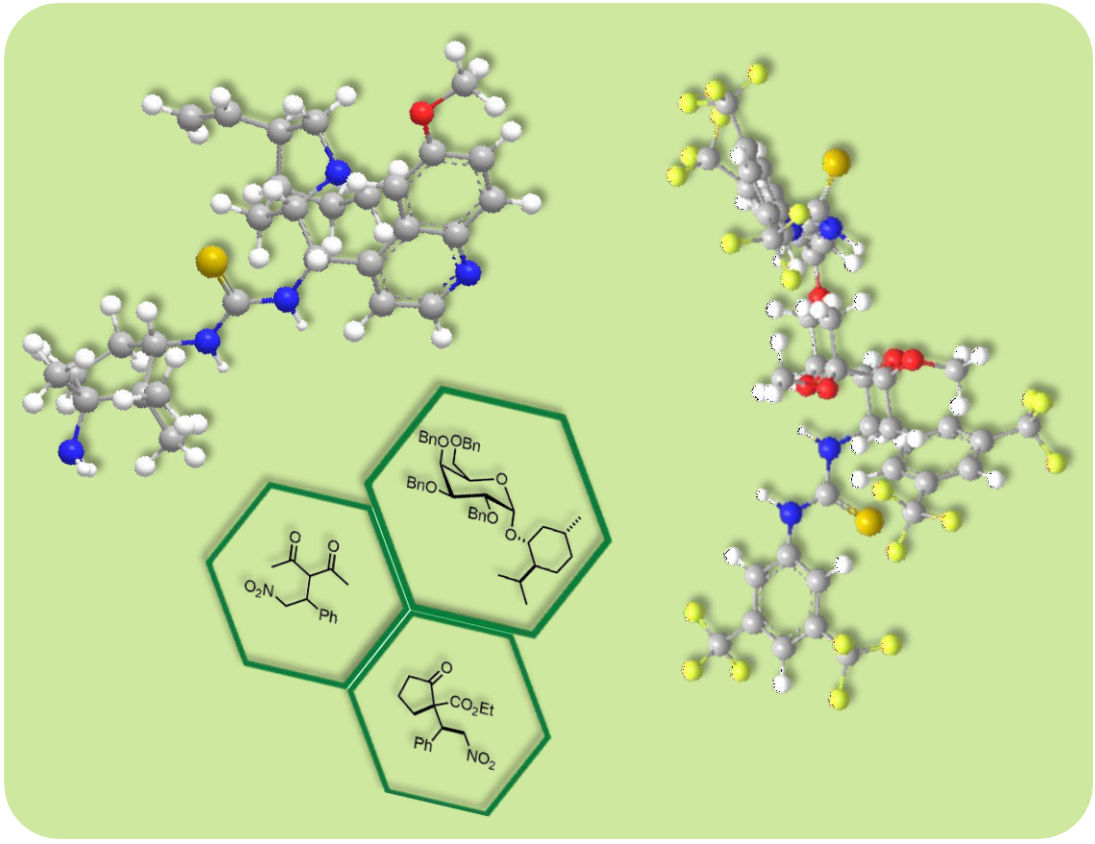
2023

Development of new thiourea organocatalysts for asymmetric reactions

Márcia Rénio



Thesis presented to obtain the **Ph.D degree in**

Sustainable Chemistry

Oeiras, 18th July, 2023

INSTITUTO DE TECNOLOGIA QUÍMICA E BIOLÓGICA ANTÓNIO XAVIER | UNIVERSIDADE NOVA DE LISBOA

ITQB NOVA, Avenida da República, 2780-157 Oeiras, Portugal | Tel +351 214 469 100 | itqb.unl.pt

Development of new thiourea organocatalysts for asymmetric reactions

Márcia Alexandra dos Reis Ribeiro Rénio

Dissertation presented to obtain the degree of Doctor in Sustainable Chemistry

Instituto de Tecnologia Química e Biológica António Xavier | Universidade Nova de Lisboa

Oeiras, 18th of July 2023

Development of new thiourea organocatalysts for asymmetric reactions

Márcia Alexandra dos Reis Ribeiro Rénio

Thesis supervisor:
Dr. M. Rita Ventura

Head of the Bioorganic Chemistry Laboratory at Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa

Thesis co-supervisor:
Professor Dina Murtinho

Assistant Professor of Chemistry at University of Coimbra

The research work described in this thesis was performed at the Bioorganic Chemistry Group, ITQB NOVA, Oeiras, Portugal and the Organic Chemistry Group, FCTUC, Coimbra, Portugal. This work was supported by Fundação para a Ciência e Tecnologia through a PhD grant to Márcia Rénio (PD/BD/135494/2018).

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

itqb nova

1 2 9 0 UNIVERSIDADE D COIMBRA

Acknowledgments

A escrita destas páginas encerra um processo que começou há quatro anos, foi um processo tortuoso, com altos e baixos, no entanto teria sido muito menos prazeroso sem a presença destas pessoas na minha vida.

À minha orientadora, Doutora Rita Ventura, agradeço por toda a orientação, apoio e confiança durante estes anos, e também por me providenciar todas as ferramentas necessárias à execução deste trabalho.

À minha coorientadora, Professora Dina Murtinho, agradeço pela amizade ao longo destes anos, pelo apoio e orientação científica mesmo que por email ou telefone.

Ao professor Christopher Maycock, gostaria de agradecer por toda a disponibilidade, por toda a ajuda, por todas as discussões científicas e até mesmo políticas e económicas. E também por manter todos os equipamentos do laboratório a funcionar para que nunca nada prejudicasse o nosso trabalho.

Agradeço ao CERMAX pelos serviços de NMR (projecto AAC 01/SAICT/2016) e à unidade de serviços analíticos, pelos serviços prestados.

Gostaria de agradecer ao programa doutoral CATSUS e à Fundação para a Ciência e Tecnologia agradeço o apoio financeiro, através da atribuição da minha bolsa de doutoramento ((PD/BD/135494/2018) e (COVID/BD/152506/2022).

Não podia deixar de agradecer aos meus colegas do grupo de Química Bioorgânica, Bia, Daniela, Diogo, Eva, Miguel, Osvaldo, entre outros, por todos os momentos de descontração, por todas as conversas sobre tudo e sobre nada e por toda a entreajuda. Um especial obrigado também ao Gonza por toda a ajuda, disponibilidade, simpatia, paciência e amizade que sempre me mostrou.

Alguns destes colegas tornaram-se grandes amigos, um obrigada especial ao CJ por toda a ajuda, por todas as conversas, por me ouvir em todas as minhas depressões, por todos os cafés, acima de tudo pela bonita amizade e irmandade que construímos.

Não podia deixar de agradecer aos meus amigos, alguns já desde Coimbra e por cá continuam outros que Lisboa me deu, que sempre estiveram disponíveis para me ouvir, para partilharem angústias, para conversas durante longas horas, por me distraírem dos problemas com bebedeiras e aventuras que guardarei para sempre no meu coração.

Agradeço ao Miguel por todo o apoio ao longo deste processo que nem sempre foi fácil, por acreditar sempre em mim, às vezes mais do que eu própria, por me ouvir quando as reações teimavam em não dar nada e por me encorajar a arranjar sempre um novo plano para continuar.

Um enorme obrigada aos meus pais por me terem dado todas as condições para que eu pudesse chegar até aqui e pelos valores que me passaram que fizeram de mim a pessoa que sou hoje, entre muitas coisas mostraram-me que com luta conseguimos alcançar aquilo a que nos propomos.

À minha irmã, a pessoa que me faz querer ser uma pessoa um pouquinho melhor todos os dias, um obrigado do tamanho do mundo por estares sempre lá nas minhas conquistas, mas também nos meus piores momentos, por me ouvires sempre, por me dares na cabeça quando é preciso, por me apoiares e encorajares em tudo, por me dares força quando acho que não sou capaz.

Table of contents

Abbreviations

Aq	Aqueous
BINOL	1,1′-Bi-2-naphthol
Boc	*Tert*-butyloxycarbonyl
c	Concentration
Cbz	Carboxybenzyl
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dr	diastereomeric ratio
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
eq.	equivalents
FMOC	Fluorenylmethoxycarbonyl
FMOC-OSU	N-(9-Fluorenylmethoxycarbonyloxy)succinimide
FTIR	Fourier Transform Infrared Spectroscopy
HPLC	High Performance Liquid Chromatography
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectrometry
IBO	Isobutylene Oxide
LTA	Lead Tetraacetate

LUMO	Lowest Unoccupied Molecular Orbital
mp	Melting point
MS	Molecular Sieves
NMR	Nuclear Magnetic Ressonance
PEG	Polyethylene glycol
r.t.	Room Temperature
Satd.	Saturated
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TCDI	1,1'-Thiocarbonyldiimidazole
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMOF	Trimethyl orthoformate
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
$[\alpha]_D$	specific rotation

Nomenclature used for the NMR spectra description:

^{1}H-NMR	Proton Nuclear Magnetic Ressonance
^{13}C-NMR	Carbon Nuclear Magnetic Ressonance
br	Broad
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
J	coupling constant

m	multiplet
NOESY	Nuclear Overhauser Effect Spectroscopy
ppm	parts per million
q	quartet
s	singlet
t	triplet
td	triplet of doublet
δ	Chemical Shift

Abstract

Nowadays it is almost impossible to find a synthesis of a natural product or drug candidate that does not use a catalyst. Typically, catalysts used in organic synthesis are metal compounds; however the use of other catalytic methods has been increasing, namely organocatalysis. This type of catalysis describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound that does not contain a metal atom. A growing number of publications has appeared in this area, describing not only the application of known organocatalysts for new reactions but also the development of new organocatalysts. The potential of this research area was recognised in 2021, when the Nobel prize Chemistry was awarded to Benjamin List and David MacMillan for their efforts on the development of asymmetric organocatalysis, a new precise tool for molecular construction.

The main purpose of this dissertation was the development of new organocatalysts derived from inexpensive and natural sources of chirality, and their application in different types of asymmetric reactions.

In the first part of this work, described in Chapter 2, organocatalysts derived from L-tartaric acid and (+)-camphoric acid were synthesised.

Eight new mono- and bis-thiourea and squaramide organocatalysts derived from L-tartaric acid were developed with moderate to good overall yields (3-33%). From (+)-camphoric acid six novel thiourea and squaramide organocatalysts were synthesised, in good to very good overall yields (23-57%).

These organocatalysts were applied in different types of asymmetric reactions. In Chapter 3 their application in the Michael addition reaction is described. The organocatalysts derived from (+)-camphoric acid were successfully used in the Michael addition reaction between 1,3-dicarbonyl compounds and several *trans*-β-nitrostyrenes. Yields up to 98% and enantiomeric excesses up to 74% and high

diastereoselectivities, when applicable, (*dr* up to 93:7) were obtained in these reactions.

The use of thioureas has been described to control the stereochemical outcome of the glycosylation reaction. In Chapter 4 the application of the synthesised organocatalysts derived from L-tartaric acid in the glycosylation reaction is described. The results reveal that these catalysts are able to activate glycosyl phosphates for stereoselective nucleophilic substitution reactions, providing the desired 1,2-*cis* glycosides in good yields (up to 85%) and high diastereoselectivity (up to *dr* 93:7).

Since the efficiency of the developed organocatalysts was proven in the two above mentioned reactions, we decided to test them in the alcoholysis of styrene oxide and in the phosphonation of *N*-aryl tetrahydroisoquinolines by cross-dehydrogenative coupling reaction of $C(sp^3)$-H. The synthesis of α-aminophosphonates was not successful with our catalysts while the alcoholysis of styrene oxide with methanol gave the respective regioselective β-alkoxy alcohol in 60% yield without enantioselectivity. However, the developed bis-thiourea organocatalysts were able to participate in a cooperative phenomenon with Brønsted Acids.

Keywords: organocatalysis, L-tartaric acid, (+)-camphoric acid, thiourea organocatalysts, Michael reaction, glycosylation reaction, asymmetric reactions

Resumo

Atualmente é quase impossível encontrar uma síntese de um produto natural ou de um fármaco que não recorra ao uso de catalisadores. Tipicamente, os catalisadores usados em síntese orgânica são compostos metálicos; no entanto, outros métodos catalíticos têm vindo a ser utilizados, nomeadamente a organocatálise.

Este tipo de catálise descreve a aceleração de reações químicas através da adição de uma pequena quantidade de um composto orgânico que não contém átomos metálicos na sua estrutura. Um número crescente de publicações tem surgido nesta área, descrevendo não só a aplicação de organocatalisadores conhecidos a novas reações, mas também o desenvolvimento de novos organocatalisadores. A importância desta área de investigação foi reconhecida em 2021 com a atribuição do prémio Nobel de Química a Benjamin List e David MacMillan, pelos seus esforços no desenvolvimento da organocatálise assimétrica, uma nova ferramenta útil para a construção molecular.

O principal objetivo desta dissertação é o desenvolvimento de organocatalisadores, derivados de fontes quirais naturais e acessíveis, e a sua aplicação em diferentes tipos de reações assimétricas.

Na primeira parte deste trabalho, descrita no Capítulo 2, foram sintetizados organocatalisadores derivados do ácido L-tartárico e ácido (+)-canfórico. Desenvolveram-se oito novos organocatalisadores do tipo mono- e bis-tioureias e esquaramida derivados do ácido L-tartárico, com rendimentos globais moderados a bons (3-33%). A partir do ácido (+)-canfórico foram também sintetizados 6 novos organocatalisadores do tipo tioureia e esquaramida, com rendimentos globais bons a muito bons (23-57%).

Estes catalisadores foram testados em diferentes tipos de reações assimétricas. No Capítulo 3 é descrito o seu uso na reação de Michael. Os organocatalisadores derivados do ácido (+)-canfórico mostraram-se eficientes neste tipo de reação, utilizando como reagentes compostos 1,3-dicarbonílicos e vários *trans*-β-nitroestirenos. Foram obtidos rendimentos até 98% e excessos enantioméricos até 74%, bem como, quando aplicável, diastereosseletividades elevadas (até 93:7).

Na literatura tem sido descrita a utilização de tioureias para controlar a estereoquímica da reação de glicosilação. No Capítulo 4 é referida a utilização dos catalisadores derivados do ácido L-tartárico e os resultados mostram que estes catalisadores são capazes de ativar fosfatos glicosídicos em reações de substituição nucleofílica, originando os compostos desejados com bom rendimentos (até 85%) e diastereosseletividades elevadas (α:β até 83:17).

Como a eficiência dos organocatalisadores desenvolvidos foi demonstrada nas reações acima referidas, decidimos testá-los na alcoólise do óxido de estireno e na fosfonação de *N*-aryl tetrahydroisoquinolinas por reação de acoplamento desidrogenativo cruzado de C(sp^3)-H. A síntese de α-aminofosfonatos não foi bem-sucedida enquanto a alcoólise do óxido de estireno com metanol originou o respetivo β-alcóxiálcool regiosseletivamente, com 60% de rendimento, mas racémico. No entanto, as bis-tioureias desenvolvidas são capazes de participar num fenómeno cooperativo com ácidos de Brønsted.

Palavras-chave: organocatálise, ácido L-tartárico, ácido (+)-canfórico, organocatalisadores tioureia, reação de Michael, reação de glicosilação, reações assimétricas

Chapter 1

General Introduction

1.1 Asymmetric synthesis

A chiral molecule and its mirror image are called enantiomers – one is dextrorotatory (d) and the other is levorotatory (l). Chemical reactions that create a new chiral centre in the product, produce L- and D-molecules in equal amounts - a racemic mixture. Nevertheless, nature is a source of chiral compounds, with almost always only one of the two enantiomers present. For example, most amino acids are in the L form and most sugars are found in the D form.[1]

The stereochemical properties of an organic compound are often essential to its bioactivity, the two enantiomers might have different types of activity, one can be therapeutically active and the other can be non-active or toxic. One known example of this is thalidomide, a widely used drug in the late 1950s and early 1960s for the treatment of nausea in pregnant women. Thalidomide was commercialised in its racemic form, however, it was later found that the enantiomer *R* was responsible for the desired sedative effects and the enantiomer *S* caused irreversible damage to the fetus and thousands of children were born with severe congenital malformations.[2]

Therefore, the need for stereochemically pure pharmaceutical products is an example of the importance of asymmetric synthesis.[3,4] Emil Fisher is considered a pioneer in this field due to his contributions to carbohydrate chemistry. However, it was Marckwald who, in 1904, defined the asymmetric synthesis as a set of reactions that produce optically active substances from achiral compounds with the intermediate use of optically active materials. Nowadays, asymmetric synthesis is defined as a formation of a new chiral centre by the influence of another chiral group.[5,6]

Different strategies can be followed for the generation of a chiral centre – chiral pool synthesis, the use of chiral auxiliaries and asymmetric catalysis.[4,6,7]

One of the strategies is to use a chiral enantiomerically pure starting material, which is called the chiral pool strategy.

Some compounds are commercially available at low costs as single enantiomers. Using this strategy, two situations can occur:

1) the chiral centre present in the starting material has the desired configuration of the chiral centre of the target molecule (**Figure 1**).

2) for the formation of a new chiral centre, the stereocentre present in the starting material induces chirality and controls the configuration of the new stereocentre in the product.

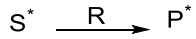


Figure 1. Method using chiral pool[5,6]

The chiral pool strategy is used, for example, for the synthesis of the (+)-muscopyridine from (*R*)-citronellene (**Figure 2**).[8]

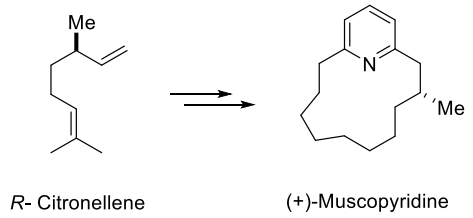


Figure 2. Chiral pool synthesis from a monoterpene[8]

More challenging is when the starting material used is not optically active. In this approach, a stoichiometric chiral auxiliary is covalently attached to the substrate followed by a diastereoselective reaction in which chirality in the auxiliary controls the asymmetric induction. The substrate-auxiliary is a new chiral compound that undergoes the diastereoselective reaction to give a major diastereomeric product-auxiliary which may be separated from the minor diastereomer and purified by conventional techniques such as column chromatography. The desired diastereomer is then subjected to a cleavage that separates the chiral auxiliary from the final enantiomeric product (**Figure 3**).[9]

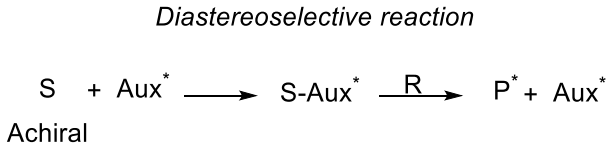
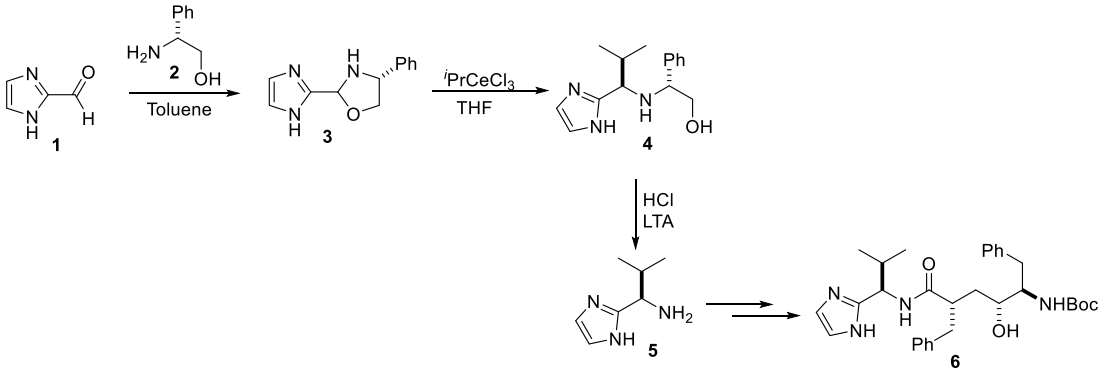


Figure 3. Methods controlled by a chiral auxiliary[9]

Chiral phenylglycinols have been used as chiral auxiliaries for the asymmetric induction of imine addition reactions. For example, the chiral auxiliary **2** can be used for the synthesis of the key intermediate **6** which is used in the preparation of a potent protease inhibitor (**Scheme 1**).[10]



Scheme 1. The use of a chiral auxiliary

Another strategy is the use of enantioselective reactions. A chiral catalyst, chemical or biological, may well differentiate the two enantiotopic faces or groups of an achiral molecule, providing the preferred formation of one enantiomer of the product (**Figure 4**). This is called asymmetric catalysis and presents some advantages over other methods, namely being a more green and sustainable approach because only a small amount of catalyst is needed to produce larger quantities of enantiomerically enriched product.

Enantioselective Reaction

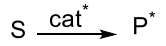
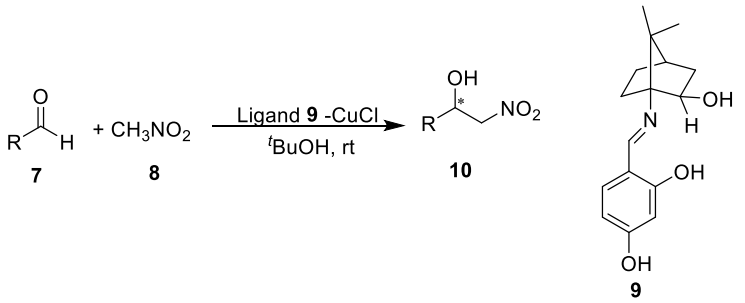


Figure 4. Methods controlled by a chiral catalyst[9]

An example of a chiral catalyst controlled method is the asymmetric Henry reaction between an aldehyde and nitromethane using copper chloride combined with the chiral ligand **9** (**Scheme 2**).[11]



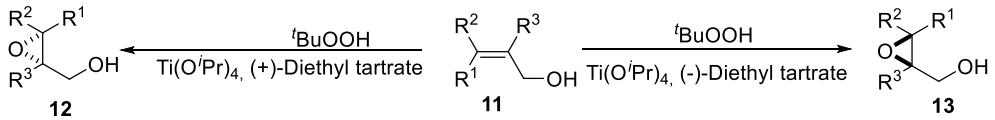
Scheme 2. Example of a method controlled by a chiral catalyst

1.2 Asymmetric catalysis

In the beginning of the 20th century many attempts were made to prepare optically active compounds from achiral substrates. The first examples of asymmetric catalysis fall back on the use of enzymes or moulds to catalyse various transformations.

In 1908, Rosenthaler described the use of an emulsin (crude extract from bitter almonds) as biocatalyst to catalyse the HCN addition to benzaldehyde and the respective cyanohydrin was obtained with 9% of enantiomeric excess.[12] However, the first well-established enantioselective reaction on a prochiral substrate, with an entirely chemical system, could be attributed to Bredig and Fiske in 1913. They reported the synthesis of mandelonitrile, *ee* up to 8%, from benzaldehyde and HCN, using quinine or quinidine as chiral catalysts.[6]

In 2001, the Nobel prize of chemistry was attributed to Sharpless, Knowles e Noyori for their efforts in catalytic asymmetric synthesis. Sharpless reported the first metal catalysed asymmetric epoxidation process which is far more selective than any of the previously described methods, using [(+) or (-)-diethyl tartrate, titanium tetraisopropoxide and *tert*-butyl hydroperoxide (**Scheme 3**).[13]



Scheme 3. Sharpless Epoxidation

Catalysts are traditionally metal compounds but despite their proven usefulness and efficiency there are some drawbacks to their use, which can be overcome with the use of other catalytic methods such as organocatalysis.[14]

1.3 Organocatalysis

Organocatalysis is a well recognised field of catalysis that describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound which does not contain a metal atom. Organocatalysts are non-toxic, do not produce dangerous waste and are usually unexpensive. This type of catalysis allows saving time, costs and energy and organocatalysed reactions occur under mild conditions and reduce chemical waste.[14,15]

Another important feature of several organocatalysts is that they are capable of different modes of activation, for example enamine, iminium, hydrogen bonding or counterion catalysis.[14]

The first application of the enamine catalysis was described in two independently research works developed by Hajos and Parrish and by Weichert, Sauer and

Eder, in 1971. They described the use of chiral proline to catalyse the intramolecular aldol reaction of an achiral triketone giving the product with 93% enantiomeric excess (*ee*). However, only with the work of Barbas, Lerner and List, more than 30 years later, that described the use of proline to catalyse the aldol reaction, this type of catalysis has started to receive attention.

