_3H), 3.36 m (1H, C_2H), 2.94 dd (1H, J_{13} = 10.0 Hz, J_{23} = 8.4 Hz, C_4H); ^{13}C NMR (600 MHz, $CDCl_3$): δ 184.1, 140.5, 131.7 (2C), 124.0, 123.1, 118.7, 83.4, 79.8, 79.7, 79.3, 71.8, 70.7, 61.3, 60.7, 59.0 (2C); ^{19}F NMR (300 MHz, $CDCl_3$): δ -62.9 ; m/z: ($C_{18}H_{21}F_6N_2O_4S$, M = 506.13), 529.1 $(M + Na)^+$.

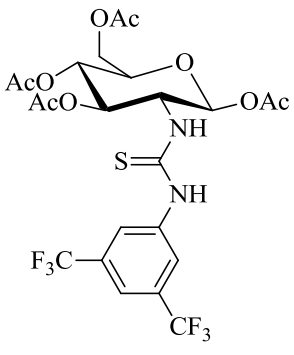
N-(2,3,4,6-Tetra-*O*-trimethylsilyl-β-D-glucopyranosyl)-*N*'-(3,5-bis-trifluoromethylphenyl thiourea (**XXIII**)



XVIII

To the dissolved compound **67** (50.0 mg, 0.2 mmol) in DCM (1.0 ml) 3,5-bis-triflouromethylphenyl isothiocyanate (**69**) (0.04 ml, 0.2 mmol) was added and the mixture was stirred at 25 °C overnight. After solvent removal under reduced pressure the residue was applied to a column chromatography (hex/EtOAc 8:1). It was obtained XX mg of compound **XVIII** (yield XX %). $\alpha]_D$: 69.0 (*c* 0.3, $CHCl_3$); IR (KBr) ν = 3282, 3052, 2959, 2923, 2893, 1724, 1709, 1688, 1544, 1529, 1476, 1377, 1278, 1248, 1177, 1135, 1108, 1084, 884, 851, 680 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 9.38 s (1H, ArN*H*), 8.18 s (2H, Ar), 7.56 s (1H, Ar), 6.76 s (1H, C_1N*H*), 5.31 d (1H, *J* = 2.4 Hz, C_1H), 4.00 dd (1H, J_{13} = 10.8 Hz, J_{23} = 8.7 Hz, C_6Ha), 3.86 dd (1H, J_{13} = 11.4 Hz, J_{23} = 8.2 Hz, C_6Hb), 3.74-3.59 m (3H, C_3H, C_4H, C_5H), 3.40 t (1H, J = 8.1 Hz, C_2H), 0.15 (36H, -Si(CH_3)$_3$); ^{13}C (600 MHz, $CDCl_3$): δ 184.1, 140.4, 133.5, 133.3, 131.9, 131.7, 124.0 (2C), 118.8, 82.1, 75.1, 73.1, 73.8, 71.7, 71.6, 62.4, 1.3, 1.0, 0.8, 0.7; ^{19}F (300 MHz, $CDCl_3$): δ -62.9; m/z: ($C_{27}H_{48}F_6N_2O_9SSi_4$, M = 738.2), 761.4 $(M + Na)^+$.

N-(1,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranos-2-yl)-*N*'-(3,5-bis-trifluoromethyl)phenyl thiourea (**XIX**)

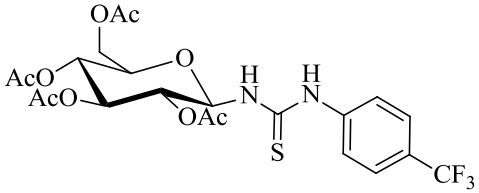


XIX

To the compound **66** (0.5 g, 1.4 mmol) dissolved in DCM (6 ml), 3,5-bis-trifluoromethylphenyl isothiocyanate (**69**) (0.3 ml, 1.4 mmol) was added and mixture was stirred overnight. After solvent removal under reduced pressure, the residue was applied to a column chromatography on silica gel; R_f = 0.5 (hex/EtOAc 1:1). After concentration, residue was mixed with DCM and solvent was evaporated to obtain 0.2 g of pure **XIX** (yield 40 %). $\alpha]_D$: 7.8 (*c* 0.4,