In 2000, iminium catalysis was reported[16] as the first activation mode identified as being suitable for more than one reaction type and it is based on the capacity of chiral amines to function as enantioselective LUMO-lowering catalysts for several transformations that traditionally use Lewis acid catalysts (**Figure 5**).[15,17]

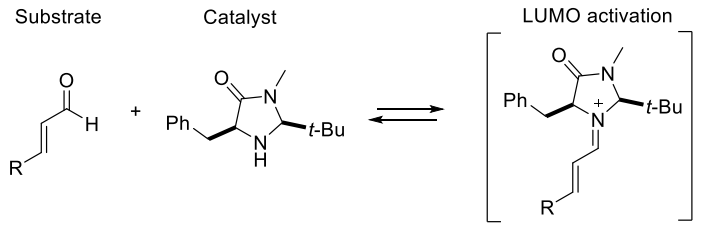


Figure 5. Iminium activation[15]

The enamine activation consists of the interaction between the amine-containing catalyst and a ketone substrate to form an enamine intermediate but this catalyst simultaneously engages with an electrophilic reaction partner through either hydrogen bonding or electrostatic attraction (**Figure 6**).[15]

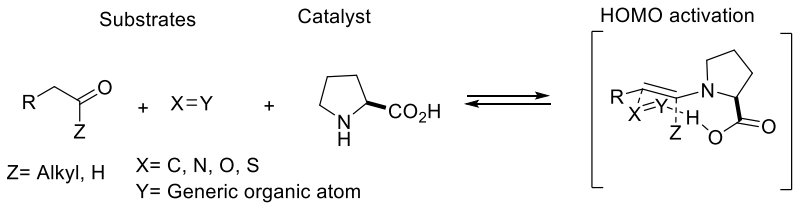


Figure 6. Enamine activation[15]

In the early 1980s, there were already reports describing the use of hydrogen bonding interactions for the activation of a substrate and the organisation of the transition state.

However, these reports were considered to be exceptions to the generally held idea that hydrogen bonding was insufficiently activating or directional for use in asymmetric catalysis.[15] In 1998 and 1999, Jacobsen[18] and Corey,[19] respectively, published an asymmetric variant of the Strecker reaction that resorted to the use of well-defined hydrogen-bonding organocatalysts that activate imine electrophiles (**Figure 7**).

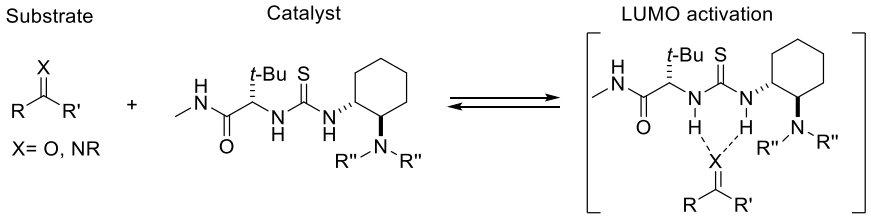


Figure 7. Hydrogen-bonding activation[15]

Jacobsen and Anna Wenzel were the great drivers of the hydrogen bonding catalysis, extending the scope of this activation mode. In 2002, they reported the use of urea derivatives as highly effective catalysts for the asymmetric Mannich addition of silyl ketene acetal derivatives to aldimines.[20]

In 2008, Jacobsen developed a new generic organocatalytic mode of activation that is able to promote highly enantioselective additions into transiently generated N-acyl-iminium ions and oxocarbenium ions.[21,22] In counterion catalysis, chiral thiourea catalysts form strong complexes with halide ions, electrostatically bind to, and ionise, the weak carbon–chlorine bonds of chloramides and chloroacetals to generate a transient ion pair. This resulting complex works as a chiral

counterion, biasing the approach of nucleophiles to a single face of one enantiomer of the transient α-hetero atom-stabilised cationic species (**Figure 8**).[15]

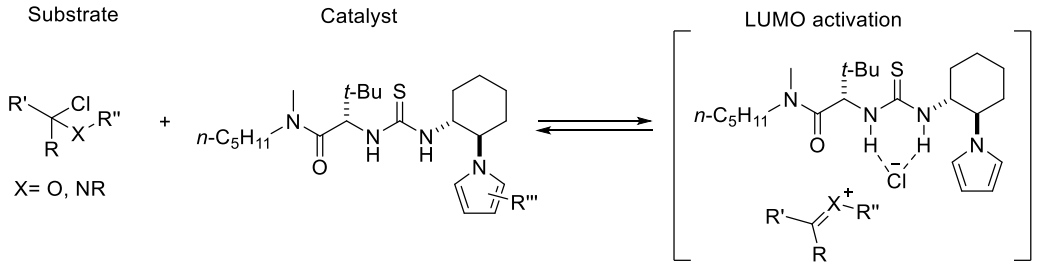


Figure 8. Counterion activation[15]

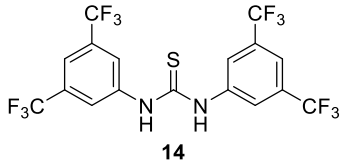
Owing to the huge growth and impact of organocatalysis in the past decades, the Nobel prize of chemistry was attributed to Benjamin List and David MacMillan in 2021, for the development of asymmetric organocatalysis, a new precise tool for molecular construction.

Besides the identification of important transformations and new reactivities that are not available using other branches of catalysis, numerous efforts will continue to be directed towards the development of catalysts with better efficiency. Among several types of organocatalysts, thioureas are a type of catalysts extremely diverse and versatile.

1.4 Thioureas

During the last decades, the use of thiourea derivatives as catalysts in asymmetric synthesis has been increased. One of the main features is their capacity to activate substrates and subsequently stabilise partially developing negative charges in the transition states using explicit double hydrogen bonding.

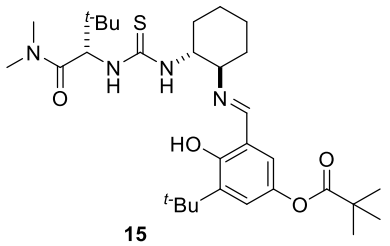
Curran's pioneering work showed that various types of nucleophilic addition reactions have been found to be effectively promoted by a catalytic amount of well-designed ureas and thioureas.[23,24] In 1998, Schreiner decided to use thioureas derivatives as catalysts because they have some advantages over urea ones: higher solubility in a variety of solvents, easier preparation and less favourable self-association.[23] He developed the *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea **14**, commonly known as Schreiner thiourea (**Figure 9**), which was applied in the Diels-Alder and dipolar cycloaddition reactions with good results.[25,26] The Schreiner thiourea has played a very important role in the development of H-bond organocatalysts.



14

Figure 9. Schreiner's thiourea[25,26]

Jacobsen's group is pioneer in the area of enantioselective catalysis using thiourea catalysts. They had developed a series of chiral Schiff base thioureas and applied them in Strecker[18,27,28] and Mannich[29] reactions. After a thorough study to optimise the structure of the catalyst, the best results were obtained with the catalyst **15**, represented in **Figure 10**.



15

Figure 10. Jacobsen's Schiff Thiourea[28]

Even though these thiourea derivatives had been successfully used as organocatalysts, the application of these catalysts to enantioselective reactions could be limited. Therefore, Takemoto's group designed chiral bifunctional thioureas bearing a chiral scaffold and a basic functionality expecting a dual activation to promote several nucleophilic addition reactions (**Figure 11**).[30]

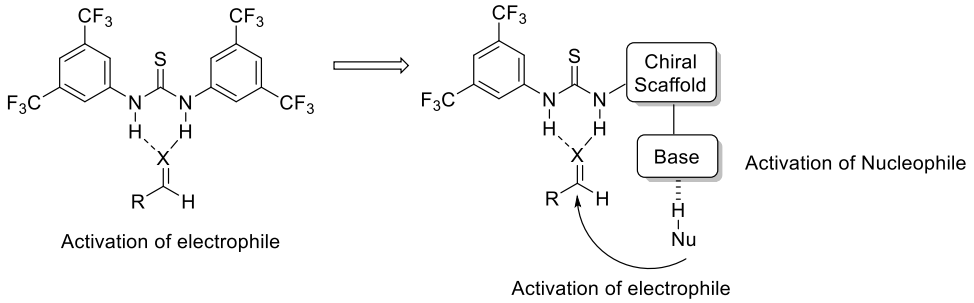
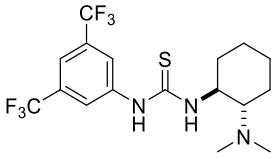


Figure 11. Design of bifunctional thioureas[30]

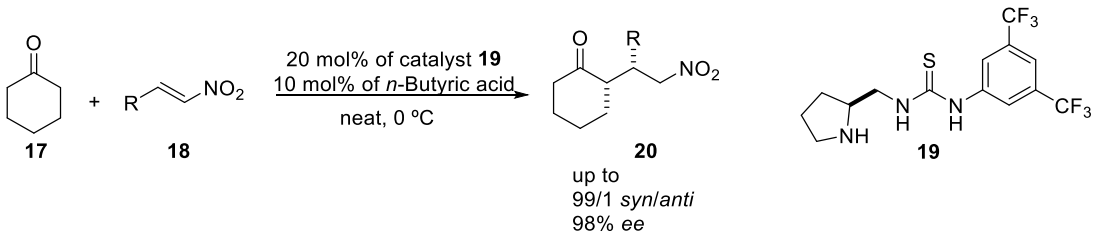
Among the synthesised bifunctional amino thioureas the most effective for the Michael addition reaction of malonates to nitroolefins was the thiourea catalyst **16** prepared with (*R*,*R*)-*N*,*N*-dimethyl-*trans*-diaminocyclohexane and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**Figure 12**).[31,32] It is assumed that weak tertiary amine bases can coexist with a thiourea moiety without deactivating each other. Extensive work on C-C bond forming reactions involving these types of bifunctional catalysts was described by the Takemoto group. [30]



16

Figure 12. Takemoto's Catalys[31,32]

A chiral bifunctional pyrrolidine-thiourea **19** was reported by Tang's group, in 2006. This catalyst promoted a highly enantioselective Michael addition of cyclohexanone to nitroolefins (**Scheme 4**).[33]



Scheme 4. Michael addition of cyclohexanone to nitroolefins catalysed by bifunctional pyrrolidine-thiourea **19**

Usually, the chirality of enantiopure thioureas used in asymmetric organocatalysis is due to the presence of stereogenic centres. However, another group of derivatives characterised by the presence of other stereogenic elements has their importance in enantioselective catalysis. Wang's group developed a bifunctional binaphthyl-thiourea **21**, which contained both a basic binaphthyl moiety and a thiourea moiety (**Figure 13**). This organocatalyst exhibits axial chirality/helicity because of the presence of the biaryl fragment characterised by a restricted rotation around the C_{aryl}–C_{aryl} bond.

This catalyst was successfully applied in the asymmetric Morita–Baylis–Hillman reaction of cyclohexenone with a series of aldehydes[33] and in the asymmetric Michael addition of diketones to nitroalkenes.[34]

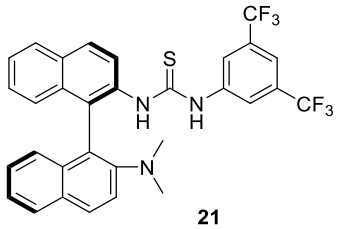
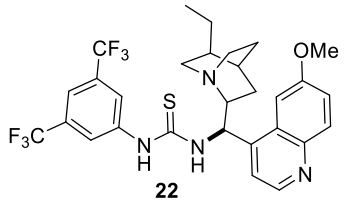


Figure 13. Wang's catalyst[33,34]

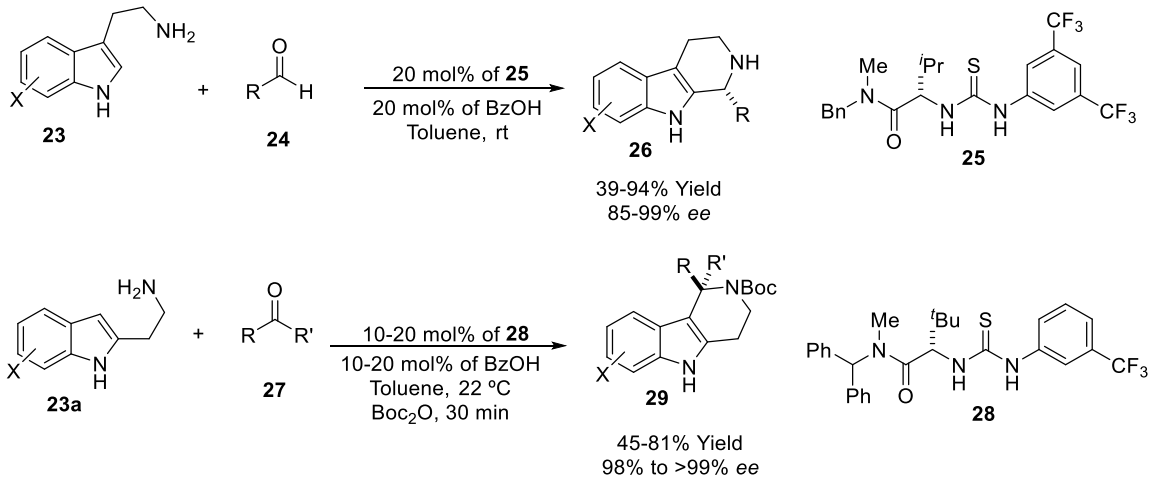
The *Cinchona* alkaloid is a motif present in various structures useful in asymmetric synthesis.[34] Soos *et al.* and Connon *et al.*, independently, developed a bifunctional organocatalyst that combined a *Cinchona* alkaloid derivative and a thiourea moiety (**Figure 14**). After a simple reaction it was possible to convert the hydroxyl group at the C9 position into an amine and its reaction with the corresponding isothiocyanate gave the desired bifunctional *cinchona* alkaloid-thiourea **22**. This catalyst was first tested in the enantioselective addition of malonates to nitroalkenes[35] and in the enantioselective addition of nitroalkanes to chalcones[36] with promising results and since then it has been extensively used in asymmetric organocatalysis.



22

Figure 14. Soos's and Connon's cinchona alkaloid thiourea[35,36]

A natural and readily available source of chirality is amino acids and their derivatives. Therefore, Jacobsen's group described the synthesis of amide-thiourea catalysts derived from valine **25** and leucine **28** and their application in Pictet-Spengler and Iso-Pictet-Spengler reactions (**Scheme 5**).[37–39]



Scheme 5. Application of chiral thioureas derived from amino acids in Piclet-Spengler reactions

Some novel thiourea organocatalysts based on carbohydrates were developed and they are frequently combined with other functionalities. For example, Liu *et al.* synthesised five novel thioureas **30-34** derived from D-mannitol and containing a *Cinchona* alkaloid in their structure (**Figure 15**). These organocatalysts were used in the asymmetric Henry reaction.[40]

Bifunctional organocatalysts combining a carbohydrate moiety and a primary amine derived from 1,2-diamino-cyclohexane were prepared by Ma and collaborators and tested in enantioselective Michael additions with high yields and stereoselectivities.[41]

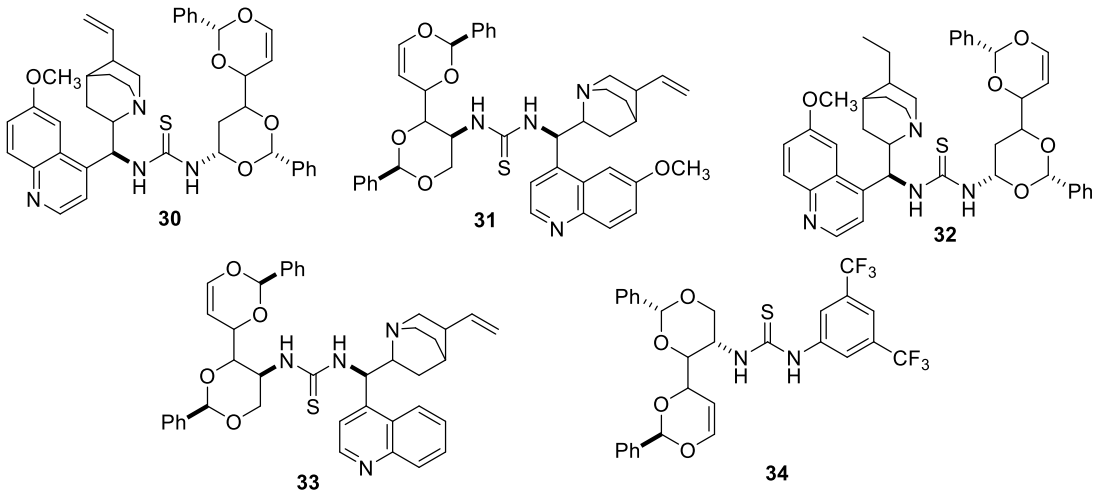


Figure 15. D-Mannitol derived thiourea organocatalysts[40]

With the objective to recycle the thiourea catalyst, polymer-based thioureas were developed and widely used in some organic transformations. In 2006, Takemoto's group demonstrated that in the presence of PEG-bound thiourea **35** (**Figure 16**) Michael and tandem Michael reactions of *trans*-β-nitrostyrene proceeded enantioselectively.[42] More recently, Pedrosa's group have developed supported thiourea organocatalysts which were tested in several enantioselective catalytic reactions.[43–47]

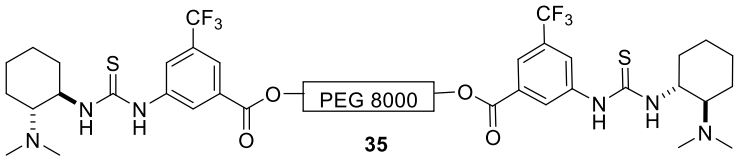


Figure 16. PEG-bound thiourea catalyst **35**[42]

Chapter 2

Synthesis of Organocatalysts

This chapter contains published data.

Rénio, M.; Murtinho, D.; Ventura, M. R. New Bifunctional 1,3-Diamine Organocatalysts Derived from (+)-Camphoric Acid for Asymmetric Michael Addition of 1,3-Dicarbonyl Compounds to Nitroolefins. *Chirality* **2022**, 1–14.

The author contributed fully to this chapter, namely in the planning of the experimental work, performing the experiments and writing the manuscript.

Abstract

In this chapter the synthetic sequences for the preparation of the organocatalysts are described. New mono, bis-thioureas and squaramide organocatalysts derived from L-tartaric acid were obtained with moderate to good overall yields (3-33%). The attempts for the synthesis of the desired cyclic bis-thiourea derived from L-tartaric acid are also presented. The syntheses of novel 1,3-diamine-derived bifunctional thiourea and squaramide organocatalysts synthesised from (+)-camphoric acid in good to very good overall yields (23-57%) are also described.

2.1 Introduction

Our group has been focused on the development of organocatalysts derived from inexpensive and natural sources of chirality and their application in different types of catalytic reactions. Starting from natural compounds readily available in pure enantiomeric forms, such as L-tartaric acid and (+)-camphoric acid, several modifications were made in order to obtain adequate organocatalyst structures to be applied in various asymmetric catalytic reactions.
The syntheses of these organocatalysts will be presented and discussed in this chapter.

2.2 Results and Discussion

2.2.1 Organocatalysts derived from L-tartaric acid

Tartaric acid is one of the most useful naturally occurring organic acids, it is present in many types of fruit, especially grapes. Tartaric acid contains two asymmetric carbon atoms allowing three stereogenic forms and it was isolated for the first time by the Swedish chemist Scheele, in 1769. The naturally-occurring form is L, (*R*,*R*)-(+)-tartaric acid, while the D form, (*S*,*S*)-(-)-tartaric acid, is rarely

present in natural sources. The meso-tartaric acid, optically inactive, can be synthetically obtained (**Figure 17**).[48,49]

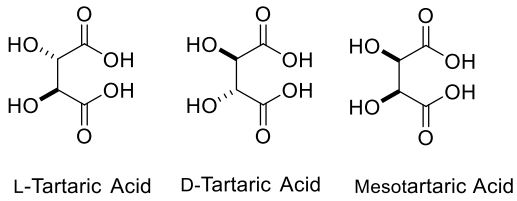


Figure 17. Possible forms of tartaric acid[48,49]

L-Tartaric acid is obtained by acid hydrolysis of calcium tartrate, which is prepared from potassium tartrate, a by-product of wine production. D-Tartaric acid is obtained from the racemic acid by several resolution procedures or from D-xylose.[50] Due to the ease of functionalisation and C2 symmetry both tartaric acid enantiomers are chiral chemical building blocks with broad industrial and scientific applications. In chemical synthesis they are used as resolving agents or chiral auxiliaries in the synthesis of bioactive molecules, additionally, they are also inexpensive sources for chiral ligands and new asymmetric organocatalysts.[49,51]

Tartaric acid is the starting material to obtain systematically fine-tuned derivatives such as tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanols (TADDOLs)[51], widely used, or dimethyl (2*R*,3*R*,5*R*,6*R*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dicarboxylate (**Figure 18**), a rigid and stereo-defined bis-acetal that provides additional stereocentres, which have been used in our group to induce stereoselectivity in some organocatalytic asymmetric reactions with good results.[52]

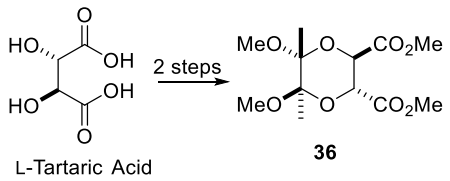
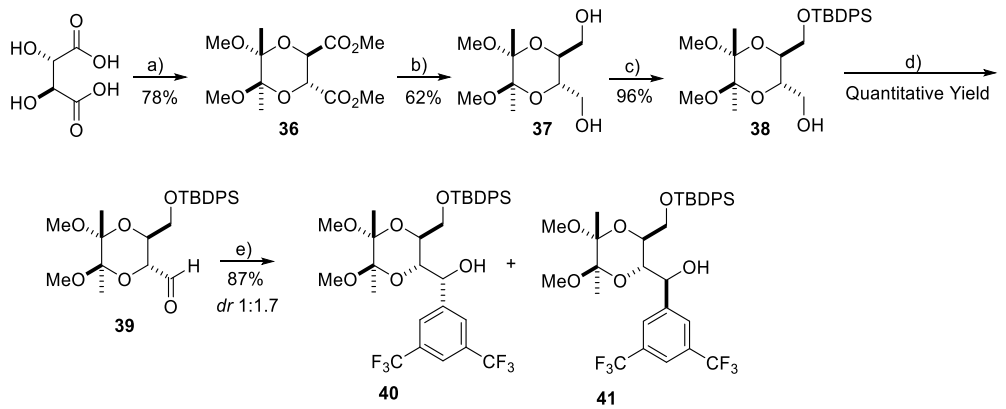


Figure 18. Dimethyl (2*R*,3*R*,5*R*,6*R*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dicarboxylate easily obtained from L-tartaric acid[52]

In this work, we synthesised a series of organocatalysts derived from this rigid tartrate structure with a thiourea moiety and different functional groups - hydroxyl, amino or ester - in the organocatalyst's structure. It seemed interesting to us to explore the influence of the proximity of the asymmetric centre to the catalytic important atoms for the stereoselective outcome of the studied stereoselective reactions. The effect of having a mono- or bis-thiourea in the catalyst structure was also compared.

One of the important reactions in which we decided to apply our organocatalysts derived from L-tartaric acid was the glycosylation reaction and after some research in the literature[53] we decided to synthesise a cyclic bis-thiourea type organocatalyst.

The dimethyl (2*R*,3*R*,5*R*,6*R*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dicarboxylate **36** was easily obtained from L-tartaric acid following a literature procedure[54,55] and this was the structural base unit used for these type of organocatalysts. Firstly, the L-tartaric acid was treated with $SOCl_2$ and methanol and the dimethyl L-tartrate thus obtained was immediately converted into the desired tartrate **36** by reaction with 2,3-butadione, trimethyl orthoformate and CSA. The reduction of compound **36** with lithium aluminium hydride provided the corresponding diol **37** in 62% yield (**Scheme 6**). The yield of this step was low, since the extraction of the compound to the organic layer was difficulted by the presence of lithium salts, thus, before extraction it is important to lower the pH to 2-3 in order to destroy these salts and facilitate the extraction of the diol. Compound **38** was obtained by monosilylation of diol **37**. The reaction occurred in two steps, first the reaction with sodium hydride to form the alkoxide which reacts with TBDPSCl, giving the desired compound in excellent yield (96%). A new chiral centre was introduced through Swern oxidation, to afford aldehyde **39** in quantitative yield, followed by a Grignard reagent addition giving a mixture of diastereomers, **40** and **41**, 1.7:1 (the diastereomeric proportion was determined by ^{1}H NMR), (**Scheme 6**).



Scheme 6. a) i. $SOCl_2$, CH_3OH, reflux, 3 h; ii. 2,3-butadione, TMOF, CSA, reflux, overnight, **78%**; b) $LiAlH_4$, THF, 0 °C to rt, 1 h, **62%**; c) i. NaH, THF, 0 °C to rt, 10 min.; ii. TBDPSCl, 0 °C to r.t., 1 h, **96%;** d) i. $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 1 h; ii. Et_3N, -78 °C to rt, 1 h, **quantitative yield**; e) 3,5-Bis(trifluoromethyl)phenylmagnesium bromide, THF, -78 °C, 1h, **87%** (dr 1.7:1 **40:41**).

The two diastereomers were separated by flash chromatography and the configuration of the new chiral centre was determined by NOESY and confirmed by x-rays diffraction of **42** (**Figure 19**). Compound **40,** the major diastereomer, has the proton at the new chiral centre on the same plane as the proton of the adjacent CH on the tartrate moiety, for this reason it was possible to see the correlation in the NOESY spectrum (**Figure 20**). On the NOESY spectrum of compound **41** this correlation does not exist thus proving that the proton of the new chiral centre is not in the same plane of the CH on the tartrate moiety (**Figure 21**).

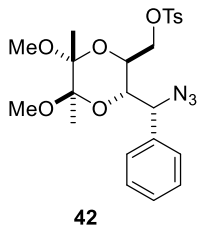


Figure 19. Analogue compound used to confirm the configuration of the diastereomers by X-ray diffraction.

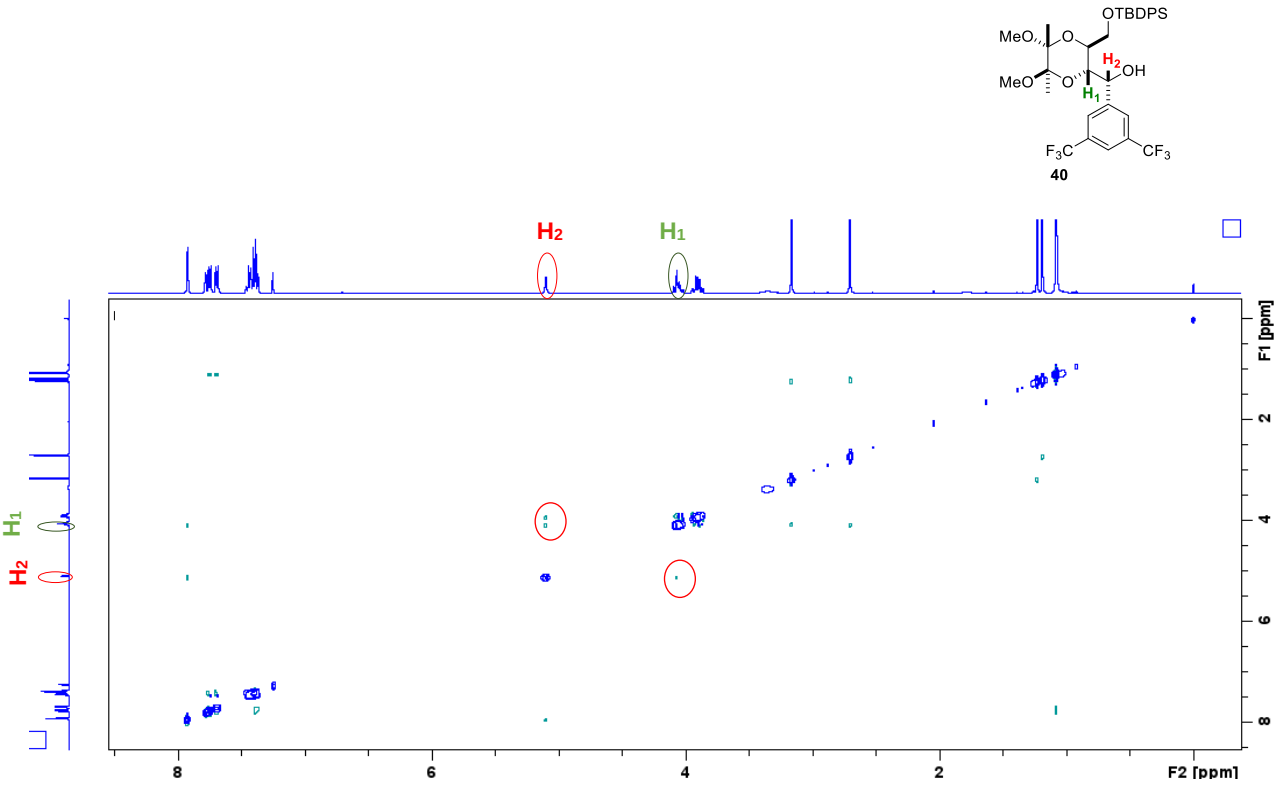


Figure 20. NOESY spectrum of compound **40**

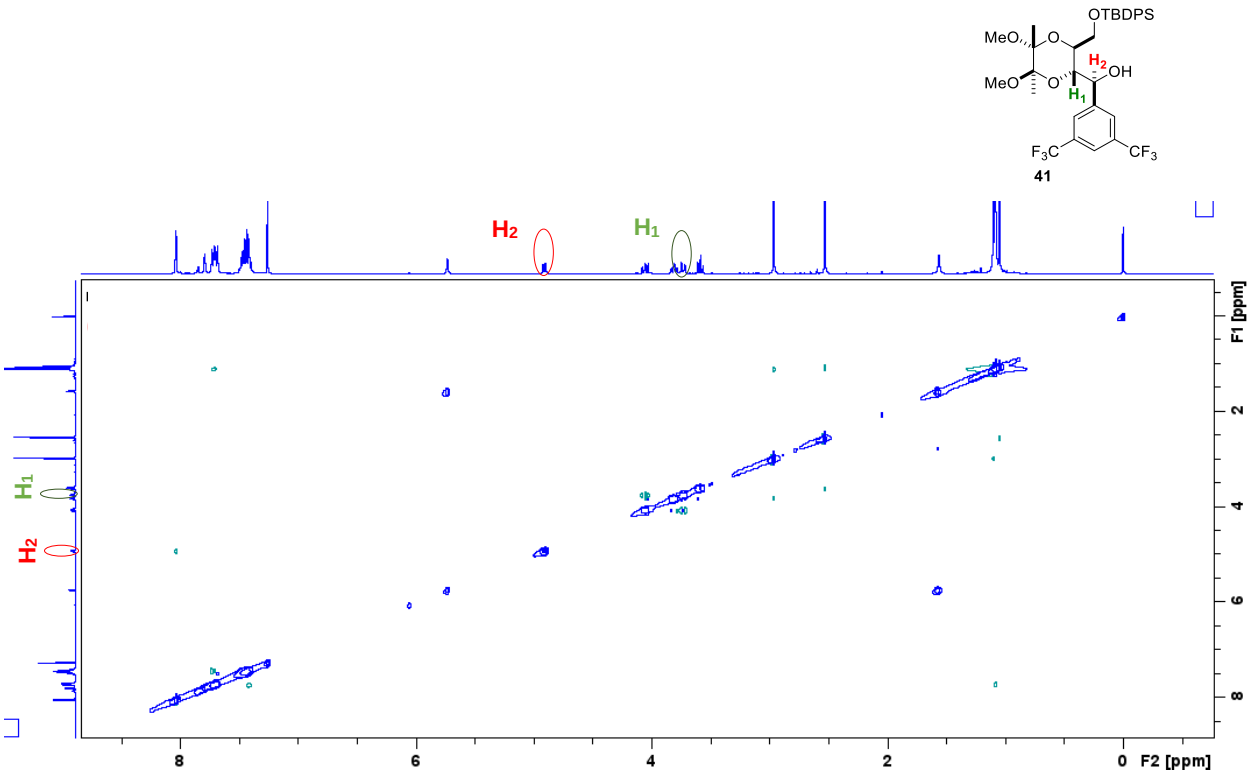
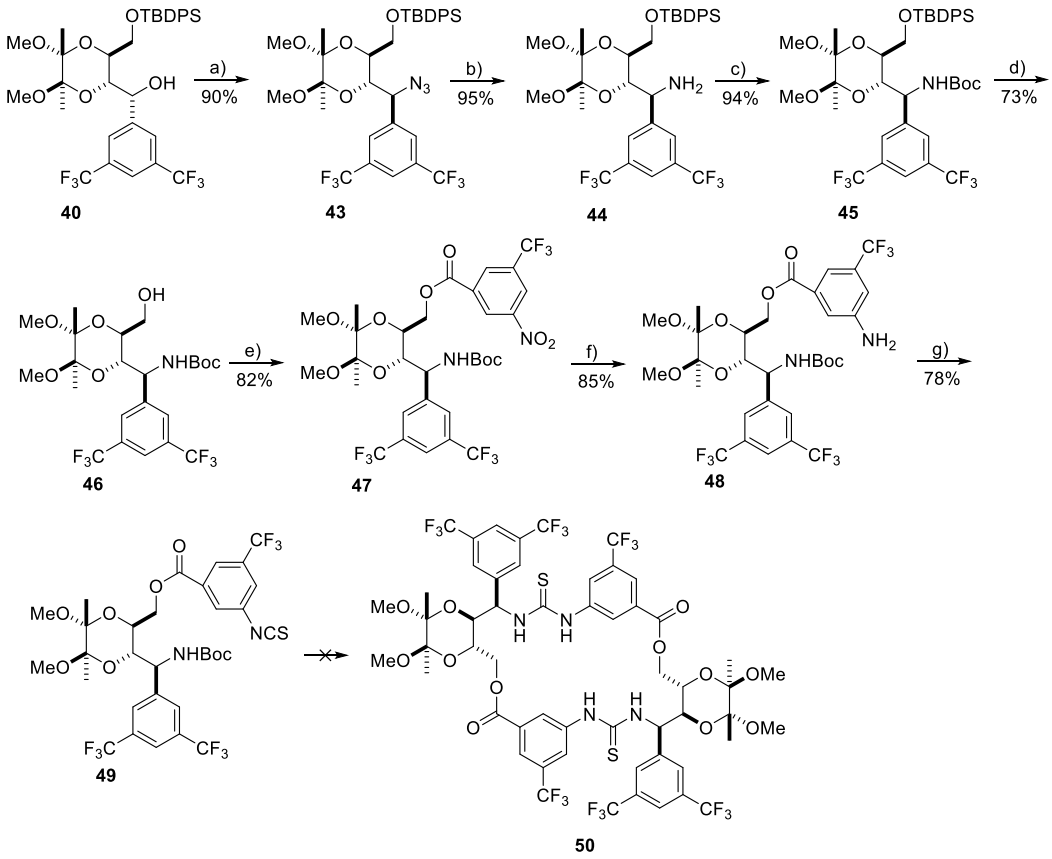


Figure 21. NOESY spectrum of compound **41**

The following reactions of the synthetic sequence are represented for only the major diastereomer however, the synthesis from the minor diastereomer followed the same route, with very similar yields.

In the Mitsunobu reaction the stereogenic centre was inverted (**Scheme 7**) and this inversion can also be shown by the NOESY spectrum of the compound **43**, confirmed by the X-ray determination of the configuration of an analogous compound, **42** (**Figure 22**). The new asymmetric proton is in a different plane of the vicinal CH on the tartrate moiety, so it was not possible to see a strong correlation in the spectrum (**Figure 23**).



Scheme 7. a) DIAD, PPh_3, DPPA, THF, 0 °C to rt, overnight, **90%**; b) PPh_3, THF:H_2O (8:2), reflux, 2h, **95%**; c) Boc_2O, Et_3N, CH_2Cl_2, 0 °C to r.t, overnight, **94%**; d) TBAF, THF, 1h, **73%**; e) 3-Nitro-5-(trifluoromethyl)benzoic acid, EDC.HCl, DMAP, CH_2Cl_2, 0 °C to rt, overnight, **82%**; f) Pd/C 10%, H_2, 50 psi, EtOH, overnight, **78%**; g) TCDI, imidazole, CH_2Cl_2, overnight, **78%**.

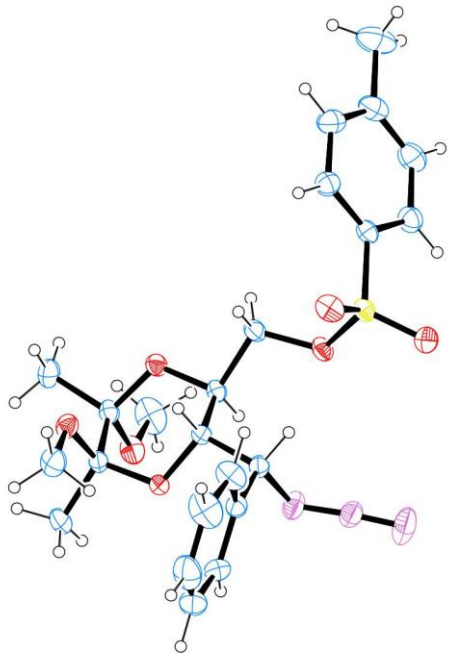


Figure 22. X-ray of compound **42**

Even though compound **42** is not equal to the obtained diastereomers it was possible to compare the ^{1}H NMR spectra of diastereomers **43** and **43'**, which contain an azide substituent in the same position that **42**, and are similar to diastereomers **51** and **51'**.

Knowing, by x-ray analysis of compound **42**, that the diastereomer *R* contains the phenyl substituent behind the plane, so the diastereomer *S* contains the phenyl substituent in front of the plane. Therefore, was possible to compare the ^{1}H NMR spectrum of compound **43** with that of compound **51** (Spectrum **A** vs. Spectrum **B** in **Figure 24**), more specifically the chemical shift of the signal of the asymmetric proton (H_2 - 4.61 ppm in spectrum **A** and H_2 - 4.41 ppm in spectrum **B** in **Figure 24**) of the two compounds and observe that they were similar. Therefore, we could conclude that also in compound **43** the 3,5-bis(trifluoromethyl)phenyl substitute is in front of the plane.

Also, comparing the ^{1}H NMR spectrum of the compound **43'** with that of compound **51'** (Spectrum **C** vs. Spectrum **D**) , the signal of of the asymmetric proton (H_2 – 5.01 ppm in spectrum **C** and H_2 – 4.93 ppm in spectrum **D**) it is possible to conclude that they were also similar, proving that the 3,5-bis(trifluoromethyl)phenyl substitute is behind the plan. This comparative conclusion allowed us to confirm our results obtained in the NOESY spectrum of compound **43**.

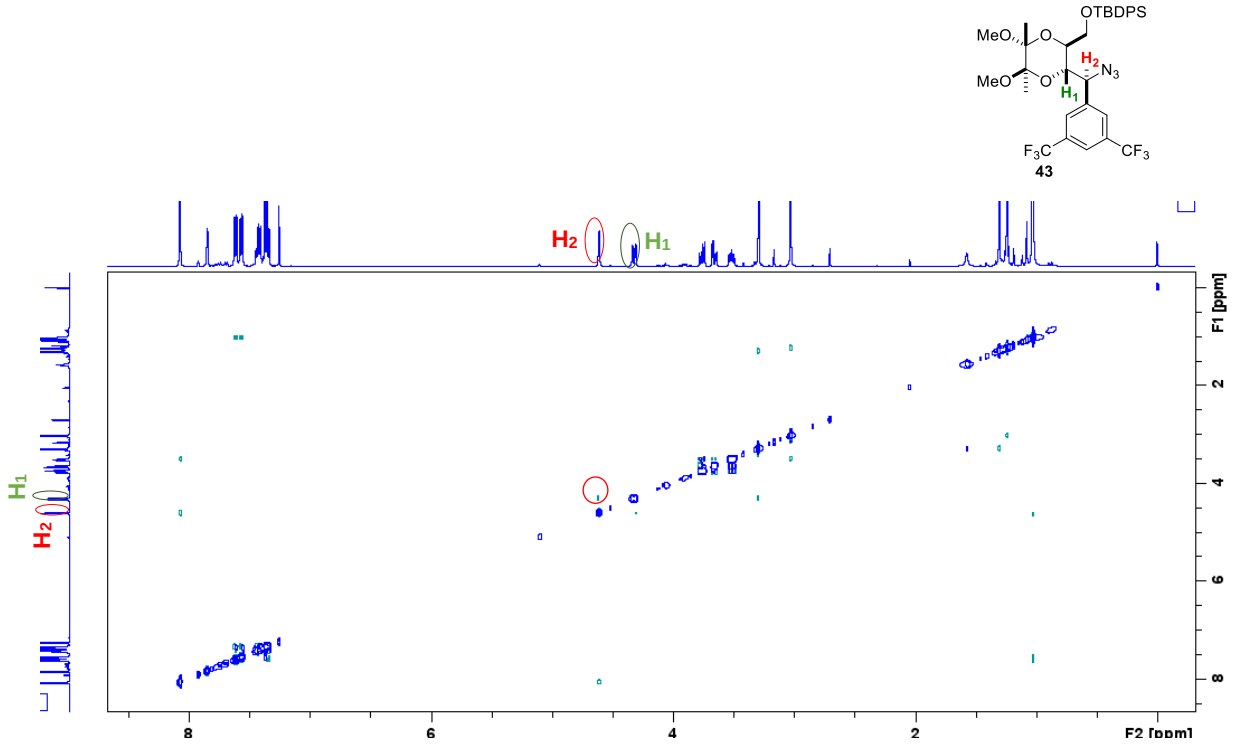


Figure 23. NOESY spectrum of compound **43**

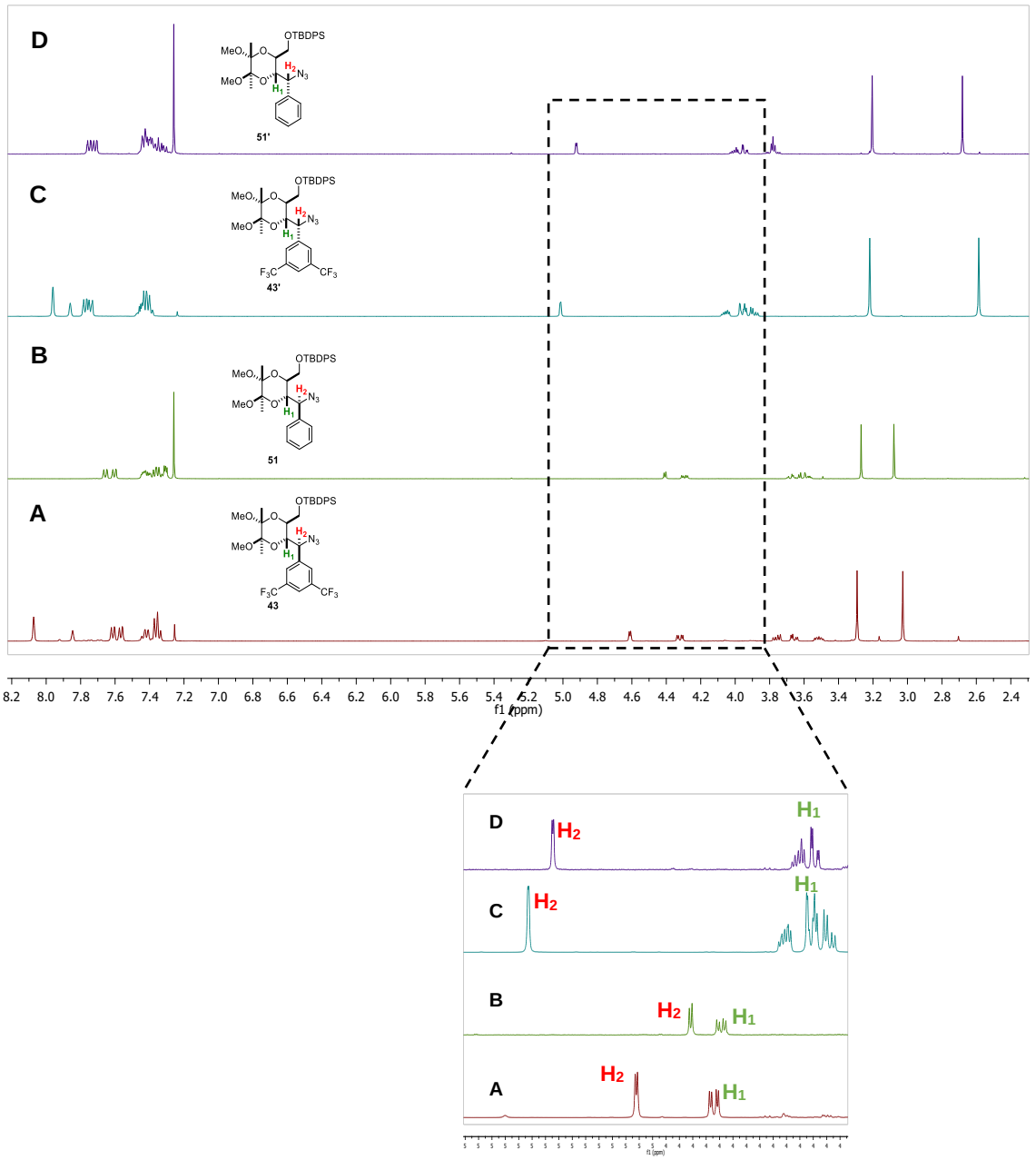


Figure 24. Comparison of ^{1}H NMR spectra between 2.4 – 8.2 ppm of the diastereomers **43** and **51, 43'** and **51'**

A Staudinger reaction converted the azide into the corresponding amine **44** which was protected with *t*-butoxycarbonyl group, by reaction with $(Boc)_2O$ giving compound **45** (**Scheme 7**). Cleavage of the silyl group followed by coupling with 3-nitro-5-(trifluoromethyl)benzoic acid, using EDC.HCl and DMAP in dichloromethane, afforded product **47** in 82% of yield. The nitro group was reduced by catalytic hydrogenation giving the compound **48** which reacts immediately with 1,1'-thiocarbonyldiimidazole and imidazole in dichloromethane to afford compound **49**. By removing the Boc protecting group it would be possible to obtain the desired organocatalyst **50** however, several reaction conditions were attempted without success (**Scheme 7**).

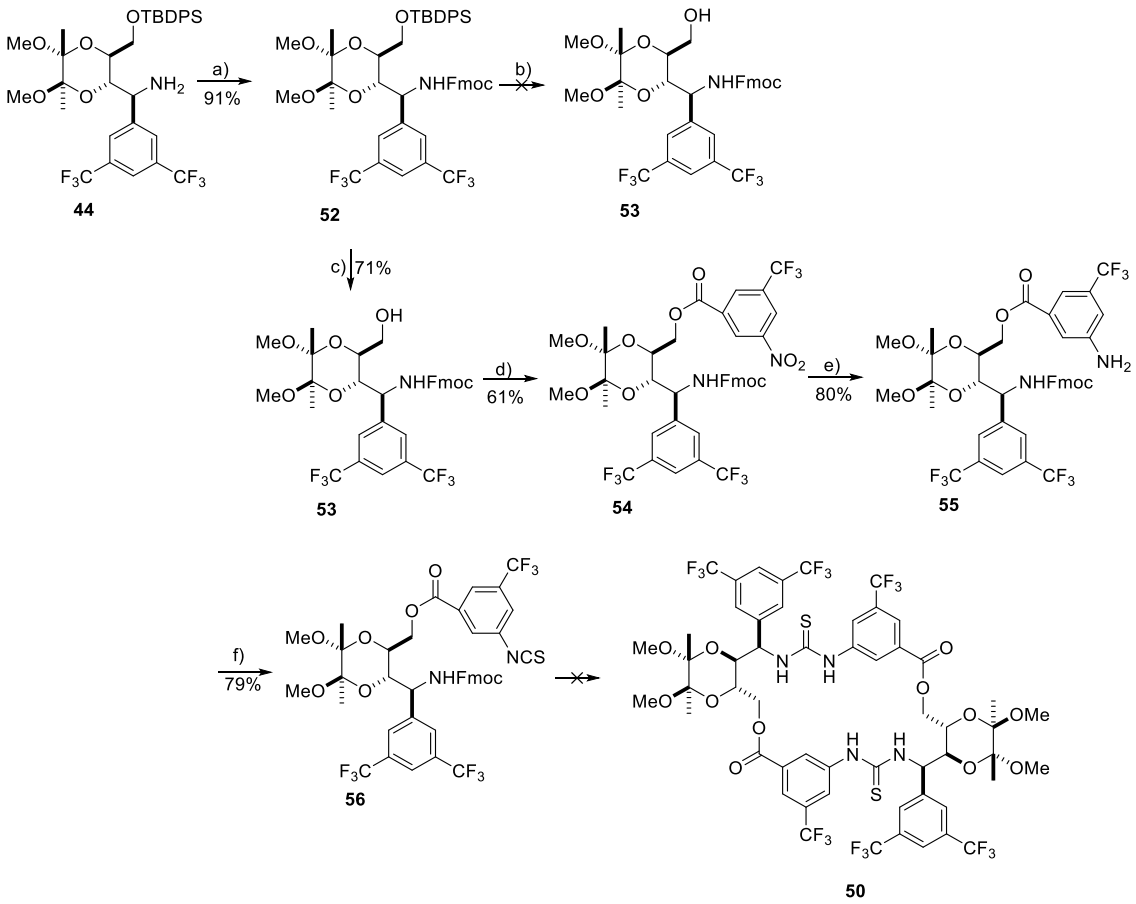
Using 1.1 equivalents of TFA the reaction did not occur and increasing to 7 equivalents of TFA the TLC showed decomposition of the compound because the tartrate derivative is sensible to pH lower than 2. According to the literature[56] it is possible to remove the protecting Boc group with formic acid, but in this case this did not happen and degradation products were also obtained.