$CHCl_3$); IR (KBr) ν = 3321, 3058, 2956, 2929, 2869, 1751, 1538, 1467, 1377, 1278, 1227, 1183, 1135, 1081, 1039, 952, 893 677 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 s (1H, ArN*H*), 7.90 s (2H, Ar), 7.72 s (1H, Ar), 6.16 d (1H, *J* = 9.6 Hz, C_1N*H*), 5.75 d (1H, *J* = 8.1 Hz, C_1*H*), 5.23 t (1H, *J* = 9.3 Hz, C_3*H*), 5.11 t (1H, *J* = 9.3 Hz, C_4*H*), 4.99 br s (1H, C_1N*H*), 4.32 dd (1H, J_{13} = 12.6 Hz, J_{23} = 7.8 Hz, C_6*H*a), 4.19-4.09 m (1H, C_6*H*b, C_5*H*) 3.84-3.79 m (1H, C_5*H*), 2.17 s (1H, C*H*$_3$CO), 2.11 s (1H, C*H*$_3$CO), 2.10 s (1H, C*H*$_3$CO), 2.05 s (1H, C*H*$_3$CO); ^{13}C NMR (600 MHz, $CDCl_3$): δ 182.0, 171.7, 170.7, 170.4, 169.2, 138.9, 133.4, 133.0, 132.8, 132.6, 124.3 (2C), 122.6, 119.7, 92.9, 73.1, 72.8, 67.3, 61.7, 57.8, 21.0, 20.8, 20.7, 20.5; ^{19}F NMR (300 MHz, $CDCl_3$): δ -63.0 m/z: ($C_{23}H_{24}F_6N_2O_9S$, M = 618.5), 641.1 (M + Na)$^+$.

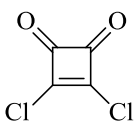
N-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N'*-(4-trifluoromethyl)phenyl thiourea (**XX**)



XX

To the mixture of **58** (0.5 g, 1.4 mmol) in DCM (3.0 ml) solution of 4-trifluoromethylphenyl isothiocyanate (**70**) (0.3 g, 1.4 mmol) was added. The mixture was stirred at 25 °C for 4 h. The crude product was purified by flash chromatography on silica gel; R_f = 0.5 (hex/EtOAc 1:1). It was obtained 0.3 g of **XX** (yield 35 %). α]$_D$: -2.3 (*c* 0.4, $CHCl_3$); IR (KBr) ν = 3318, 3046, 2941, 1751, 1616, 1532, 1434, 1371, 1329, 1233, 1171, 1120, 1069, 1042, 845, 603 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 br s (1H, ArN*H*), 7.70 d (2H, *J* = 8.4 Hz, Ar), 7.41 d (2H, *J* = 7.8 Hz, Ar), 6.81 d (1H, *J* = 4.4 Hz, C_1N*H*), 5.79 t (1H, *J* = 9.3 Hz, C_1*H*), 5.37 t (1H, *J* = 9.6 Hz, C_2*H*), 5.05 t (1H, *J* = 10.2 Hz, C_3*H*), 4.95 t (1H, *J* = 9.3 Hz, C_4*H*), 4.37 dd (1H, J_{13} = 12.6 Hz, J_{23} = 7.8 Hz, C_6*H*a), 4.16 dd (1H, J_{13} = 18.3 Hz, J_{23} = 11.4 Hz, C_6*H*b) 3.90-3.84 m (1H, C_5*H*), 2.10 s (1H, C*H*$_3$CO), 2.07 s (1H, C*H*$_3$CO), 2.04 s (1H, C*H*$_3$CO). ^{13}C NMR (300 MHz, $CDCl_3$): δ 182.1, 171.3, 170.7, 169.8, 169.6, 127.2, 127.1, 124.66, 83.2, 73.8, 72.6, 70.7, 68.2, 61.6, 20.8, 20.7, 20.6, 20.6; ^{19}F NMR (300 MHz, $CDCl_3$): δ -62.6; m/z: ($C_{22}H_{25}F_3N_2O_9S$, M = 550.1), 573.2 (M + Na)$^+$.