Another procedure described in the literature[57] to remove the Boc group is the reaction with *para*-toluenesulfonic acid monohydrate in acetonitrile, but once again the starting material was obtained. As we needed a way of removing the protecting group under mild conditions, we found in the literature a Boc deprotection strategy using H_2O near reflux temperature[58] and this green alternative was attempted without success. Thereby, we decided to change the protecting group from Boc to Fmoc.

Starting from compound **44** the amine was protected with the Fmoc group using Fmoc-OSu in dioxane, giving the protected amine **52** in very good yield (71%, **Scheme 8**). The hydrolysis of the silyl group with TBAF did not afford the desired compound, because the TBAF reagent removes both the silyl and Fmoc protecting groups. Hence, a different source of fluor was required and we decided to use triethylamine trihydrofluoride in THF. The reaction time was longer however the desired compound **52** was obtained. In order to reduce the reaction time other

fluorinated reagents were tested, HF and CsF, but the reaction did not proceed with good results and we decided to maintain the triethylamine trihydrofluoride in THF as reagent for this reaction. The coupling with 3-nitro-5-(trifluoromethyl)benzoic acid, using EDC.HCl and DMAP in dichloromethane, afforded product **54** in 61% yield, and the reduction of the nitro group to the amino group without removal of the Fmoc group was complicated. Firstly, the catalytic hydrogenation with Pd/C or Raney nickel was attempted but the reduction was not possible without the deprotection of the amino group. In the literature[59], a procedure using tin(II) chloride dihydrate was described and adjusting the equivalents of the reagent to our reduction reaction it was possible to obtain the desired product **55** in 80% yield. This amine was reacted with 1,1'-thiocarbonyldiimidazole and imidazole in dichloromethane to afford compound **56** and after removing the protecting group the desired organocatalyst **50** would be obtained. Once again, the cleavage of this group was not successful (**Scheme 8**).

The common procedure uses basic conditions, piperidine, triethylamine, DBU and DIPEA were attempted however, these amines preferably reacted with the isothiocyanate present in the structure and did not remove the Fmoc protecting group. In other reactions, we observed that by catalytic hydrogenation the Fmoc group was removed, so we tried the same conditions using Pd/C but the presence of the sulfur atom poisoned the palladium and the starting material was recovered. The use of TBAF to remove the TBDPS protecting group also removed the Fmoc group, thus this strategy was attempted but without success, the desired organocatalyst **50** was not obtained. Therefore, we decided to simplify the synthesis of the cyclic bis-thiourea derived from L-tartaric acid, without the presence of a new chiral centre.

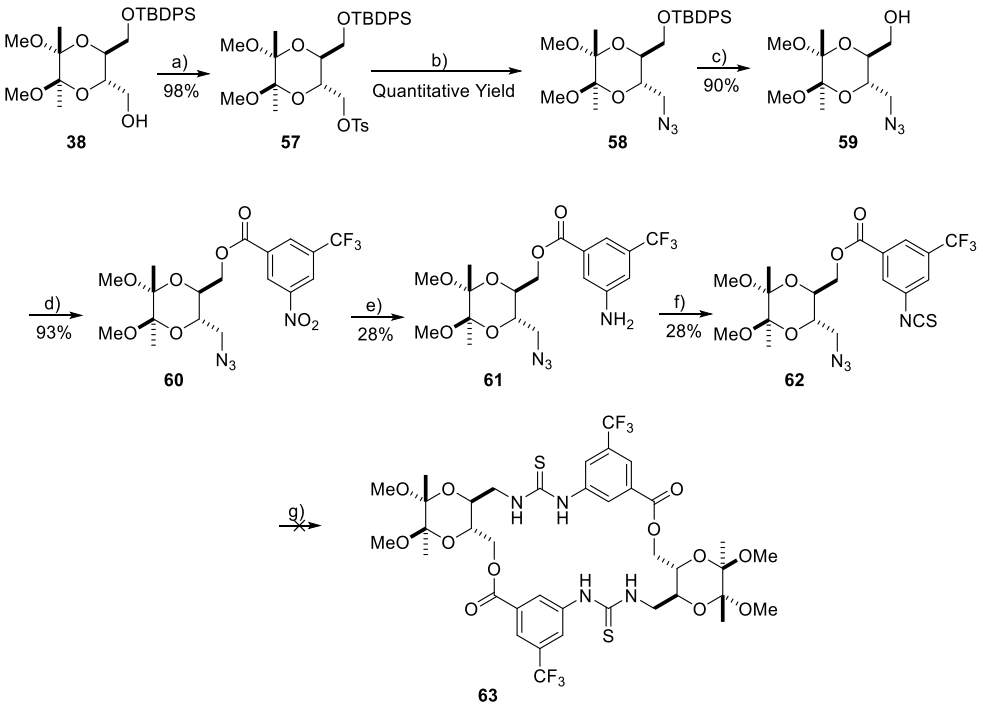


Scheme 8. a) Fmoc-OSu, $NaHCO_3$ (1M), Dioxane, 0 °C to r.t, 4 h, **91%**; b) TBAF, THF, 1h; c) $Et_3N.3HF$, THF, 5 days, **71%**; d) 3-Nitro-5-(trifluoromethyl)benzoic acid, EDC.HCl, DMAP, CH_2Cl_2, 0 °C to rt, overnight, **61%**; e) $SnCl_2.2H_2O$, AcOEt, 50 °C, overnight, **80%**; f) TCDI, imidazole, CH_2Cl_2, overnight, **79%**.

Starting from mono silylated compound **38** and by tosylation of the free hydroxyl it was possible to obtain compound **57** in excellent yield (98%). The substitution of the resulting tosyl group with sodium azide followed by cleavage of the TBDPS group with TBAF afforded compound **59** in 90% yield and the coupling with the corresponding carboxylic acid gave the desired compound **60**. The nitro group present on the aromatic ring was reduced to the amino group with tin(II) chloride dihydrate in ethyl acetate at 50 °C giving the compound **61**. The corresponding

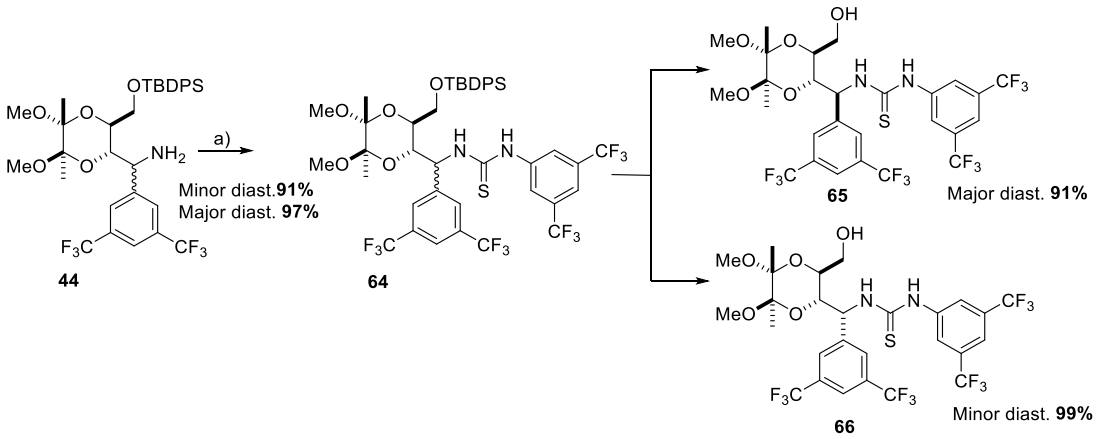
isothiocyanate **62** was obtained by reaction of this amine with 1,1'-thiocarbonyldiimidazole and imidazole in dichloromethane. The desired organocatalyst **63** would be obtained by Staudinger reaction, unfortunately the compound was not formed (**Scheme 9**).

The synthesis of the cyclic bis-thiourea was not possible, nevertheless all synthetic attempts generated important knowledge for the synthesis of the other organocatalysts derived from L-tartaric acid.



Scheme 9. a) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, overnight, **98%**; b) NaN_3, DMF, 70 °C, overnight, **quantitative yield**; c) TBAF, THF, 1h, 90%; d) 3-Nitro-5-(trifluoromethyl)benzoic acid, EDC.HCl, DMAP, CH_2Cl_2, 0 °C to rt, overnight, **93%**; e) $SnCl_2.2H_2O$, AcOEt, 50 °C, overnight, **28%**; f) TCDI, imidazole, CH_2Cl_2, overnight, **28%**; g) PPh_3, THF:H_2O (8:2), 50 °C, 3h.

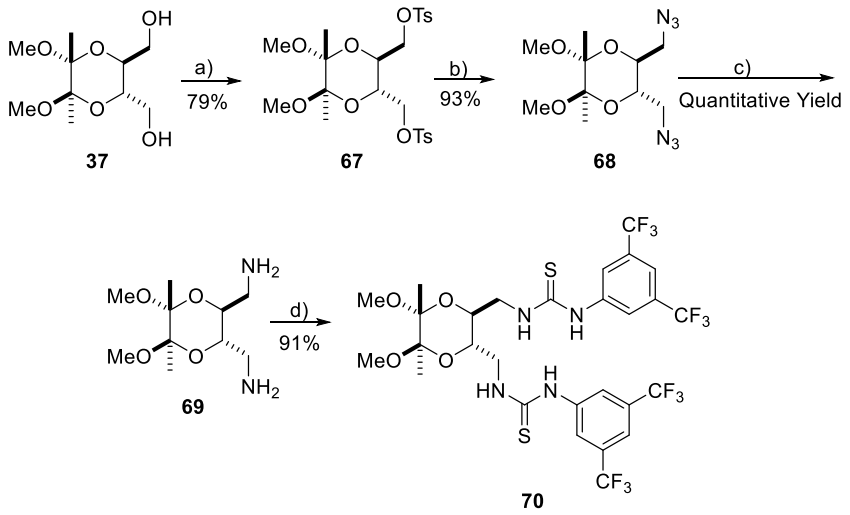
The two diastereomers derived from L-tartaric acid were converted into two mono-thioureas. Following the synthetic steps described in **Scheme 6** and we obtained compound **44**, which by reaction with the 3,5-bis(trifluoromethyl)phenyl isothiocyanate gave the corresponding thiourea **64**. Then the hydrolysis of the hydroxy protecting group afforded the desired mono-thiourea organocatalysts **65** and **66** in 91% and 99% yield, respectively (**Scheme 10**).



Scheme 10. a) 3,5-Bis(trifluoromethyl)phenyl isothiocyanate, CH_2Cl_2, rt; b) TBAF, THF, 1h.

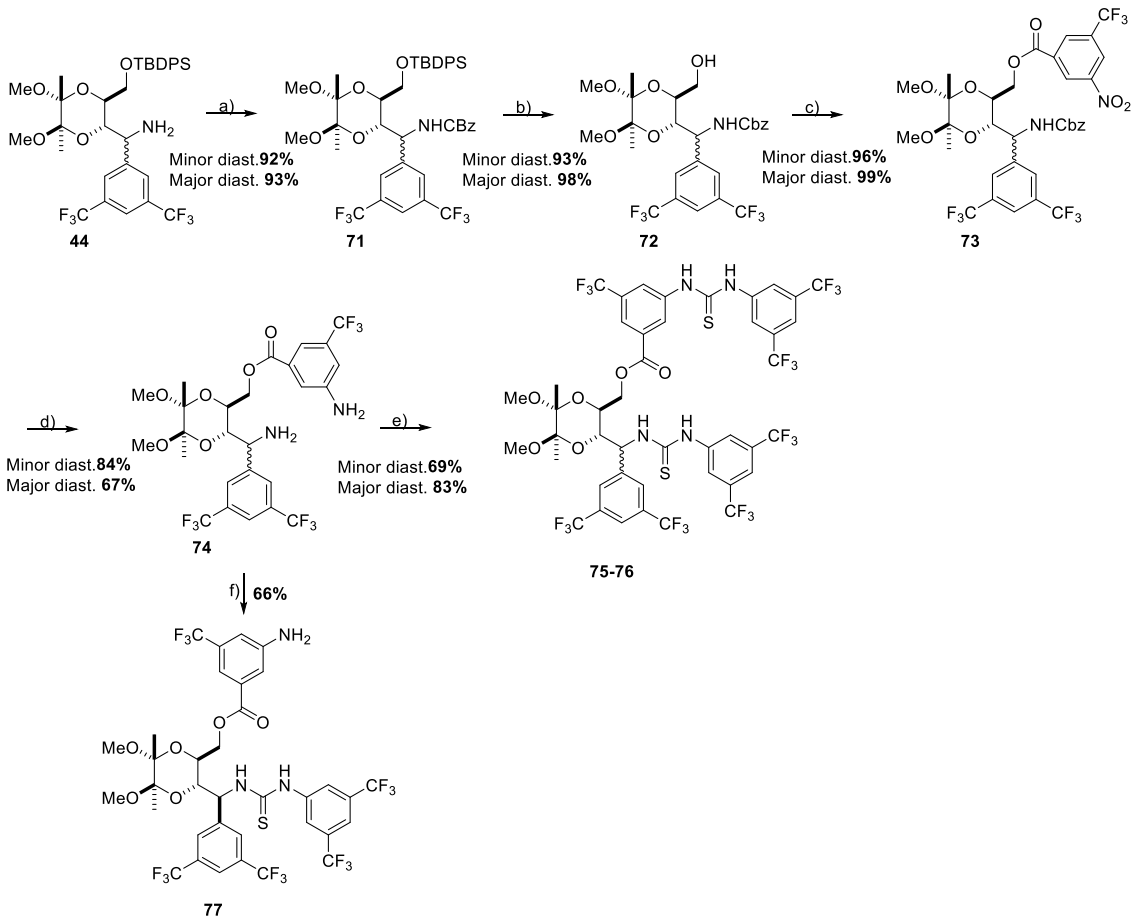
For the synthesis of bis-thiourea **70** we started with tosylation of the free hydroxyl groups with tosyl chloride, DMAP and triethylamine to obtain compound **67**. The substitution of the resulting tosyl group with sodium azide furnished diazide **68** in quantitative yield. The diamine **69** was obtained by catalytic hydrogenation with hydrogen and Pd/C and reacted immediately with 3,5-bis-(trifluoromethyl)phenyl isothiocyanate giving the corresponding bis-thiourea organocatalyst **70** in 91% yield (**Scheme 11**).

On the cyclic bis-thiourea structure the presence of the ester group is important, as explained in chapter 3, as well as the presence of a bis-thiourea, so we decided to synthesise a bis-thiourea organocatalyst based on the cyclic structure **50** using the reaction conditions already optimised.



Scheme 11. a) TsCl, Et_3N, DMAP, CH_2Cl_2, 0°C to rt, overnight, **79%**; b) NaN_3, DMF, 70°C, overnight **93%**; c) Pd/C 10%, H_2, 50 psi, AcOEt, overnight **quantitative yield**; d) 3,5-Bis(trifluoromethyl)phenyl isothiocyanate, CH_2Cl_2, rt, 1 h, **91%**.

Starting from compound **44** and protecting it with the Cbz group compound **71** was obtained (**Scheme 12**). Cleavage of the silyl group, followed by coupling with 3-nitro-5-(trifluoromethyl)benzoic acid, using EDC.HCl and DMAP in dichloromethane, afforded product **73**. The advantage of the use of the Cbz protecting group is that by catalytic hydrogenation it was possible in one step to reduce the nitro group to the amino group and to remove the amino protecting group giving the diamine **74.** This compound was immediately reacted with 3,5-bis(trifluoromethyl)phenyl isocyanate affording the new bis-thiourea organocatalysts – minor diastereomer **75** in 69% yield and major diastereomer **76** in 83% yield. By adjusting the equivalents of the isothiocyanate it was possible to obtain the corresponding mono-thiourea organocatalysts **77** with a free amino group on the aromatic ring that is a less nucleophilic amine (**Scheme 12**).

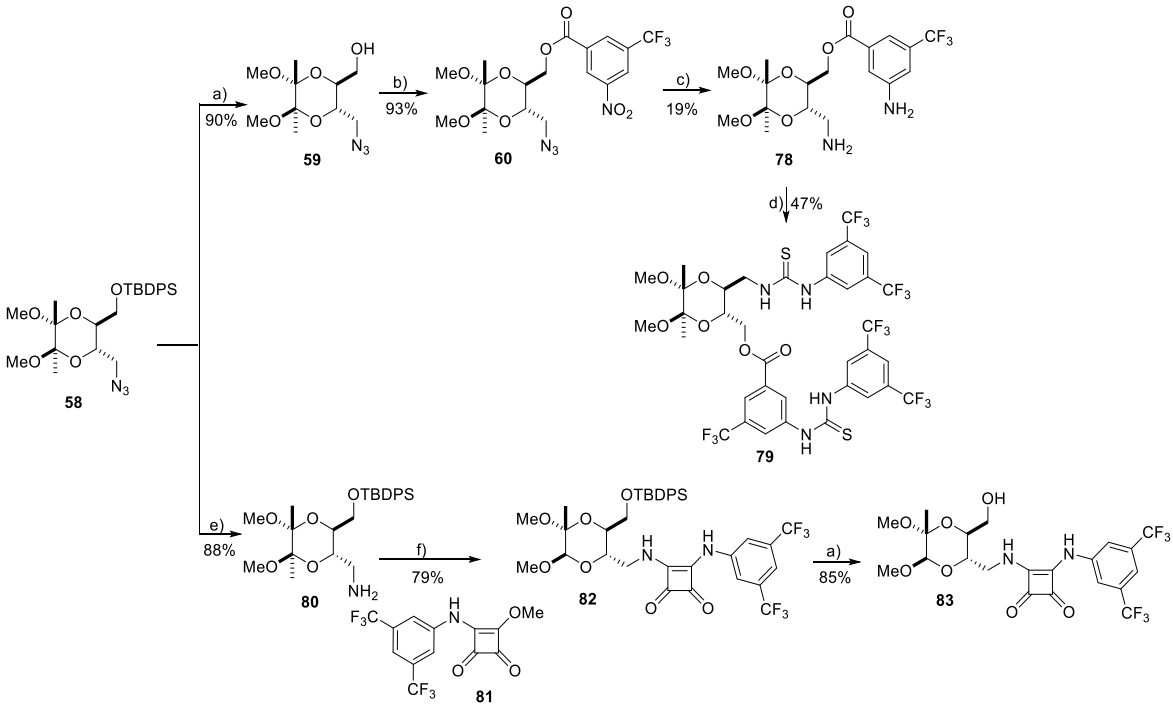


Scheme 12. a) Benzyl chloroformate 95%, Et_3N, CH_2Cl_2, 0 °C to rt, overnight; b) TBAF, THF, 1 h; c) 3-Nitro-5-(trifluoromethyl)benzoic acid, EDC.HCl, DMAP, CH_2Cl_2, 0 °C to rt, overnight; d) Pd/C 10%, H_2, 50 psi, AcOEt, 50 min; e) and f) 3,-Bis(trifluoromethyl)phenyl isothiocyanate, CH_2Cl_2, rt, 1h.

The organocatalysts **79** and **83** were also synthesised. The bis-thiourea organocatalyst **79** does not contain the additional stereocentre vicinal to the thiourea moiety in its structure and organocatalyst **83** contains a squaramide moiety. Following the optimised reaction conditions described in **Scheme 9** compound **60** was successfully obtained, which was hydrogenated to diamine **78** and reacted immediately with 3,5-bis(trifluoromethyl)phenyl isothiocyanate,

providing the desired new organocatalyst **79** in moderate yield (47%) (**Scheme 13**).

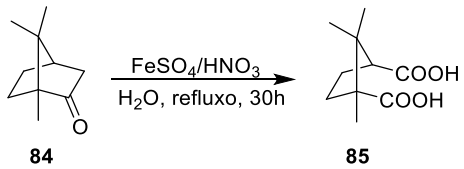
A different strategy was used to obtain catalyst **83** from compound **58**. This compound was hydrogenated to compound **89** in very good yield (88%) and the obtained amine was reacted with modified squaric acid **80**, synthesised using a literature procedure.[60] The deprotection of the hydroxyl group in compound **82** afforded the desired squaramide catalyst **83** in 85% yield (**Scheme 13**).



Scheme 13. a) TBAF, THF, 1h, **90%**; d) 3-Nitro-5-(trifluoromethyl)benzoic acid, EDC.HCl, DMAP, CH_2Cl_2, 0 °C to rt, overnight, **93%**; c) Pd/C 10%, H_2, 50 psi, AcOEt, 50 min; d) 3,5-Bis(trifluoromethyl)phenyl isothiocyanate, CH_2Cl_2, rt, 1h, **47%**; e) Pd/C 10%, H_2, 50 psi, AcOEt, 50 min **88%**; f) **46**, CH_2Cl_2, r.t, 48 h, **79%**.

2.2.2 Organocatalysts derived from (+)-camphoric acid

The (1*R*,3*S*)-1,2,2-trimetilciclopentane-1,3-dicarboxylic acid, IUPAC name of (+)-camphoric acid, is a white solid obtained from oxidation of camphor with nitric acid in the presence of iron (II) sulfate (**Scheme 14**).[61]



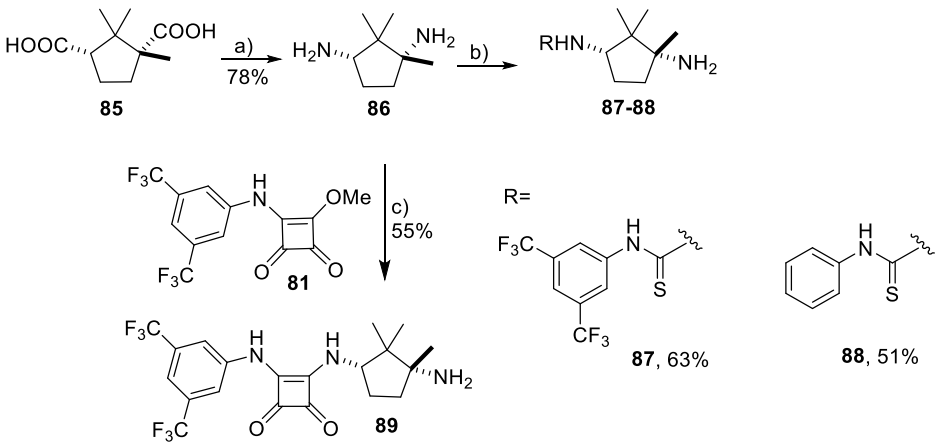
Scheme 14. Synthesis of (+)-camphoric acid

(+)-Camphoric acid was isolated for the first time by Vauquelin, a French pharmacist, but was Van 't Hoff who firstly proposed its molecular structure and optical properties, in 1874. It is an inexpensive source of chirality and readily available in both enantiomeric forms. The (+)-camphoric acid is used in the pharmaceutical industry because, like camphor, it has a powerful stimulant effect on the respiratory and vasomotor centres and on the heart itself besides it is an excellent remedy against pathological sweats, such as those occurring in pulmonary tuberculosis.[62]

Several works have been reported using chiral ligands derived from camphoric acid for enantioselective metallic catalysis with good results, namely in alkylation[63,64], ketone reduction[65] or trimethylsilylation[66]. Camphor derivatives have already been used in organocatalysis with good results[67–70].

Therefore, we decided to synthesise 1,3-diamine bifunctional thiourea and squaramide organocatalysts derived from (+)-camphoric acid. The aim was to assess the applicability of (+)-camphoric acid as a stereo directing group in the reactions studied, the role of the amino group and the relevance of the 1,3-diamine functionality.

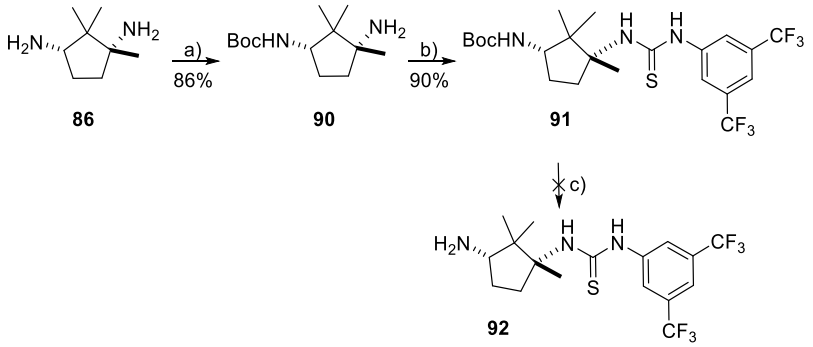
The effect of the other thiourea substituent was also studied. Finally, we compared the effect of having a thiourea or a squaramide in the catalyst structure. Diamine **86** was prepared from commercial (+)-camphoric acid through a Curtius rearrangement, following a literature procedure[63], and this diamine could be easily converted into several organocatalysts. Thioureas **87** and **88** were obtained by the reaction of 3,5-bis(trifluoromethyl)phenyl isocyanate or phenyl isocyanate, respectively, with an excess of diamine **86** in dichloromethane at room temperature. Squaramide **89** was prepared by reaction of diamine **86** with the modified squaric acid **81** (**Scheme 15**).



Scheme 15. a) NaN_3, H_2SO_4, $CHCl_3$, 55-60 °C, overnight, **78%**; b) 3,5-Bis(trifluoromethyl)phenyl isothiocyanate **63%** or phenyl isothiocyanate **51%**, CH_2Cl_2, rt, 0.5 h; c) **45**, CH_2Cl_2, r.t, 48 h, **55%**.

The synthesis of organocatalyst **92** was attempted from diamine **86** via two additional steps (**Scheme 16**). The least hindered amino group was selectively protected with the Boc group and the remaining free amine was reacted with

isothiocyanate to obtain thiourea **91** in 90% yield. Finally, an attempt was made to remove the Boc group with trifluoroacetic acid, but the product **92** was obtained in residual quantity showing that with our compounds it was not possible to remove the Boc group in good yields in the presence of a thiourea.

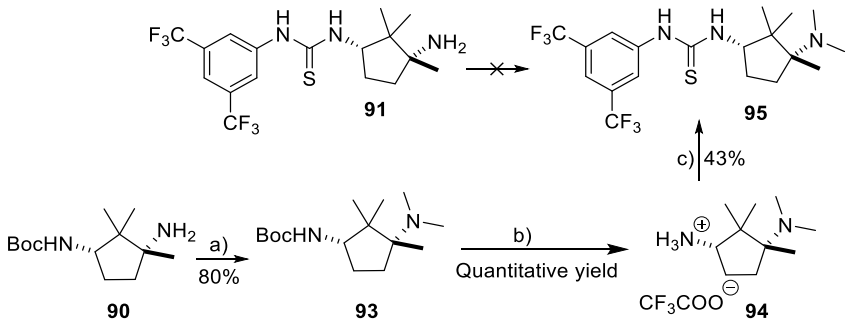


Scheme 16. a) Boc_2O, Na_2CO_3, THF:H_2O (2:1), 0 °C to rt, 24 h, **86%**; b) 3,5-Bis(trifluoromethyl)phenyl isothiocyanate, CH_2Cl_2, rt, 1h, **90%**; c) TFA, CH_2Cl_2, 0 °C to rt, 30 min.

The organocatalyst **95** with a dimethylated amine in its structure was also synthesised. According to the literature[71,72], it would be possible to obtain the desired compound in one step by reductive amination of organocatalyst **87** already synthesised using 40% aqueous formaldehyde and sodium cyanoborohydride in dichloromethane. After 6 hours a saturated solution of sodium hydrogen carbonate was added, however the product was not formed. We decided to change the synthetic procedure, however using formaldehyde, sodium cyanoborohydride and acetic acid the product was not obtained. Therefore, the reducing agent was changed to sodium borohydride, more harsh than sodium cyanoborohydride, but only the monomethylated amine was obtained in low yield. This compound reacted again with formaldehyde, sodium borohydride and acetic acid but the desired product was not obtained. Probably the problem was the steric hindrance in the compound once it has the thiourea moiety and two methyl groups in its structure (**Scheme 17**).

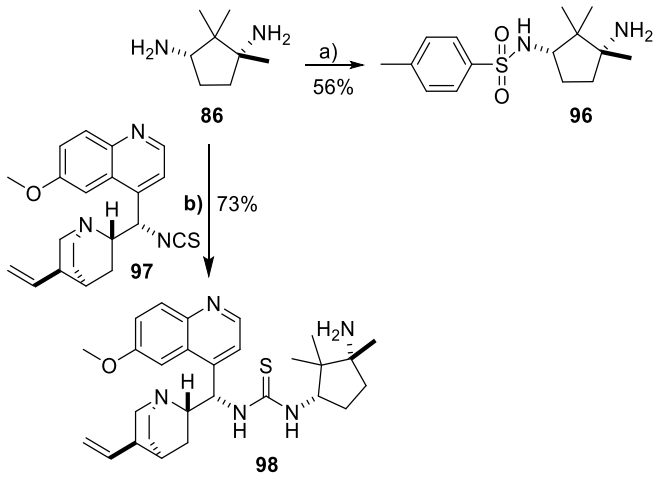
Therefore, a different approach was then used, and a new synthetic sequence was established in order to prepare the organocatalyst **95**. Dimethylation of compound **90** with methyl iodide in acetonitrile at 50 °C in a sealed tube, using potassium carbonate as base, provided compound **93**.

The Boc protecting group was then removed with TFA to afford the salt **94,** which was reacted with the corresponding isothiocyanate in the presence of potassium carbonate to give the desired catalyst **95** in 43% yield (**Scheme 17**).



Scheme 17. a) CH_3I, K_2CO_3, CH_3CN, 50 °C, 3h, **80%**; b) TFA, CH_2Cl_2, 0 °C to rt, 30 min, **quantitative yield**; c) 3,5-Bis(trifluoromethyl)phenyl isothiocyanate, K_2CO_3, CH_2Cl_2, rt, 1h, **43%**.

Sulfonamide **96**, another organocatalyst, was prepared from diamine **86** and tosyl chloride following a literature procedure.[63] (8*S*,9*S*)-9-isothiocyanate-(9-deoxy)-epiquinine **97**, synthesised from quinine,[40] have been used as a substrate in some organocatalysts with good results.[73–76] Therefore, the condensation of compound **97** with an excess of diamine **86** afforded the organocatalyst **98** (**Scheme 18**).



Scheme 18. a) TsCl, EtOH, 0 °C to rt, overnight, **32%**; b) Quinine isothiocyanate **96**, CH_2Cl_2, overnight, **73%**.

2.3 Conclusion

The principal aim of this chapter was the synthesis of organocatalysts derived from inexpensive and natural sources of chirality. Eight organocatalysts derived from L-tartaric acid and seven organocatalysts derived from (+)-camphoric acid were synthesised.

The synthesis of the cyclic bis-thiourea **50** derived from L-tartaric acid was not achieved, because the thiourea formation step was not successful. However, important knowledge was acquired to design synthetic strategies for the synthesis of the new class of mono- or bis- thioureas and squaramide organocatalysts in moderate to excellent yield.

A novel type of 1,3-diamine-derived bifunctional thiourea and squaramide organocatalysts based on (+)-camphoric acid has also been developed. The new catalysts were easily prepared in a few steps from readily available reagents, with moderate to good yield, in a flexible approach that facilitates their structure modification.

The synthesised organocatalysts will be applied in different types of asymmetric catalytic reactions and the results will be presented in the next chapters.

Acknowledgements

This work was supported by Fundação para a Ciência e Tecnologia (FCT) through a grant to M.R. (PD/BD/135494/2018) and (COVID/BD/152506/2022) and through MOSTMICRO-ITQB R&D Unit (UIDB/04612/2020, UIDP/04612/2020) and LS4FUTURE Associated Laboratory (LA/P/0087/2020) and and Centro de Química de Coimbra (UIDB/00313/2020). The NMR data was acquired at CERMAX, ITQB-NOVA, Oeiras, Portugal with equipment funded by FCT, project AAC 01/SAICT/2016.

Chapter 3

Michael Addition Reaction

This chapter contains published data.

Rénio, M.; Murtinho, D.; Ventura, M. R. New Bifunctional 1,3-Diamine Organocatalysts Derived from (+)-Camphoric Acid for Asymmetric Michael Addition of 1,3-Dicarbonyl Compounds to Nitroolefins. *Chirality* **2022**, *34*, 782-795.

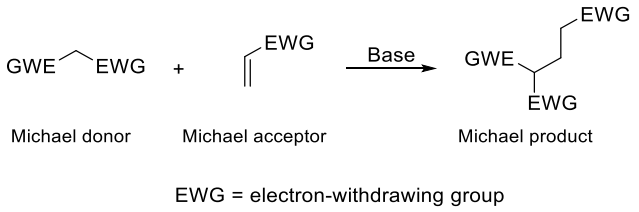
The author contributed fully to this chapter, namely in the planning of the experimental work, performing the experiments and writing the manuscript.

Abstract

The 1,3-diamine-derived bifunctional thiourea and squaramide organocatalysts derived from (+)-camphoric acid were tested in asymmetric Michael additions of 1,3-dicarbonyl compounds to several *trans*-β-nitrostyrenes. Yields up to 98% and enantiomeric excesses up to 74% and high diastereoselectivities, when applicable (*dr* up to 93:7), were obtained in these reactions showing that 1,3-diamine bifunctional thioureas derived from (+)-camphoric acid are promising chiral structural motifs for this catalytic reaction. The organocatalysts derived from L-tartaric acid were not effective for the Michael addition reaction.

3.1 Introduction

The Michael reaction is one of the most important synthetic tools and represents one of the most powerful and efficient methods for carbon-carbon bond formation. This reaction was discovered in 1887 by Artur Michael.[77] It is described as a reaction between a nucleophile (Michael donor) and an electron deficient alkene (Michael acceptor), catalised by a base, creating a new covalent bond between them, the Michael product, as depicted in **Scheme 19**.



Scheme 19. General scheme for Michael reaction

There are other types of Michael addition reactions such as phospha-Michael, oxa-Michael, thio-Michael, sulfa-Michael and aza-Michael reactions, that promote the corresponding carbon-heteroatom bond formation and are known as hetero-Michael reactions.[78]

The Michael reaction can be an important process for a stereoselective C-C bond formation since it can result in optically active products that are often key intermediates in the preparation of a large number of pharmaceutical compounds. Therefore, during the last decades, great efforts have been made to develop organocatalytic asymmetric Michael reactions and the asymmetric control of this reaction has been achieved with organocatalysts prepared from inexpensive components such as diamines,[79–84] amine-thioureas[85–89] and *Cinchona* derivatives.[90–98]

The development of chiral bifunctional hydrogen-bonding organocatalysts, which can activate nucleophiles and electrophiles at the same time, have emerged as powerful organocatalysts. Since the pioneering work of Sigman and Jacobsen,[18] Schreiner and Wittkopp,[25] and Takemoto *et al*,[30,32,99,100] bifunctional amine-thioureas have become some of the most versatile catalysts for many enantioselective reactions; in general, the 1,2-diamine moiety is present in several efficient bifunctional organocatalysts. Despite their large utility, these organocatalysts are derived from a very limited range of chiral structural scaffolds such as cyclohexane-1,2-diamine, 1,10-binaphthyl-2,20-diamine or *cinchona* alkaloids (**Figure 25**).[78]

The bifunctional aminothiourea organocatalysts **16**, **99** and **100** developed by Takemoto were applied to a wide range of diastereo- and enantioselective reactions: Michael reaction of 1,3-dicarbonyl compounds with nitroolefins, aza Henry reaction of nitroalkanes with *N*-Boc imines and hydrazination of cyclic β-keto esters (**Figure 25**).[30,32,99,100] A bifunctional 1,2-diamine thiourea organocatalyst derived from cyclohexane-1,2-diamine **101** was used by Yan for

the conjugate addition of aldehydes and ketones to nitroalkenes (**Figure 25**).[101] Highly efficient Michael reactions of malonates with nitroalkenes catalysed by novel chiral thioureas derived from optically pure BINOL **102** were reported by Liu[102] and *cinchona* alkaloid-derived thioureas **103** were used as the bifunctional catalysts for the same transformation.[103]

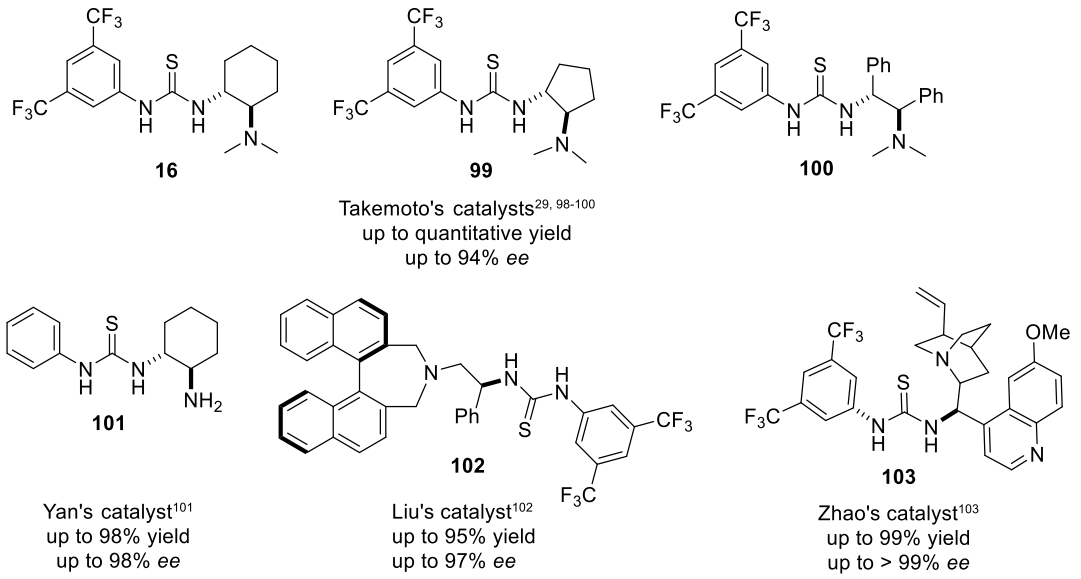


Figure 25. 1,2–diamine derived bifunctional thiourea organocatalysts reported in the literature.

Although the organocatalysts derived from these chiral structural motifs have been successfully applied in the Michael addition reaction, it is crucial to explore efficient alternatives to be applied in this reaction because these classes of chiral and stereodefined 1,2-diamines readily available from the chiral pool are limited. In this chapter, we proposed to evaluate two different types of organocatalysts – 1,3-diamine organocatalysts derived from (+)-camphoric acid and the organocatalysts derived from L-tartaric acid.

3.2 Results and Discussion

3.2.1 1,3-Diamine organocatalysts derived from (+)-camphoric acid for asymmetric Michael addition

After a revision of the literature, it was possible to understand that efficient 1,3- and 1,4-diamine thioureas have been less explored than 1,2-diamine thioureas. Self-assembled proline and 1,3-diamine thioureas **104**, used as cocatalyst,[104] complex and synthetic challenging chiral cyclobutane containing 1,3-diamines[105] **105** and ferrocene-based bifunctional amine thioureas[106,107] **106** and **107** were applied to Michael addition of 1,3-dicarbonyl compounds and aldehydes to nitroolefins (**Figure 26**). Bifunctional 1,3-diamine thiourea and squaramide organocatalysts derived from camphor **108** and **109** (**Figure 26**) were also used for the same transformations; however, these organocatalysts required five to nine synthetic steps.[67,70] Likewise, 1,3-diamine-tethered guanidium/bisthiourea organocatalysts **110** have been used in Michael reactions between 1,3-dicarbonyl compounds and nitroolefins,[108] and in the enantioselective phospha-Michael addition of diphenyl phosphonate to nitroolefins (**Figure 26**).[109]

The lack of 1,3-diamine thiourea organocatalysts encouraged us to further investigate the structure/activity relationship of the bifunctional amine-thioureas and to probe the efficacy of 1,3-diamine thioureas as catalysts (**Figure 27**).

Firstly, we examined the efficacy of our synthesised bifunctional 1,3-diamine thioureas in the Michael reaction between different Michael donors **111a-f** and *trans*-β-nitrostyrene **112a** using organocatalyst **87**, that was more simple and easy to synthesise, following the literature conditions,**Table 1**.[41,67,100,101,110,111]

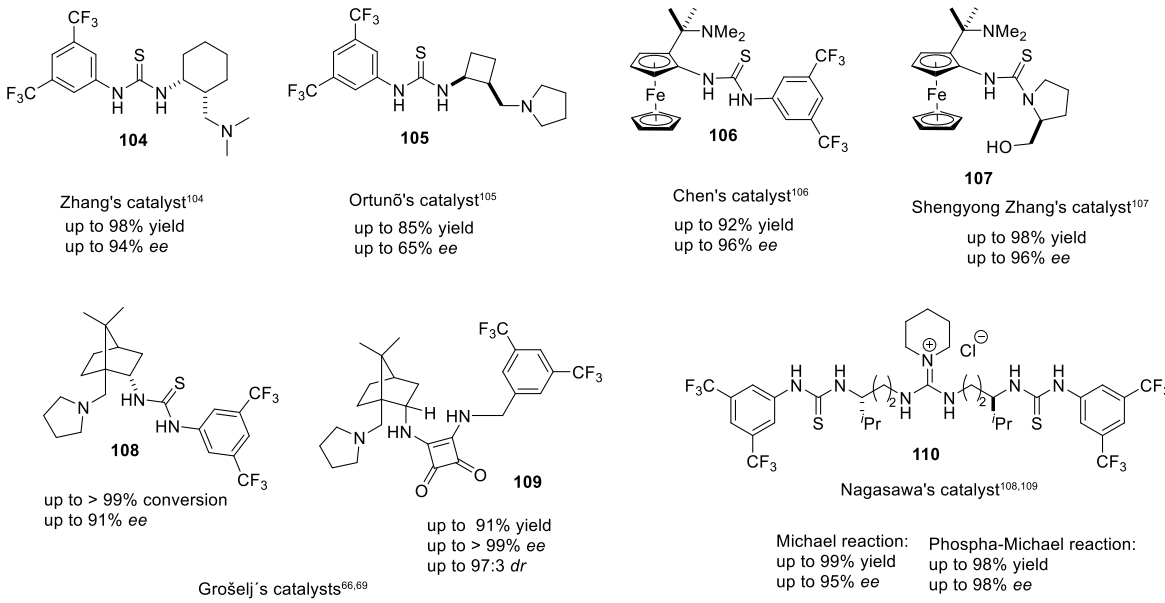


Figure 26. 1,3- and 1,4-diamine thiourea organocatalysts reported in the literature.

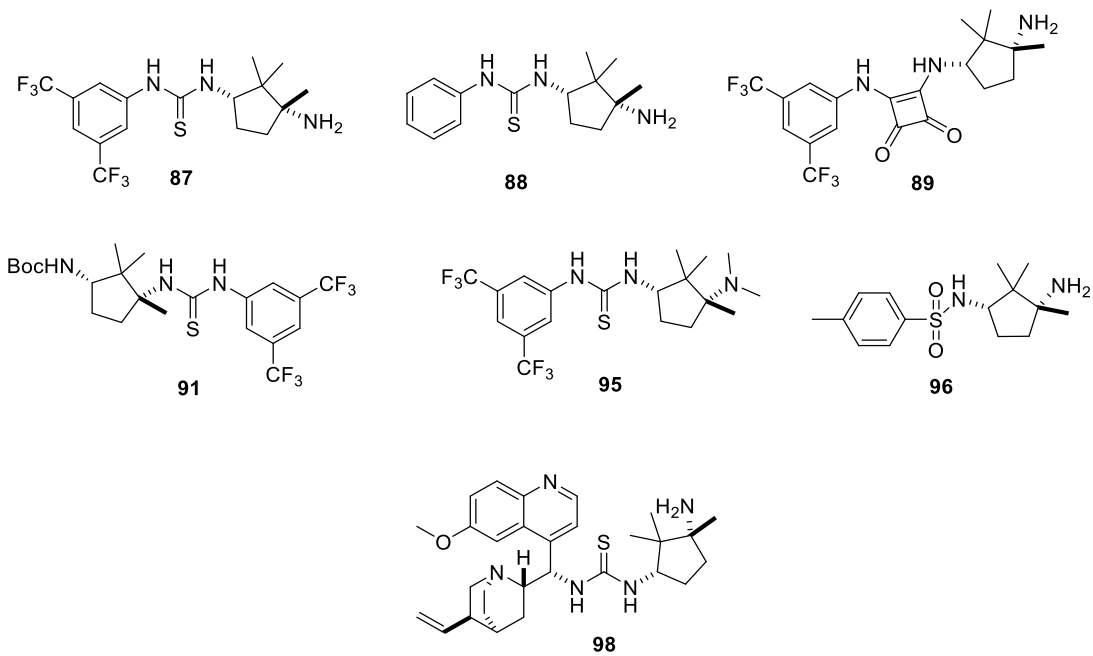
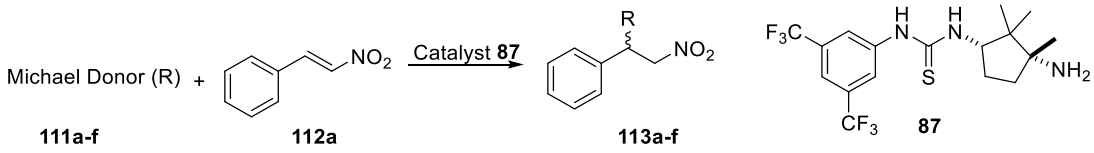
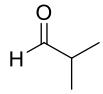
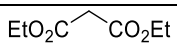
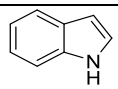
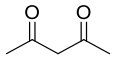


Figure 27. Synthesised organocatalysts derived from (+)-camphoric acid

Table 1. Michael substrate study



Entry[a]	Michael Donor	Solvent	Additive	Loading of catalyst (%mol)	Yield[b] (%)	*ee*[c] (%)
1	 **111a**	$CHCl_3$	DMAP	20	31	22 (*S*)
2	 **111b**	Toluene	Et_3N	10	No Product	
3	 **111c**	CH_2Cl_2	-	20	54	*rac*
4	 **111d**	Toluene	-	5	61	19 (*R*)
5	 **111e**	1,2-Dioxane	Benzoic acid	15	No Product	
6	 **111f**	CH_2Cl_2	-	15	No Product	

[a]All reactions were performed at 25ºC for 24h, except with substrate **111c** which reaction time was 66h and substrate **111f** which was 96h.

[b]Isolated Yield

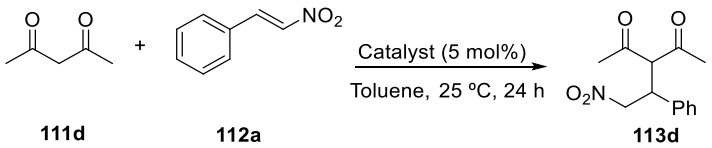
[c]Determined by HPLC on a chiral column (the full conditions are described in the experimental procedures chapter)

The obtained results are presented in **Table 1** and show that our organocatalyst is able to promote the Michael reaction with some Michael donors such as isobutyraldehyde **111a** and acetylacetone **111d** in moderate yield and enantioselectivity (entries 1 and 4). With Michael donors **111b, 111e** and **111f** it was not possible to obtain the Michael addition product (entries 2, 5 and 6) and using indole **111c** as a donor the Friedel-Craft alkylation gave the desired product but without selectivity (entry 3).

The most promising results were obtained with acetylacetone (entry 6 vs. entries 1-5) giving the desired Michael product **113d** in 61% of yield and 19% of *ee*, using only 5 mol% of catalyst (**Table 1**, entry 4). Therefore, we decided to use this Michael donor for the optimisation of the reaction conditions, including organocatalyst, solvent and temperature.

Thereby, in order to optimise the reaction conditions, the synthesised organocatalysts present in **Figure 27** were evaluated in the Michael reaction of acetylacetone **111d** and *trans*-β-nitrostyrene **112a** in toluene at 25 °C for 24 h. The obtained results are presented in **Table 2**.

Table 2. Screening of catalysts



111d **112a** **113d**

Entry[a]	Catalyst	Yield[c] (%)	*ee*[d] (%)
1	**87**	61	19 (*R*)
2	**88**	22	19 (*R*)
3	**89**	61	14 (*R*)
4	**91**[b]	69	*Rac*
5	**95**	14	5 (*R*)
6	**96**	26	14 (*R*)
7	**98**	82	45 (*S*)
8[b]	**Schreiner Thiourea**	84	*Rac*

[a]Performed on *trans*-β-nitrostyrene **112a** (0.14 mmol) and acetylacetone **111d** (0.28 mmol, 2 eq.) at room temperature for 24 h in toluene (0.37 mL) using 5 mol% of catalyst

[b]The use of Et_3N was necessary

[c]Isolated Yield

[d]*R* Enantiomer was determined by HPLC Chiralpack AD-H column at 205 nm (hexane/iPrOH = 90/10, 1 mL/min t_R(minor) = 10.9 min, t_R(major) = 14.5 min). and *S* Enantiomer was determined by HPLC with Chiralpack AD-H column at 205 nm (hexane/iPrOH = 90/10, 1 mL/min t_R(major) = 10.9 min, t_R(minor) = 14.5 min).