3,4-Dichloro-3-cyclobutene-1,2-dione (**76**)



76

Squaric acid (**74**) (5.0 g, 43.9 mmol) was dissolved in CCl_4 (22.0 ml) and DMF (0.18 ml) at 25 °C. Reaction mixture was cooled down with N_2 (l) and oxalyl chloride (**75**) (7.5 ml, 87.8 mmol) was added. Mixture was stirred and warmed to

25 °C and subsequently was stirred for 2 hours at 50 °C. After observing colour change (to brightly yellow), mixture was concentrated under the reduced pressure to halves and transferred under the inert atmosphere (Ar). This concentrated mixture was distilled under the reduced pressure. Obtained product was transferred under the inert atmosphere (Ar) and stored into the freezer. It was obtained 5.3 g of yellow crystalline solid **76** (yield 80.2 %). ^{13}C NMR (600 MHz, $CDCl_3$): δ 189.4 (2C), 188.1 (2C); m/z: ($C_4Cl_2O_2$, M = 149.9), 131.3 (M – H^+)$^-$. MS spectrum corresponds to the product of partial hydrolysis of compound **76**, where one of the chlorine is substituted by hydroxyl group.

5. CONCLUSION

We successfully accomplished preparation of acyl- (acetyl), alkyl (methyl) and silyl-protected (trimethylsilyl) derivatives of D-glucose. Trimethylsilyl derivatives (**57** and **60**) of D-glucose were prepared as new compounds. Those derivatives were used for the preparation of new thiourea catalysts **XVI**, **XVII**, **XVIII**, **XIX** and **XX**. Catalyst **XIX** with different thiourea linkage was prepared from D-glucosamine.

Preparation of new squaramide catalyst **XXI** was not successful yet, but it remains a part of our continuing research.

Examination of the effects of catalysts **XVI** – **XX** in particular reactions was beyond the scope of this thesis.

6. LITERATURE

[1] *Sacharidy*, 1st ed., Černý, M.; Trnka, T.; Buděšínský, M.; Česká společnost chemická, 2010.

[2] *Biochemie*. 1st ed., Voet, D.; Voetová, J., Victoria Publishing, Praha, 1995, 657–658, 659–660.

[3] *Organická chemie*, 6th ed., McMurry, J.; Brooks/Cole, a Thompson Learning Company.

[4] *A Textbook of Botany for Colleges and Universities*, Int. Ed.; Coulter, J. M.; Barnes, Ch. R.; Cowles, H. Ch., American Book Company, 1910, 360.

[5] *Harperova Biochemie*, 4th ed., Murray, R. K.; Granner, D. K.; Mayes, P. A.; Rodwell, V. W., H & H Publishing, 2002.

[6] Freudenburg K., Emil Fischer and his Contribution to Carbohydrate Chemistry, *Adv. Carbohydr. Chem*. **1966**, 21, 1-38.

[7] Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122.

[8] List, B., *Chemical Reviews* **2007**, Vol. 107, No. 12.

[9] Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.

[10] Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *5*, 719-724.

[11] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

[12] Notz, W.; Tanaka, F.; Watanabe, S.; Chowardi, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas III., C. F. *J. Org. Chem.* **2003**, 9624-9634.

[13] Hu, K.; Liu, T.; Lu, A. D.; Liu, Y.; Wang, Y.; Wu, G.; Zhou, Z.; Tang, *Ch. Eur. J. Org. Chem.* **2011**, 3507-3513.

[14] Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y.; *Org. Lett.* **2004**, *6*, 625-627.

[15] Dondoni, A; Massi, A. Angew. *Chem. Int. Ed.* **2008**, *47*, 4638-4660.

[16] Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072-7080.

[17] Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381-3384.

[18] Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrhimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415-8426.

[19] Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325-335.

[20] Hydrogen Bonding in Organic Synthesis, 1st. ed., Pihko, P. M., Ed., Wiley-VCH, Weinheim, 2009, 145.