All the organocatalysts tested were efficient for this catalytic transformation, with yields ranging from 14% to 82%. The presence of CF_3 groups played a decisive role in the formation of the product (entry 1 vs entry 2), probably because these groups make the thiourea more efficient in the activation of the electrophile.[112]

A racemic product was obtained with catalyst **91**, suggesting that the amino functionality is important for enantioselectivity induction (entry 4). In this case, for the formation of product the use of triethylamine was required.

A low yield (14%) of the product was obtained with the dimethylated catalyst **95**, which shows that the presence of a free amino group is important for the formation of the product (entry 5 vs entry 1). Organocatalyst **98** was the best one for this reaction, both in terms of yield (82%) and enantioselectivity (*ee* 45%) (entry 7 vs. entries 1-6). The quinine moiety provided a large conformationally restricting skeleton that appears to be beneficial for chiral induction. The enantiomer *S* was the major product using catalyst **98** by contrast with other catalysts which afforded the enantiomer *R*, probably due to the configuration of C8 (*S*) and C9 (*S*) of the quinine-derived isothiocyanate **97**.

Although it will be necessary more precise mechanistic studies a possible transition state representing the addition of acetylacetone to *trans*-β-nitrostyrene in the presence of organocatalyst **98** is proposed in **Figure 28**. The thiourea moiety present on the catalyst interacts with the nitro group of the nitroalkene through hydrogen bonding and at the same time, the primary amine of the catalyst deprotonated an acidic proton of the acetylacetone generating a ternary complex. The *Re*-face approach of the nitroolefin accounts for the observed absolute *S* configuration of the conjugate adduct. All the other catalysts afforded the *R* Michael products. Additionally, the synergistic steric hindrance from the chiral quinine moiety of organocatalyst **98** may be responsible for the increased stereocontrol of the Michael addition reaction.

Schreiner catalyst afforded the product in high yield (84%) but as a racemic mixture, as expected (entry 8).

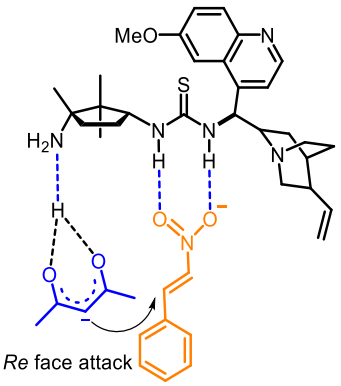
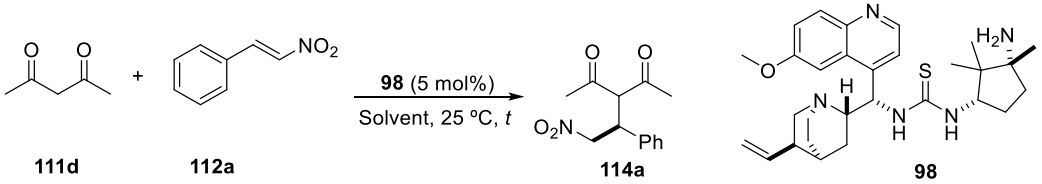


Figure 28. Proposed transition state

Using the best organocatalyst **98** the effect of the solvent was tested in this reaction. The results are presented in **Table 3** and reveal that reactions generally proceeded with moderate to excellent yields (63-89%) and good enantiomeric excess (*ee* 44-68%).

The best yields were obtained with polar aprotic solvents, CH_3CN and AcOEt (**Table 3**, entries 4 and 9). With polar protic solvents, such as methanol, the product was obtained with a high yield but low enantiomeric excess (entry 5). When the reaction was performed using acetylacetone as the solvent the consumption of the nitroalkene was very fast, in two hours (entry 10). In terms of enantioselectivity, the best solvents for organocatalyst **98** were found to be chlorinated solvents (entries 2 and 3). However, chloroform provided the desired product in a higher *ee*, 68%, and for this reason it was chosen as the solvent for this catalytic reaction. Performing the reaction at 0°C the enantioselectivity slightly increased but with a decrease in the yield (entry 11).

Table 3. Optimization of the reaction conditions for the Michael Reaction



111d **112a** **114a** **98**

Entry[a]	Solvent	*t* (h)	Yield[c] (%)	*ee*[d] (%)
1	Toluene	24	82	45
2	CH_2Cl_2	16	78	60
3	$CHCl_3$	19	80	68
4	CH_3CN	24	88	50
5	CH_3OH	3	82	18
6	THF	24	84	44
7	1,4-Dioxane	24	78	52
8	Et_2O	4	63	48
9	AcOEt	24	89	57
10	Acetylacetone	2	73	57
11[b]	$CHCl_3$	24	72	71

[a]Performed on *trans*-β-nitrostyrene **112a** (0.14 mmol) and acetylacetone **111d** (0.28 mmol, 2 eq.) at room temperature for 24 h in different solvents (0.37 mL) using 5 mol% of catalyst **98**

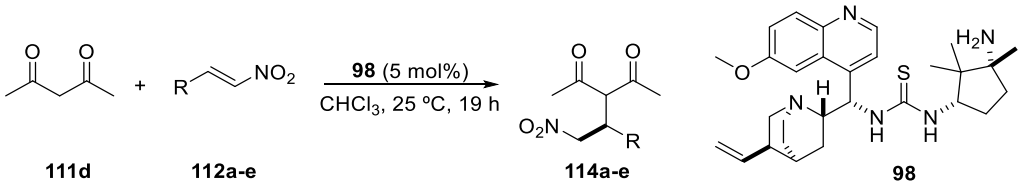
[b]The reaction was performed at 0 °C

[c]Isolated Yield

[d]Determined by HPLC with Chiralpack AD-H column at 205 nm (hexane/iPrOH = 90/10, 1 mL/min t_R(major) = 10.9 min, t_R(minor) = 14.5 min).

To evaluate the scope of the catalyst **98**, a series of *trans*-β-nitroalkenes were reacted with acetylacetone under the best reaction conditions (room temperature and $CHCl_3$ as solvent). The results are presented in **Table 4**.

Table 4. Variation of nitroalkenes **112a-e** in reactions with acetylacetone (**111d**)



111d **112a-e** **114a-e** **98**

Entry[a]	R	Product	Yield[b] (%)	*ee*[c] (%)
1	Ph (**112a**)	**114a**	80	68
2	*p*-MeO-Ph (**112b**)	**114b**	97	66
3	*p*-Cl-Ph (**112c**)	**114c**	68	65
4	*o*-Cl-Ph (**112d**)	**114d**	88	73
5	2-furyl (**112e**)	**114e**	91	56

[a]Performed on nitroalkene **112a-e** (0.14 mmol) and acetylacetone **111b** (0.28 mmol, 2 eq.) at room temperature for 19 h in $CHCl_3$ (0.37 mL) using 5 mol% of catalyst **98**

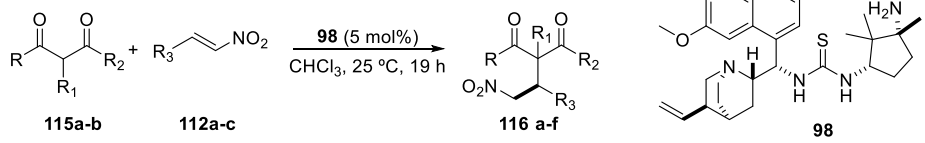
[b]Isolated Yield

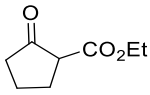
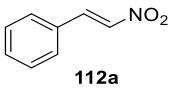
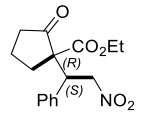
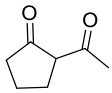
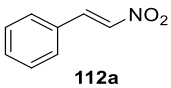
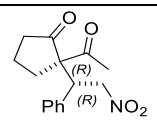
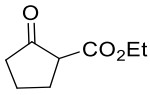
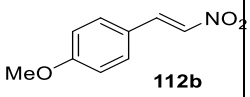
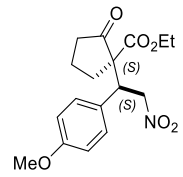
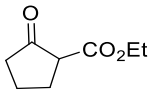
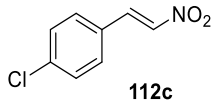
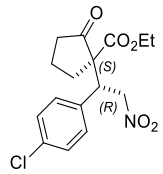
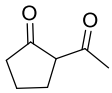
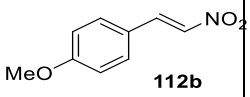
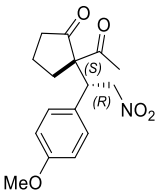
[c]Determined by HPLC on a chiral column AD-H (for more details please see the Experimental Procedures chapter)

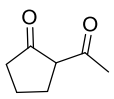
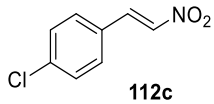
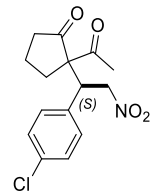
All nitroalkenes showed good yields (68-97%), nonetheless, a moderate decrease was observed in the presence of electron-withdrawing substituents in *para* position of the aromatic ring (entry 3). The best *ee* was obtained for *o*-chlorophenyl substituted β-nitroalkene (entry 4) and the worst was obtained with the furyl substituted β-nitroalkene (entry 5). In all cases, the absolute configuration of the major enantiomer was assigned as (*S*) by comparison of the retention times with reported values.[67]

With optimal conditions in hand, the substrate scope of the enantioselective Michael addition reaction of 1,3-diketones or β-keto esters and nitroalkenes **115a, 115b** and **115c** using compound **98** as chiral organocatalyst was investigated, the results are presented in **Table 5**.

Table 5. Variation of nucleophile **115a-c** in reactions with nitrostyrenes **112a**, **b** and **c**



Entry[a]	Nucleophile	Nitroalkene	Product	Yield[b] (%)	*dr*[d]	*ee*[c] (%)
1	 **115a**	 **112a**	 major diastereomer **116a**	62	91:9	74 (*R*,*S*) 36 (*S*,*S*)
2	 **115b**	 **112a**	 major diastereomer **116b**	93	67:33	63 (*R*,*R*) 69 (*S*,*R*)
3	 **115a**	 **112b**	 major diastereomer **116c**	92	89:11	74 (*S*,*S*) 25 (*R*,*S*)
4	 **115a**	 **112c**	 major diastereomer **116d**	98	93:7	71 (*S*,*R*) 23 (*R*,*R*)
5	 **115b**	 **112b**	 major diastereomer **116e**	97	80:20	58 (*S*,*R*) 47 (*R*,*S*)

6	 **115b**	 **112c**	 major diastereomer **116f**	85	67:33	36 (*S*) 41 (*S*)

[a]Performed on nitroalkene **112a-c** (0.14 mmol) and nucleophile **115a-b** (0.28 mmol, 2 eq.) at room temperature for 19 h in $CHCl_3$ (0.37 mL) using 5 mol% of catalyst **98**.

[b]Isolated Yield

[c]Determined by HPLC on a chiral column (for more details please see the Experimental Procedures chapter)

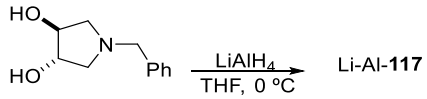
It should be noted that once again all reactions proceeded with good to excellent yield (62-98 %), whilst mixtures of diastereomers were formed in all reactions. In general, reactions using 2-oxocyclopentane-1-carboxylate **115a** as nucleophile provided higher diastereoselectivity and enantioselectivity than reactions using 2-acetylcyclopentanone **115b** (**Table 5** entries 1, 3 and 4 *vs.* entries 2, 5 and 6). Using nucleophile **115a** it was observed that the presence of substituents on the aromatic ring of the nitroalkene had not a significant influence on the diastereoselectivity or the enantioselectivity of the products. However, the yield increased with the presence of substituents on the aromatic ring of the nitroalkene (entry 1 *vs.* entries 3 and 4). Using nucleophile **115b** the presence of *para*-electron-donating substituents in the nitroalkene increased the diastereoselectivity (*dr* 80:20) (entry 5 *vs.* entries 2 and 6). On the other hand, the enantioselectivity decreased with the presence of substituents on the aromatic ring, especially with *para*-electron-withdrawing substituents (entry 2 *vs.* entry 6).

The absolute configuration of the obtained products was assigned based on a comparison of the HPLC chromatograms with those reported in the literature.[67,113,114] Compound **116f** has not been previously described, therefore the absolute configuration of the diastereomeric mixture was determined by measuring its specific rotation and comparing it with the described compounds of

the same family.[67] The specific rotation of the compound **116f** was $[\alpha]_D^{20}$= +10.53 (*c* 0.3, CH_2Cl_2) and these compounds with (+) specific rotation have (*S*) configuration, therefore we assumed that the absolute configuration of the diastereomeric mixture **116f** is (*S*) at the newly created asymmetric centre.

3.2.2 Organocatalysts derived from L-tartaric acid for asymmetric Michael additions

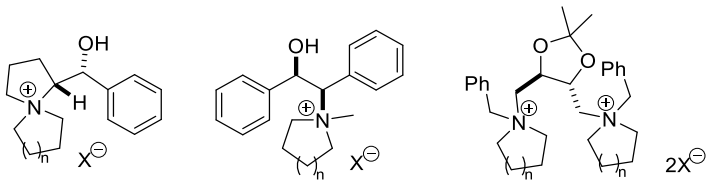
The principal aim of this chapter was the development of new chiral structural scaffolds that could be used in the Michael addition reaction. After a revision of the literature, we realised that the use of the catalysts derived from L-tartaric acid for Michael addition reactions is very rare. Chiral amines derived from L-tartaric acid were used in the Michael addition reaction of cyclohexanone to *trans*-β-nitrostyrene with high diastereoselectivity (syn / anti = 92:8) and moderate *ee* (syn: 30 %).[115] The aminodiol derived from natural L-tartaric acid **117** was reacted with $LiAlH_4$ (**Scheme 20**) and used as heterobimetallic catalyst to promote asymmetric Michael additions of malonic esters, thiophenols and nitroalkanes to cyclic and acyclic enones with excellent yields (95-98%) but low enantiomeric excess (5-32%).[116]



117 **118**

Scheme 20. Synthesis of heterobimetallic catalyst

Chiral phase transfer catalysts derived from proline, mandelic acid and L-tartaric acid **119-124** (**Figure 29**) were also used in the enantioselective Michael reaction between various malonate esters and benzalacetophenone with good results (yields up to 97% and *ee* up to 94%).[117]



119 n=1, X=Br
120 n=2, X= Br

121 n=1, X=Br
122 n=3, X= Br

123 n=1, X=Br
124 n=2, X= Br

Figure 29. Chiral phase transfer catalysts [117]

Thereby, we decided to apply some of the synthesised organocatalysts derived from L-tartaric acid, bearing a thiourea moiety in their structure, in the enantioselective Michael addition (**Figure 30**).

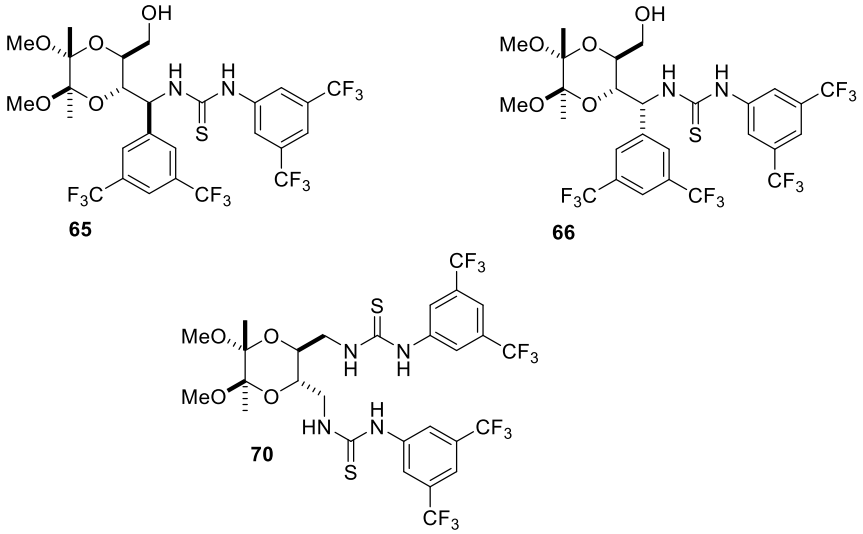
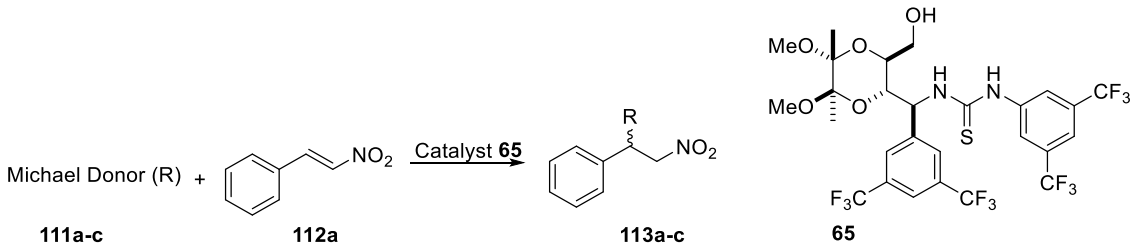


Figure 30. Synthesised organocatalysts derived from L-tartaric acid.

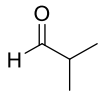
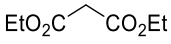
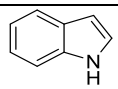
To evaluate the efficiency of organocatalysts derived from L-tartaric acid in the Michael addition reaction we applied the catalyst **65** in the reaction between

different Michael donors **111a-c** and *trans*-β-nitrostyrene **112a** following the literature conditions expressed in **Table 6**.[100,101,111]

Table 6. Michael substrate study



111a-c **112a** **113a-c** **65**

Entry[a]	Michael Donor	Solvent	Additive	Loading of catalyst (%mol)	Yield[b] (%)	*ee*[c] (%)
1	 **111a**	$CHCl_3$	DMAP	20	7	6 (*S*)
2	 **111b**	Toluene	Et_3N	10	46	16 (*S*)
3	 **111c**	CH_2Cl_2	-	20	48	32 (*S*)

[a]All reactions were performed at 25ºC for 24h, except in case of substrate **111c** that reaction time was 66h

[b]The use of Et_3N was necessary

[c]Isolated Yield

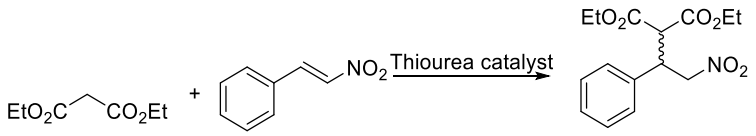
[d]Determined by HPLC on a chiral column (The complete conditions are described in the experimental procedures chapter)

The obtained results are presented in **Table 6**. All Michael donors were converted into the product, nonetheless, isobutyraldehyde **111a** proved not to be a good Michael donor giving the product in low yield (7%) and *ee* (6%, entry 1).

The results obtained with Michael donors **111b** and **111c** were promising, affording the catalytic product in moderate yield, 46% and 48%, respectively, and moderate *ee* (16% and 32%, respectively) (entries 2 and 3). In order to improve the results, the organocatalysts **66** and **70** were tested in this reaction.

The organocatalysts derived from L-tartaric acid were tested in the Michael reaction of diethyl malonate **111b** and *trans*-β-nitrostyrene **112a** (the use of triethylamine was required), in dichloromethane at 25 °C for 48 h. The obtained results are presented in **Table 7**.

Table 7. Screening of catalysts using diethyl malonate **111b** as Michael Donor



111b **112a** **113b**

Entry[a]	Catalyst	Yield[b] (%)	*ee*[c] (%)
1	**65**	46	16 (*S*)
2	**66**	50	12 (*R*)
3	**70**	No Product	

[a]Performed on nitroalkene **112a** (0.19 mmol), diethyl malonate **111b** (0.37 mmol, 2 eq.) and Et_3N (0.02 mmol, 0.1 eq.) at room temperature for 48 h in Toluene (1 mL) using 10 mol% of catalyst.

[b]Isolated Yield

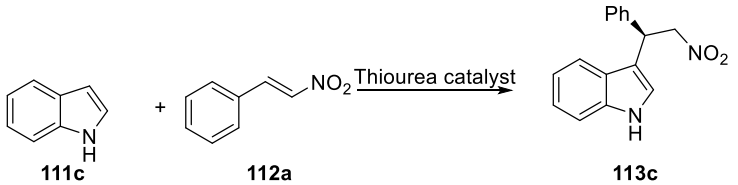
[c]Determined by HPLC with Chiralpack AD-H column at 254 nm ((Hexane/*i*PrOH = 90/10, 1 mL/min t_R = 10.9 min, t_R = 14.5 min).

The obtained results show that the bis-thiourea **70** was not able to catalyse this transformation, probably the presence of two thioureas caused steric hindrance and difficulted the formation of the transition state (**Table 7** entry 3 vs. entries 1 and 2).

Organocatalysts **65** and **66** gave the desired Michael product in moderate yield and low *ee* (entries 1 and 2), but it should be noted that, although this type of catalysts is not efficient for Michael reaction, the stereochemistry of the organocatalyst influenced the stereochemistry of the product (entries 1 and 2). Opposite configurations in the asymmetric centre vicinal to the thiourea moiety favoured the formation of opposite enantiomers of the product, albeit with low *ee*.

The synthesised organocatalysts were also tested in Friedel-Crafts alkylation of indole **111c** with *trans*-β-nitrostyrene acceptor **112a** in dichloromethane at 25 °C for 72 h. The results are presented in **Table 8**.

Table 8. Screening of catalysts in Friedel Craft Reaction



111c **112a** **113c**

Entry[a]	Catalyst	Yield[b] (%)	*ee*[c] (%)
1	**65**	48	32 (*S*)
2	**66**	43	*rac*
3	**70**	89	

[a]Performed on nitroalkene **112a** (0.19 mmol), diethyl indole **111c** (0.29 mmol, 1.5 eq.) at room temperature for 72 h in CH_2Cl_2 (1 mL) using 20 mol% of catalyst.

[b]Isolated Yield

[c]Determined by HPLC with Chiralpack AD-H column at 254 nm ((Hexane/ iPrOH = 90/10, 1 mL/min t_R = 44.4 min, t_R = 49.4 min

All organocatalysts afforded the desired product in moderate to good yield, up to 89%. However, only thiourea catalyst **65** provided the compound **113c** enantioselectively (*ee* 32%), albeit the catalyst **66** is very similar to this one, it

afforded the desired product without selectivity, which probably indicates the importance of the *S* configuration of the asymmetric centre vicinal to the thiourea to induce selectivity.

Interestingly, with organocatalyst **70** the product was obtained in 89% yield (**Table 8** entry 3), in this case the presence of the bis-thiourea was important. However, the low enantioselectivity in the presence of the three organocatalysts suggest that they need further structural tuning to be successfully applied in these Michael reactions. Organocatalyst **70** lacks asymmetric centres vicinal to the thioureas and this might be one of the reasons for obtention of the racemic product (entry 3).

3.3 Conclusion

The organocatalysts derived from (+)-camphoric acid were successfully applied on the enantioselective Michael addition of 1,3-dicarbonyl compounds to *trans*-β-nitrostyrene acceptors. The organocatalyst **98** provided the chiral product in high yields (up to 98%), good enantioselectivities (*ee* up to 74%) and high diastereoselectivities, when applicable (*dr* up to 93:7). These results suggest that 1,3-diamine-derived bifunctional thiourea organocatalysts have potential for the application in Michael additions. The (+)-camphoric acid moiety has clearly an influence in the stereoselective outcome of the Michael reactions studied, however by changing the other substituent it was possible to tune the catalyst in order to obtain either the *R* or *S* product. Quinine-derived moiety in catalyst **98** induced the formation of the *S* Michael adduct, showing that this group also participated in the stereocontrol of the reaction due to its bulkiness and probably due to the presence of additional stereocentres.

Through this approach, it was possible to prove that 1,3-diamine-derived bifunctional thiourea and squaramide organocatalysts are capable of promoting

the enantioselective Michael addition of 1,3-dicarbonyl compounds to *trans*-β-nitrostyrene acceptors, although the obtained results were not excellent.

The organocatalysts derived from L-tartaric acid have not provided good results in Michael and Friedel-Crafts reactions. In the Michael reaction of diethyl malonate with *trans*-β-nitrostyrene catalysed by the thiourea organocatalysts **65** and **66** the stereochemistry of the catalyst influenced the stereochemistry of the product. Thereby, even though the enantiomeric excesses were low, by tuning the catalyst it was possible to obtain either the *R* or *S* product. The organocatalyst **70** is not effective in the enantioselective Friedel-Crafts reaction, catalysing the transformation without differentiation of the enantiotopic faces of the substrate and thus resulting in a racemic product. Using the organocatalyst **65** it was possible to obtain the product with 32% *ee*, proving the importance of the presence of asymmetric centres vicinal to the thioureas, namely with *S* configuration.

Acknowledgements

This work was supported by Fundação para a Ciência e Tecnologia (FCT) through a grant to M.R. (PD/BD/135494/2018) and (COVID/BD/152506/2022) and through MOSTMICRO-ITQB R&D Unit (UIDB/04612/2020, UIDP/04612/2020) and LS4FUTURE Associated Laboratory (LA/P/0087/2020) and and Centro de Química de Coimbra (UIDB/00313/2020). The NMR data was acquired at CERMAX, ITQB-NOVA, Oeiras, Portugal with equipment funded by FCT, project AAC 01/SAICT/2016.

Chapter 4

Glycosylation Reaction

This chapter contains unpublished data and in preparation publish data.

The author contributed fully to this chapter, namely in the planning of the experimental work, performing the experiments and writing the manuscript.

Abstract

The synthesised organocatalysts derived from L-tartaric acid were able to activate glycosyl phosphates and glycosyl thrichloroacetamidates, in a cooperative phenomenon with Brønsted acids, for stereoselective nucleophilic substitution reactions with broad functional group compatibility under mild conditions. The influence of different functional groups and the proximity of the asymmetric centre to the catalytic important atoms for the stereoselective outcome of the glycosylation reactions was studied. Bis-thiourea **75** promoted the formation of 1,2-*cis* glycosides in 41- 85% yield and high diastereoselectivity (up to α:β 83:17) from glycosyl phosphates and 1,2-*trans* glycosides in 33-58% yield and high diastereoselectivity (up to β:α 82:18) from glycosyl thrichloroacetamidates.

4.1 Introduction

Carbohydrates can be defined as mono-, oligo- and polysaccharides,[118] they are the most abundant class of biomolecules and exhibit a colossal structural and function diversity.[119,120] This class of molecules are present in all living organisms and for this reason they have an important role in many biological processes, such as cellular respiration, cell-cell interaction and adhesion, in modulating transcription and complex signal transduction cascades, inflammation and post-translational modifications.[121] These numerous roles have led carbohydrates to be key compounds for drug and vaccine development and in the development of diagnostic tools. They are also important in materials science, one example is that certain alkyl glycosides have potential as biodegradable surfactants.[122]

Due to this great importance, a huge effort has been employed to develop new methods and strategies for the chemical synthesis of glycomolecules, mainly in the stereo and regioselective formation of glycosidic bonds.

The chemical synthesis of carbohydrates typically involves a reaction between a fully protected glycosyl donor with a leaving group at its anomeric centre and a suitably protected glycosyl acceptor, which generally contains only one free hydroxy group; this transformation is commonly named glycosylation reaction and a new glycosidic bond is formed.[123]

However, the details of this very important reaction remain not all understood, except in the case of the neighbouring group participation, at C-2.[124–127] According to the literature, the mechanism of glycosylation occurs as a continuum of mechanisms possibly spanning the entire range between the pure S_N2 (bimolecular) mechanism at the one extreme and the S_N1 (unimolecular) mechanism with free oxocarbenium ions at the other, in other words, the reaction mechanism is a mixture between S_N1 and S_N2 reactions (**Figure 31**).[128]

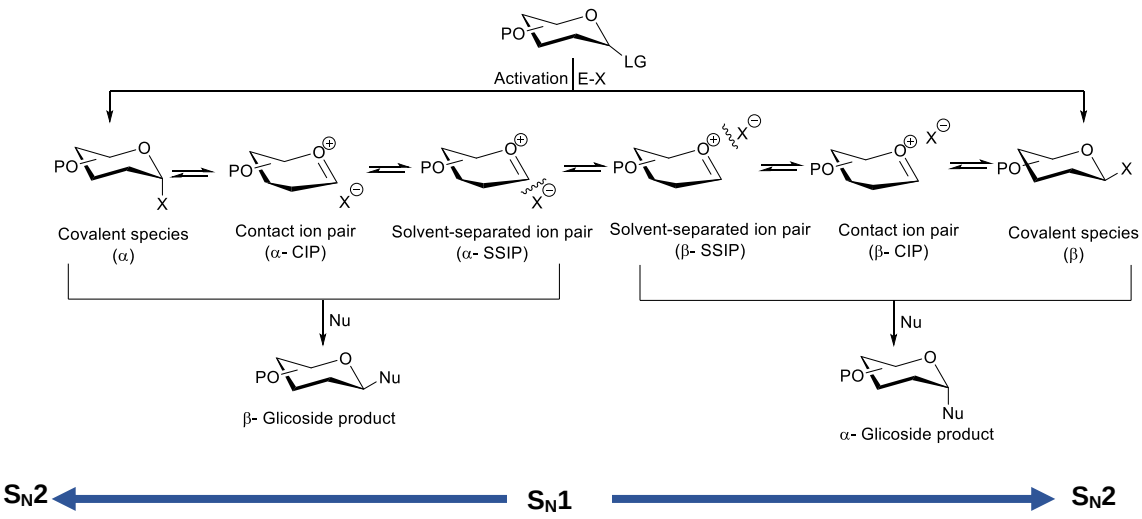


Figure 31. Proposed general mechanisms for the glycosylation reactions[128]

The activation of a donor glycoside provides a series of reactive intermediates, formed from the donor glycoside and the activator derived counterion. α- and β-configured covalent reactive intermediates can be formed and these are in

equilibrium with less stable and more reactive oxocarbenium ion-based species.[124]

The covalent species are displaced in a reaction mechanism having an associative S_N2 character, while in the oxocarbenium intermediates the nucleophile can attack either face opposite to the one shielded by the contact ion pair (CIP) - S_N2-like mechanism - or both faces of the solvent separated ion pair (SSIP; i.e. free oxocarbenium ion) - S_N1-like mechanism.

The stereoselectivity of the process depends on the reactivity of both reaction partners: the donor and acceptor glycoside, and also on other parameters such as the nature of the protecting groups, the reactivity of the promoter, the temperature, the solvent used and the steric hindrance of the acceptor.

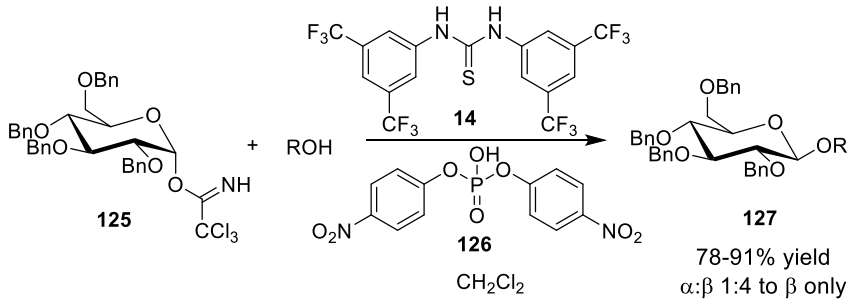
In the last years, alternative strategies have emerged and large attention has been given to hydrogen-bonding catalysed glycosylations, mainly in thiourea catalysis with organocatalysts designed to mimic glycosyltransferases.[120]

4.2 Results and Discussion

4.2.1 Cooperative catalysis with *O*-glycosyl trichloroacetimidates as glycosyl donors

In 2013, Schmidt and collaborators reported cooperative catalysis in glycosylation reactions with *O*-glycosyl thrichloroacetimidates as donors.[129] They proved that the cooperative phenomenon between Brønsted acids and hydrogen-bonding cocatalysts, already used by this group in other catalytic reactions,[130,131] was possible in glycosylation reactions. They also showed that the use of Schreiner thiourea as cocatalyst highly affects the reaction rate, yield and the selectivity of glycosylations. The scope of the reaction was tested with different acceptors and glycosyl donors, using bis-(4-nitrophenyl)phosphoric acid **126** as catalyst and

Schreiner thiourea **14** as cocatalyst, with good yield and β selectivity (**Scheme 21**).



Scheme 21. Cooperative catalysis between Schreiner thiourea and Brønsted acids in glycosylation reaction

The Schreiner thiourea facilitated the hydrogen-bond-mediated complex formation between *O*-glycosyl trichloroacetimidate donors, acceptors and acid catalysts. The authors also understood that acid–base-catalysed S_N2-type glycoside bond formation is facilitated even at room temperature and in the absence of anchimeric assistance.

Considering that Schreiner thiourea is an achiral compound, in Schmidt's study the anomeric selectivity was determined essentially by the glycosyl donor and, in the absence of directing groups, essentially by the configuration of the anomeric centre. Thus, we decided to apply a series of chiral hydrogen-bond organocatalysts **65**, **66**, **70**, **75**, **76** and **83** derived from L-tartaric acid, with a mono and bis-thiourea moiety in their structure, and to test their ability as cocatalysts in the cooperative glycosylation reaction with *O*-glycosyl thrichloroacetimidates as donors (**Figure 32**).

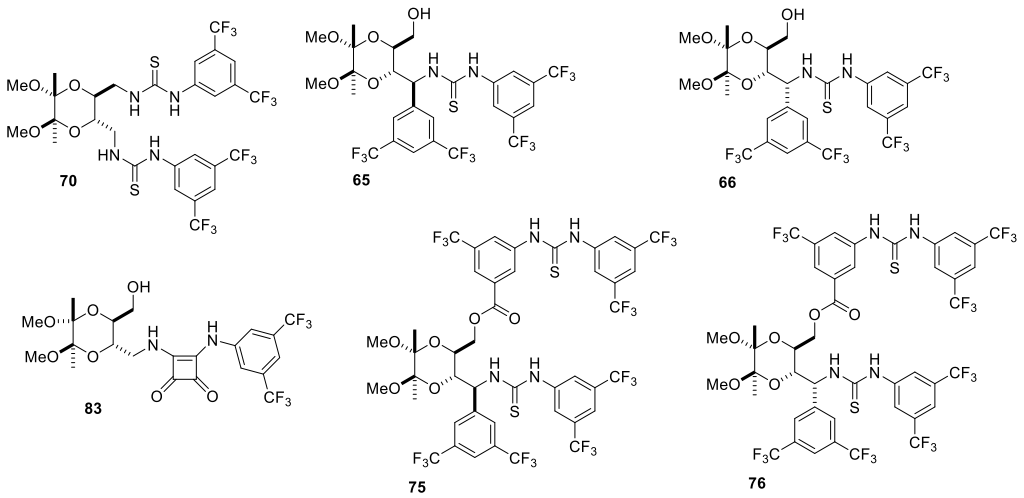
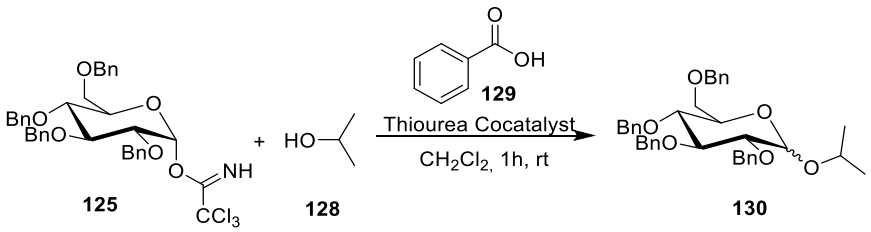


Figure 32. Organocatalysts studied in cooperative glycosylation reactions

At first, these thiourea organocatalysts were evaluated as cocatalysts in a model cooperative glycosylation reaction between *O*-glycosyl trichloroacetimidate **125** as donor and isopropanol **128** as acceptor, using benzoic acid **129** as catalyst, in dichloromethane at room temperature for 1 h. The obtained results are presented in **Table 9**.

Table 9. Cocatalyst screening



Entry[a]	Cocatalyst	Yield[b] (%)	β:α[c]
1	**-**	Residual Product	
2[d]	**70**	23	56:44
3		42	64:36
4	**65**	30	58:42
5	**66**	22	50:50
6	**83**	No product	
7	**75**	47	77:23
8	**76**	45	70:30

[a] Performed on glycosyl trichloroacetamidate **125** (1 eq.), ^{i}ProH **128** (2 eq.), benzoic acid **129** (15 mol%) in CH_2Cl_2 (1 mL) at room temperature for 1 h using 15 mol% of cocatalyst.

[b] Isolated Yield

[c] Determined by ^{1}H NMR

[d] Without Benzoic acid

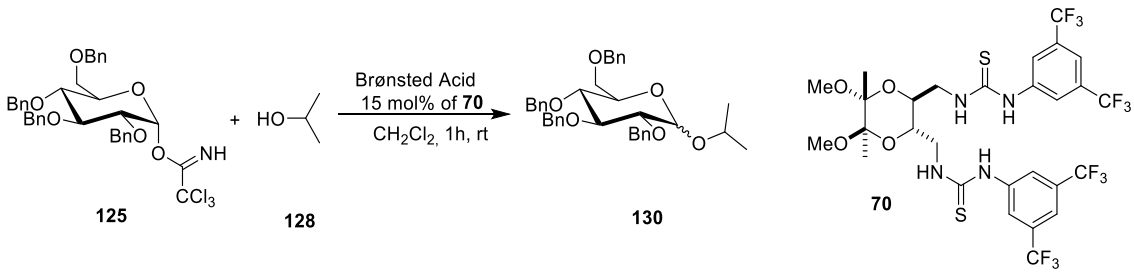
The experimental results show that when the reaction was performed without the presence of thiourea as cocatalyst the product was formed in residual quantity, giving hydrolised product (entry 1 vs entries 2-8). Conversely, using bis-thiourea **70** as cocatalyst without the presence of benzoic acid as catalyst the desired glycosylated product was obtained in 23% of yield and selectivity β:α 56:44 (entry 2), so our thioureas are able to catalyse this transformation in the absence of Brønsted acids. However, when compound **70** was used combined with benzoic acid in the glycosylation reaction the yield and selectivity increased (entry 2 vs entry 3). The glycosylation reaction with compounds **65** and **66** as cocatalysts afforded the product in lower yield and selectivity (entries 4 and 5 vs entry 3), proving that mono-thioureas are less efficient for this reaction than bis-thioureas. Using the squaramide mono-thiourea **83** the product was not obtained, revealing that the presence of a thiourea moiety in the structure of the cocatalyst is fundamental for the cooperative phenomenon (entry 6).

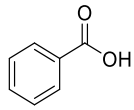
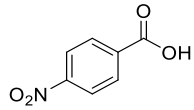
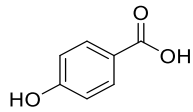
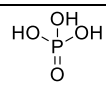
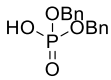
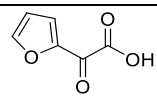
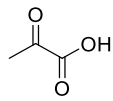
The glycosylation reaction using bis-thioureas **75** and **76** as cocatalysts produced an improvement in the results, both yield and selectivity (entries 7 and 8). The difference between them is the configuration of one of the chiral centres however, from the results obtained, we could conclude that this influence is not significant for this reaction. Bis-thiourea **75** is the best cocatalyst for the cooperative glycosylation reaction giving the desired product in 47% of yield and a β:α ratio 77:23 (entry 7).

Generally, catalytic amounts of a strong Lewis acids, such as TMSOTf or BF_3OEt_2, are required for the activation of *O*-glycosyl trichloroacetimidates. Probably, it is due to this fact that the bis-thioureas are more effective for this transformation, they have two thiourea moieties and additionally more CF_3 groups, which have been shown in the literature to influence the pKa value of the thiourea.[132]

To improve the results it was also important to test the influence of Brønsted acids. Thus, we performed the glycosylation reaction of *O*-glycosyl trichloroacetimidate **125** and isopropanol **128**, with different Brønsted acids as catalyst and bis-thiourea **70** as cocatalyst, which required less synthetic steps to be prepared than bis-thiourea **75**, in dichloromethane at room temperature for 1 h. The obtained results are presented in **Table 10**.

Table 10. Brønsted acids screening



Entry[a]	Brønsted Acid	Yield[b] (%)	β:α[c]
1		42	64:36
2		59	64:36
3		27	68:32
4		16	72:28
5		47	69:31
6		33	75:25
7		53	71:29

[a]Performed on glucosyl trichloroacetimidate **125** (1 eq.), ^{i}PrOH **128** (2 eq.), cocatalyst **70** (15 mol%) in CH_2Cl_2 (1 mL) at room temperature for 1 h using 15 mol% of catalyst.

[b]Isolated Yield

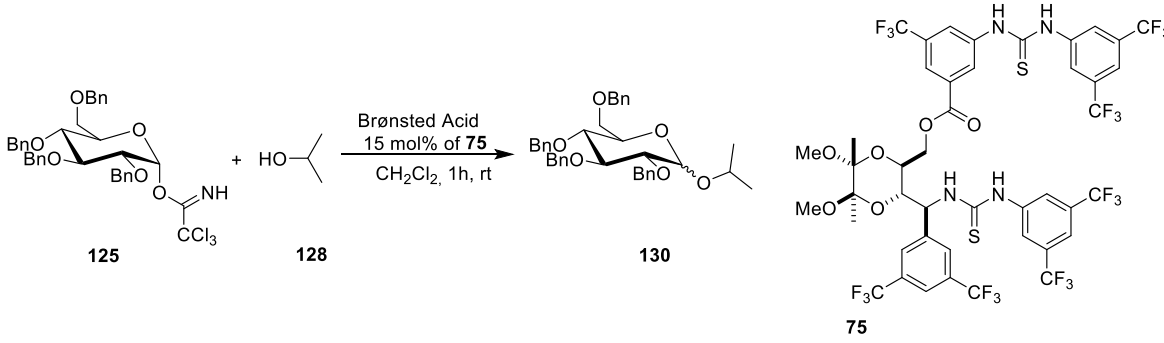
[c]Determined by ^{1}H NMR

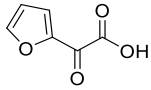
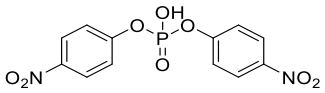
All the Brønsted acids tested proved to be efficient for this catalytic transformation, with moderate yields ranging from 16% to 58% and good selectivities ranging from β:α 64:36 to β:α 75:25. Comparing the results obtained with benzoic acid (pKa value 4.20) and substituted benzoic acid it is possible to understand the importance of the pKa of the Brønsted acid in the yield, the best result was obtained using 4-nitrobenzoic acid (pKa 3.41) (entry 2 vs entries 1 and

3). In terms of selectivity, no remarkable differences were observed. The worst yield was obtained with phosphoric acid, probably because this acid has three pKa values in solution, nevertheless, with this acid an improvement in selectivity was observed (entry 4). Dibenzyl phosphoric acid was the tested acid with the lower pKa value (1.53) and gave the product in higher yield (47%) (entry 5). Although α-keto acids afforded the desired product in moderate yield they provided the best β selectivity (entries 6 and 7). α-Oxo-2-furanacetic acid (pKa 2.02) afforded the glycosidic product in a ratio β:α 75:25, a good result for a glycosylation reaction without the use of a glycosyl donor with participating groups, which generally favours the formation of β-glucosides.

Encouraged by these promising results, we decided to apply our best bis-thiourea **75** and the catalyst that afforded the best results, α-oxo-2-furanacetic acid, and the best catalyst used in literature, bis-(4-nitrophenyl) phosphoric acid, in a model glycosylation reaction. The results obtained are presented in **Table 11**.

Table 11. Stereospecific glycosylation reactions with catalyst **75** and using the best acids



Entry[a]	Brønsted Acid	Yield[b] (%)	β:α[c]
1		33	82:18
2		58	82:18

[a]Performed on glucosyl trichloroacetimidate **125** (1 eq.), ^{i}PrOH **128** (2 eq.), cocatalyst **75** (15 mol%) in CH_2Cl_2 (1 mL) at room temperature for 1 h using 15 mol% of catalyst.

[b]Isolated Yield

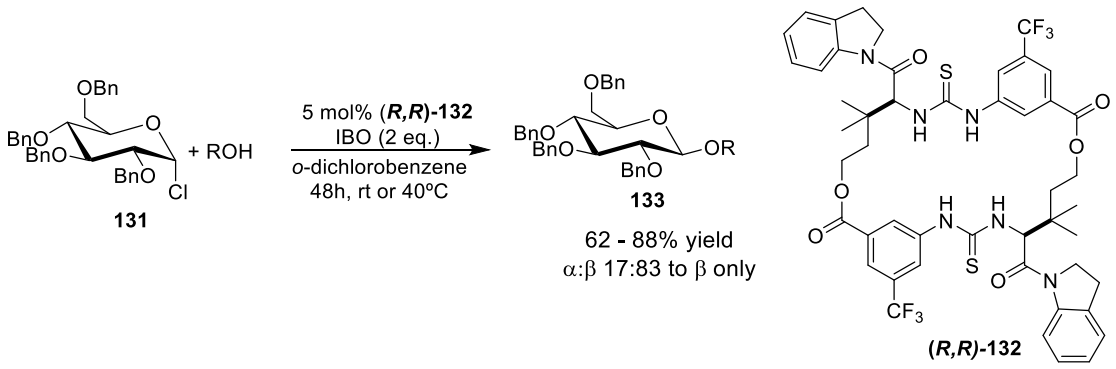
[c]Determined by ^{1}H NMR

The experimental results show that the chiral bis-thiourea **75** influences the selectivity. With this cocatalyst, the β:α ratio was improved compared to bis thiourea **70** (β:α 82:18, **Table 11**). When the bis-(4-nitrophenyl) phosphoric acid was used as a catalyst in the glycosylation reaction between *O*-glucosyl trichloroacetimidate **125** and isopropanol **128**, the yield improved to 58%, probably due to the low pKa value (1.04) of this acid, and the anomeric selectivity remained the same (82:18 β:α).

From the obtained results it was possible to conclude that our chiral synthesised thioureas were efficient as cocatalysts in cooperative glycosylation reactions with *O*-glucosyl thrichloroacetimidates as donors. In the studied model glycosylation reaction the best combination was bis-thiourea **75** as cocatalyst and bis-(4-nitrophenyl) phosphoric acid as catalyst giving the desired product in 58% of yield and a β anomeric selectivity 82:18, using benzyl ether as protective group which is a non-participating group. In the future it is important to test this cooperative conditions with different donors, different leaving groups and different acceptors for the best comprehension of the obtained results.

4.2.2 Macrocyclic bis-thioureas catalyse stereospecific glycosylation reactions

In 2017, Jacobsen and collaborators described the use of a macrocyclic bis-thiourea derivative that was able to activate glycosyl chlorides (**Scheme 22**).[53]



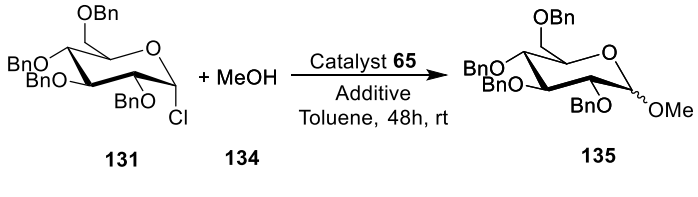
Scheme 22. Glycosylation of glycosyl chlorides using a macrocyclic bis-thiourea organocatalyst **(*R*,*R*)-132**[53]

Mechanistic studies suggest that the reaction follows a stereospecific invertive substitution pathway through a cooperative mechanism in which an electrophile and a nucleophile are simultaneously activated to carry out a stereospecific substitution reaction. To prove the efficiency of the macrocyclic bis-thiourea organocatalyst **(*R*,*R*)-132** the reaction was exemplified in the synthesis of *trans*-1,2, *cis*-1,2, and 2-deoxy glycosides with good to excellent yields and β-stereocontrol.

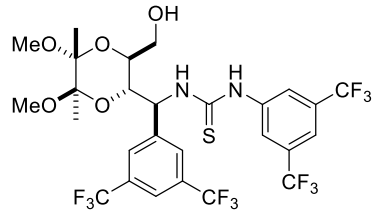
Based on these excellent results we planned to synthesise a macrocyclic bis-thiourea derived from L-tartaric acid containing several asymmetric centres and the 9-atoms distance separating the two thioureas, equivalent to the Jacobsen thiourea, for application in the glycosylation reaction of glycosyl chlorides. However, as referred in chapter 2, it was not possible to synthesise this organocatalyst.