[21] Takemoto, Y. *Org. Biomol. Chem.* **2005**, *34*, 299-306.

[22] Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259-3261.

[23] Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647-6650.

[24] Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407-414.

[25] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902.

[26] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466-468.

[27] Takemoto, Y. *Org. Biomol. Chem.* **2005**, *34*, 299-306.

[28] Connon, S. J. *Chem. Commun.* **2008**, *2*, 499-510.

[29] Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072-7080.

[30] Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589-5592.

[31] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673.

[32] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119-125.

[33] Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jap.* **2008**, *81*, 785-795.

[34] Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743.

[35] Connon, S. J. *Chem. – Eur. J.* **2006**, *12*, 5418-5427.

[36] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416-14417.

[37] Tomas, S.; Prohens, R.; Vega, M.; Rotger, M. C.; Deya, P. M.; Ballester, P.; Costa, A. *J. Org. Chem.* **1996**, *61*, 9394.

[38] Pu, X.-W.; Peng, F.-Z.; Zhang, H.-B.; Shao, Z.-H. *Tetrahedron* **2010**, *66*, 3655-3661.

[39] Shen, Ch.; Shen, F.; Xia, H.; Zhang, P.; Chen, X. Tetrahedron: *Asymmetry* **2011**, *22*, 708-712.

[40] Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648-8659.

[41] Kunz, H.; Sager, W. *Angew. Chem.* **1987**, *99*, 595-597.

[42] Kunz, H.; Sager, W.; Pfrengle, W.; Schanzenbach, D. *Tetrahedron* **1988**, *29*, 4397-4400.

[43] Hafner, A.; Duthaler, R. O. *Chem. Rev.* **1992**, *92*, 807-832.

[44] Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321-2336.

[45] Diéguez, M.; Pámies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coor. Chem. Rev.* **2004**, *248*, 2165-2192.

[46] Irmak, M.; Groschner, A.; Boysen, M. M. K. *Chem. Commun.* **2007**, 177-179.

[47] Shi, Y. *Acc. Chem. Res.*, **2004**, *37*, 488-496.

[48] Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807.

[49] Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923-925.

[50] Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965.

[51] Becker, Ch.; Hoben, Ch.; Kunz, H. *Adv. Synth. Catal.* **2007**, *349*, 417-424.

[52] Puglisi, A.; Benaglia, M.; Raimondi, L.; Lay, L.; Poletti, L. *Org. Biomol. Chem.* **2011**, *9*, 3295-3302.

[53] Řehůřková, T. *Diploma thesis*, UK, Prague 2011.

[54] Tsuji, Masashiro, Yamazaki, Hiroyuki U.S. Patent 6350865, 2002.

[55] Lindhorst, T. K.; Kieburg, Ch. *Synthesis* **1995**, *10*, 1228-1230.

[56] Kühne, M.; Györgydeák, Z.; Lindhorst, T. K. *Synthesis* **2006**, *6*, 949-951.

[57] Bergmann, M.; Zervas, L. *Chem. Ber.* **1931**, *64*, 975.

[58] André, S.; Velasco-Torrijos, T.; Leyden, R.; Gouin, S.; Tosin, M.; Murphy, P. V., Gabius, H.-J. *Org. Biomol. Chem.* **2009**, *7*, 4715-4725.

[59] Praly, J.-P.; Senni, D.; Faure, R.; Descotes G. *Tetrahedron* **1995**, *51*, 1697-1708.

[60] Wartchow, Ch. A.; Wang, P.; Bednarski, M. D.; Callstrom, M. R. J. Org. Chem. 1995, 60, 2216-2226.

[61] Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* **2004**, *34*, 1317-1323.

[62] Shiozaki, M.; Mochizuki, T.; Hanazawa, H.; Haruyama H. *Carbohydr. Res.* **1996** *288*, 99-108.

[63] Amin, M. N.; Ishiawata, A.; Ito, Y. *Tetrahedron* **2007**, *63*, 8181-8198.

[64] Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450-5453.

[65] Cui, D.; Prashar, D.; Sejwal, P.; Luk, Y.-Y. *Chem. Commun.* **2011**, *4*, 1348-1350.