Therefore, we tested mono- and bis-thiourea organocatalysts derived from L-tartaric acid in the glycosylation reaction. Firstly, mono-thiourea **65** was used as an organocatalyst in a model glycosylation reaction between *O*-glycosyl chloride **131** as the donor and methanol **134** as the acceptor, using different additives in toluene at room temperature for 48 h. The obtained results are presented in **Table 12**.

Table 12. Influence of catalyst loading and additive



131 **134** **135**



65

Entry[a]	Catalyst Loading (mol%)	Additive	Yield[b] (%)	α:β[c]
1	5	Na_2HPO_4	No Product	
2	10		No Product	
3	20	K_2CO_3	No Product	

[a]Performed on glycosyl chloride **131** (1 eq.), CH_3OH **134** (2 eq.), catalyst **65** in Toluene (1 mL) at room temperature for 48 h using different additives (2 eq.)

[b]Isolated Yield

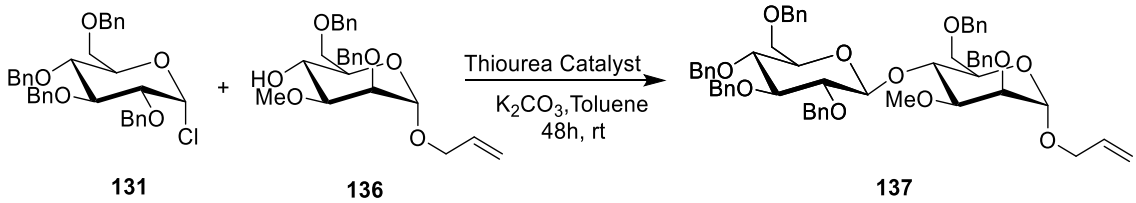
[c]Determined by ^1H NMR

The experimental results showed that organocatalyst **65** was not able to activate the glycosyl chloride **131**, not even with a higher catalyst loading. Two types of additives, used to neutralise the free HCl, were tested but unfortunately the glycosylation product was not obtained.

In order to obtain the product, we decided to change for a carbohydrate acceptor and studied the mono-thiourea organocatalyst **65** and the bis-thiourea organocatalyst **70** in the glycosylation reaction of glycosyl donor **136**, using

potassium carbonate as additive in toluene at room temperature for 48 h. The results obtained are presented in **Table 13**.

Table 13. Screening of catalysts



131 **136** **137**

Entry[a]	Catalyst	Yield[b] (%)	α:β[c]
1	**65**	No Product	
2	**70**	No Product	

[a]Performed on glycosyl chloride **131** (1 eq.), acceptor **136** (2 eq.), K_2CO_3 (2 eq.) in Toluene (1 mL) at room temperature for 48 h using 20 mol% of organocatalysts.

[b]Isolated Yield

[c]Determined by ^{1}H NMR

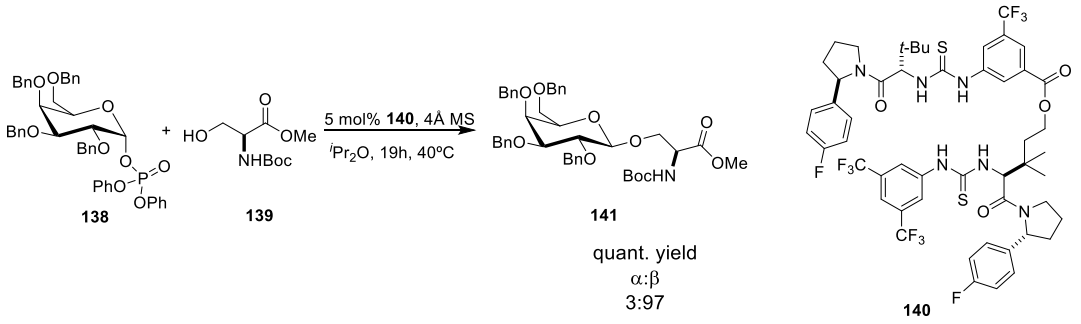
Our synthesised thioureas were not effective to activate the glycosyl chloride, thus we hypothesised that it would be required the presence of a macrocyclic bis-thiourea for this type of glycosylation reaction.

4.2.3 Catalytic activation of glycosyl phosphates for stereoselective glycosylation reactions

More recently, in 2019, Jacobsen reported the advantages of changing the anomeric chloride leaving group to a phosphate leaving group. They hypothesised, based on experimental results, that the catalytic efficiency with complex coupling partners was limited by the low Lewis basicity of the chloride leaving group.[133] Furthermore, phosphate esters and anhydrides are nature's leaving groups of choice. Due to their kinetic stability, strong Lewis basic

character and enabling specific enzymatic recognition no other residue appears to fulfil the multiple roles of phosphate in biochemistry. However, in organic chemistry phosphates are very rarely employed as leaving groups because strong acidic conditions are required for their activation.[134]

Jacobsen's group described a new strategy for the activation of phosphate leaving groups in stereoselective glycosylation reactions using bis-thiourea catalysts (**Scheme 23**).[133]



Scheme 23. Glycosylation of glycosyl phosphates using a bis-thiourea organocatalyst **140**

Jacobsen and collaborators have been inspired by the glycosyltransferases mechanism, these enzymes operate through cooperative activation of both nucleophile and α-glycosyl phosphate to produce β-glycosidic linkages (**Figure 33**). Their experimental results and mechanistic studies suggested that the glycosylation catalysed by the macrocyclic bis-thiourea **140** involves the selective promotion of a stereospecific S_N2 mechanism by the simultaneous activation of the leaving group and nucleophile to afford 1,2-*trans* and 1,2-*cis* glycosides.[53]

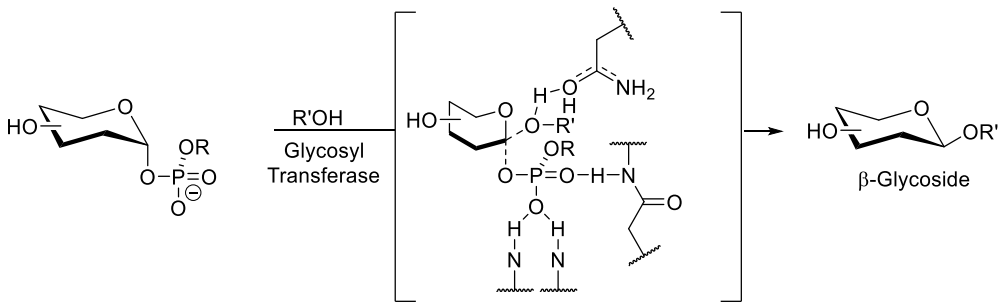


Figure 33. Enzymatic mechanism for enzymatic glycosylation reactions[53]

Taking into consideration these results we studied a series of chiral hydrogen-bond organocatalysts **65**, **70**, **83**, **75**, **76**, **77** and **79** derived from L-tartaric acid in this reaction (**Figure 34**). The aim was to assess the applicability of L-tartaric acid as a stereo directing group in the activation of glycosyl phosphates for stereoselective glycosylation reactions and the role of the different functional groups - hydroxyl, amino or ester- in the organocatalyst. The influence of the proximity of the asymmetric centre to the catalytic important atoms for the stereoselective outcome of the glycosylation reactions has also been studied. Finally, we compared the effect of having a mono- or a bis-thiourea in the catalyst structure.

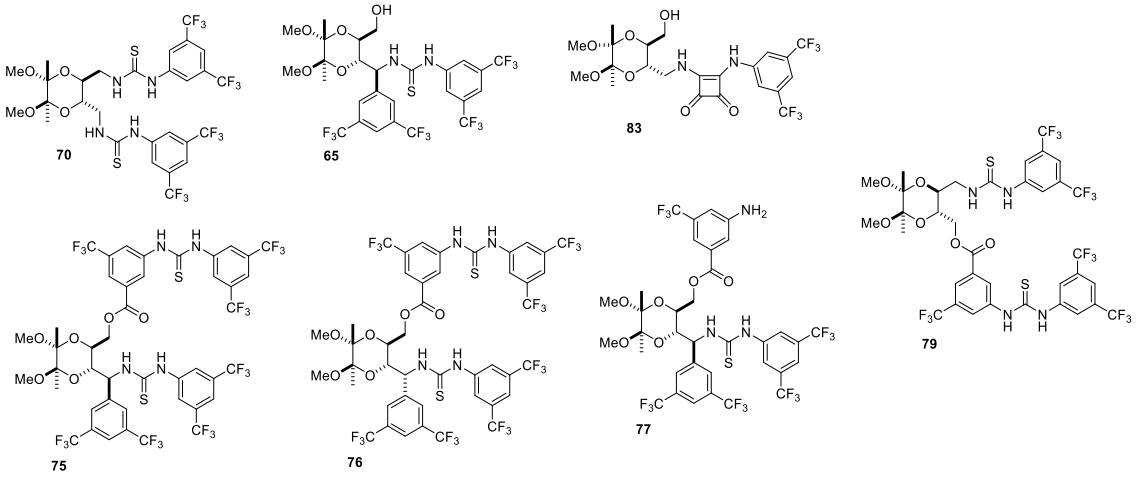
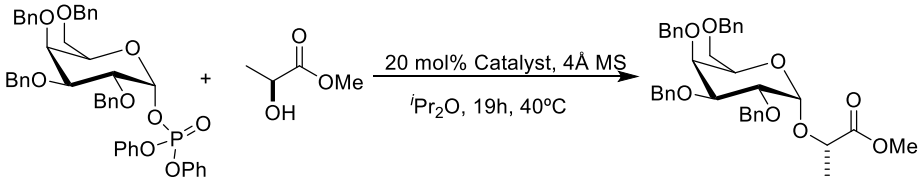


Figure 34. Organocatalysts studied in the activation of phosphate glycosyl donors

Firstly, the synthesised organocatalysts were evaluated in a model glycosylation reaction between the galactosyl phosphate **138** and L-methyl lactate **142** as the acceptor in isopropyl ether ($^{i}Pr_2O$) at 40°C for 19h. The obtained results are presented in **Table 14**.

Table 14. Catalyst screening studies



138 **142** **143**

Entry[a]	Catalyst	Yield[c] (%)	α:β[d]
1[b]	**TMSOTf**	27	60:30
2	**70**	57	68:32
3	**65**	Residual product	
4	**75**	85	83:17
5	**76**	77	82:18
6	**77**	Residual product	
7	**83**	Residual product	
8	**79**	71	80:20

[a]Performed on galactosyl phosphate **138** (0.043 mmol), molecular sieves 4 Å Ms (0.043 g), L-methyl lactate **142** (0.085 mmol, 2 eq.) in $^{i}Pr_2O$ (427 µL) at 40 °C for 19 h using 20 mol% of catalyst.

[b]Performed on galactosyl phosphate **138** (0.030 mmol), molecular sieves 4 Å Ms (0.030 g), L-methyl lactate **142** (0.069 mmol, 2 eq.) in $^{i}Pr_2O$ (298 µL) at 40 °C for 19 h using TMSOTf (0.045 mmol, 1.5 eq.).

[c]Isolated Yield

[d]Determined by ^{1}H NMR

Generally, strongly Lewis acidic reaction conditions are required for these reactions however, the obtained results showed that the synthesised bis-thioureas were more efficient than TMSOTf (entry 1 vs entries 2, 4, 5 and 8). Therefore, the glycosylation reaction was more efficient if strong Lewis acids were replaced by organocatalysts and these were more tolerant to a larger range of functional groups. Only catalysts that have two thiourea groups were able to promote an efficient glycosylation reaction (entries 2, 4, 5 and 8 vs entries 2, 6 and 7). Comparing the results obtained with bis-thiourea **70** and other bis-thioureas, it was possible to understand the importance of an appropriate 9-atom spacer between the two thiourea units (entry 2 vs. entries 3, 4 and 7). According to Jacobsen's mechanistic studies, thiourea catalysts form non-productive dimeric aggregates in the resting state and it was important that these aggregates must dissociate before two molecules of catalyst recombine with substrates to promote rate- and enantioselectivity-determining bond formation (**Figure 35**).[135]

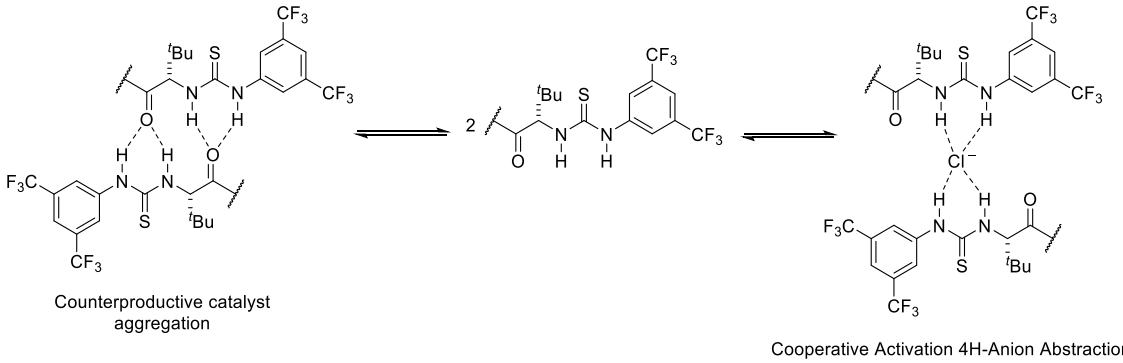
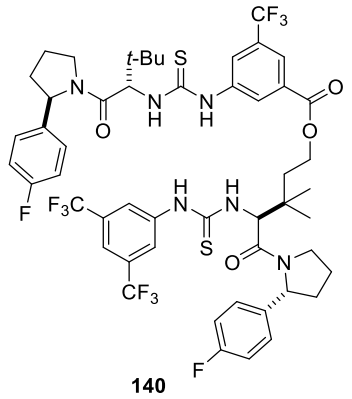


Figure 35. Anion-abstraction catalysis involving the cooperative action of two amido-thiourea catalysts[135]

In the solid state, the authors could observe that the distance between the *tert*-butyl group of one molecule and the aryl thiourea of the other is considerably greater in the non-productive aggregate than in the Cl–bound complex.

This observation suggested that a connection between these groups might achieve the desired purpose, therefore they understood that an appropriate linker between these two groups should be long enough to allow the same 4H-binding arrangement that is accessible to the unlinked monomers but it must be short enough to prevent intramolecular formation of the non-productive aggregate. Jacobsen's group developed a pseudo-dimeric complex **140** for cooperative activation of a chloroether electrophile by a 4H mechanism while disfavouring non-productive groundstate aggregation (**Figure 36**).[135] This is the reason why organocatalyst **140** was used to activate glycosyl phosphates in stereospecific glycosylation reactions.



140

Figure 36. Pseudo-dimeric complex for cooperative activation[135]

In our studies, the presence of free hydroxyl and free amino groups in the catalyst prevented the formation of the glycosylation product (entries 3, 6 and 7, **Table 14**). All synthesised bis-thioureas proved to be efficient for this catalytic transformation, with yields ranging from 57% to 85%. The organocatalyst **75** was the best one for this reaction, both in terms of yield (85%) and diastereoselectivity with a proportion α:β 83:11 (**Table 14**), and the introduction of a new chiral centre

led to a slight improvement on the diastereoselectivity and yield (entries 4 and 5 vs entry 8).

As mentioned above, the stereochemical outcome of the glycosylation reaction is dependent on multiple factors – nature of the protecting groups, the reactivity of the glycosyl donor, acceptor and promoter, solvent, steric hindrance of the acceptor, the temperature at which the reaction takes place and the presence/nature of additives.

There are two classical limiting mechanisms of nucleophilic substitution reactions, S_N1 and S_N2 for the development of catalytic glycosylation strategies. The use of catalysts that promote the stereoselective glycosylation S_N1 type pathway has to influence the addition of the nucleophilic partner preferably to one diastereotopic face of an oxocarbenium intermediate generated by ionisation of the electrophilic partner (**Figure 37A**). Nonetheless, designing catalysts capable of paramount the stereochemical biases of chiral glycosyl electrophiles is the real challenge. Another approach is the S_N2 type pathway, where the stereochemistry of the product would be dictated entirely by the configuration of the electrophile at the anomeric position (**Figure 37B**).

Nonparticipating protecting groups allow the approximation of the nucleophile from either face of the oxocarbenium ion intermediate, reducing stereocontrol and affording mixtures of 1,2-*cis* and 1,2-*trans* glycosides. 1,2-*trans* glycosides can be easily synthesised using participating protecting groups at C-2 to control the diastereoselectivity, but the selective formation of 1,2-*cis* glycosides is considerably more challenging.[136] In the glycosylation reaction model described in **Table 14**, the protecting group used is the benzyl group, an ether-type nonparticipating substituent. Hence the most important factor for the stereochemical result of this reaction is the configuration of the electrophilic partner, in other words, the glycosyl donor.

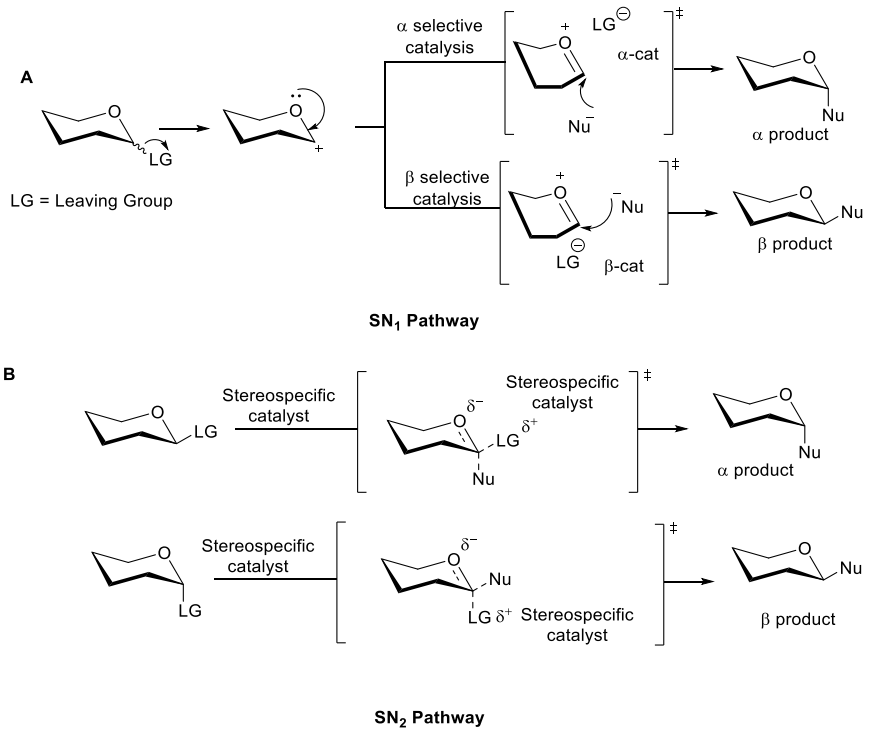


Figure 37. Catalyst-controlled stereoselective glycosylations[53]

As already mentioned, Jacobsen has been inspired by the glycosyltransferases mechanism and their experimental results and mechanistic studies suggest that the glycosylation catalysed by the macrocyclic bis-thiourea involves the selective promotion of a stereospecific S_N2 mechanism by the simultaneous activation of the leaving group and the nucleophile to afforded either 1,2-*trans* or 1,2-*cis* glycosides.[53]

Our experimental results showed that with the organocatalysts derived from L-tartaric acid an excess of α-product was obtained, suggesting that some of our organocatalysts are effective for the activation of the leaving group and in the studied glycosylation reaction inversion of the configuration was not observed, suggesting that it proceeded via a S_N1 mechanism, contrary to what was

observed with Jacobsen bis-thioureas, where the products were obtained via an invertive nucleophilic substitution reaction.

Generally, in the glycosylation reaction the leaving group activation would be expected to promote either the S_N1 or S_N2 pathways but, although it will be necessary more precise mechanistic studies, our results suggest that the nucleophile activation would promote the S_N1 mechanism preferably.

The bis-thiourea organocatalyst **75** allows the simultaneous activation of the reacting partners, we consider that the thiourea moiety (surrounded by a red circle in **Figure 38**) interacts with the phosphate leaving group of the glycoside through hydrogen bonding promoting its activation and consequent dissociation, providing the oxocarbenium intermediate and forming a transient ion pair with the phosphate leaving group. Moreover, the alcohol nucleophile is activated by a hydrogen bond interaction with the ester carbonyl (surrounded by a yellow circle in **Figure 38**) and the other thiourea moiety (surrounded by a green circle in **Figure 38**) in the catalyst. The existence of the rigid tartrate structure present on the catalyst directs the position of the ester carbonyl group and orientates the nucleophile attack to the α position, thus explaining why a higher α proportion was obtained with this catalyst.

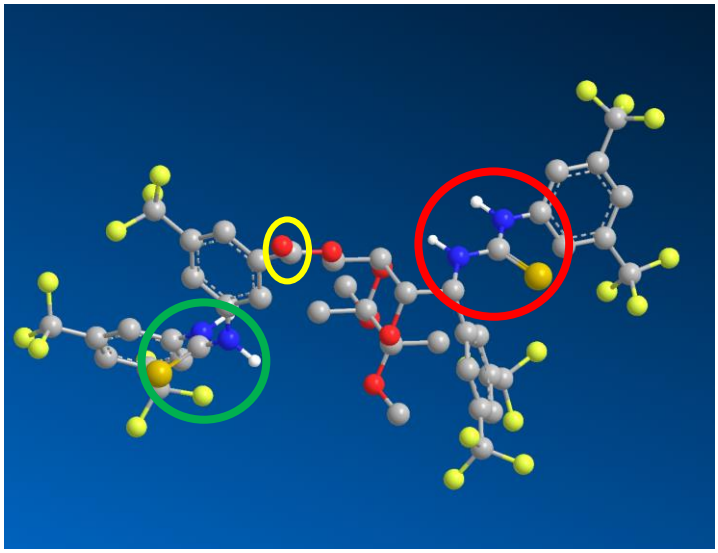
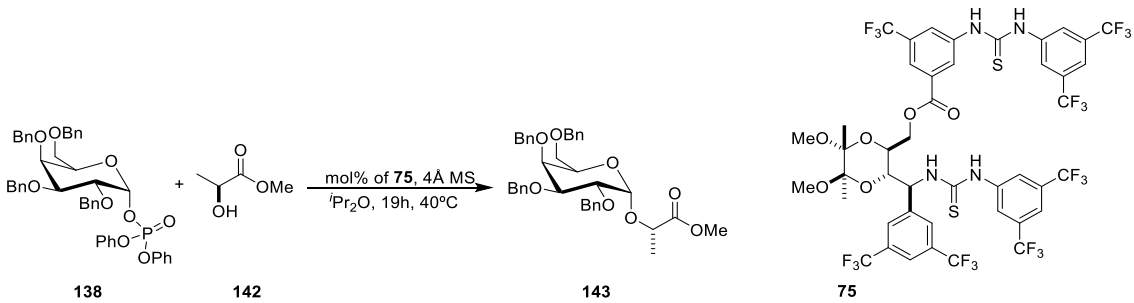


Figure 38. Organocatalyst **75** in Chem3D

To test the catalytic efficiency of our organocatalyst, we decided to lower the loading of the catalyst, the results are presented in **Table 15**.

Table 15. Catalyst loading studies



138 **142** **143** **75**

Entry[a]	mol % of catalyst	Yield[b] (%)	α:β[c]
1	5	48	83:17
2	10	70	83:17
3	20	85	83:17

[a]Performed on galactosyl phosphate **138** (0.043 mmol), molecular sieves 4 Å Ms (0.043 g), L-methyl lactate **142** (0.085 mmol, 2 eq.) in $^{i}Pr_2O$ (427 µL) at 40 °C for 19 h.

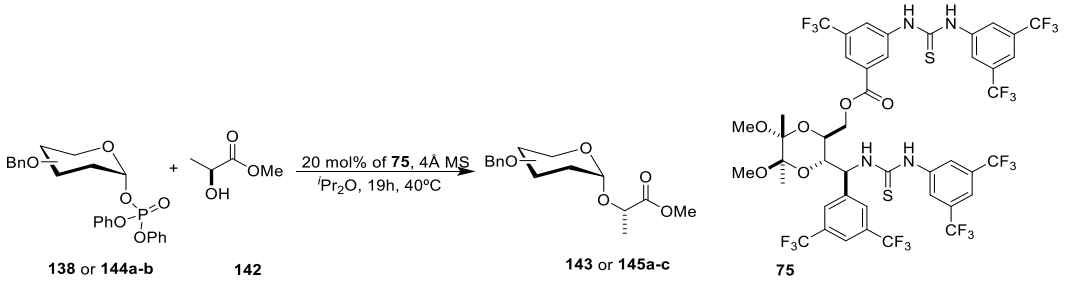
[c]Isolated Yield

[d]Determined by ^{1}H NMR

The results showed that the anomeric selectivity remained the same however, the yield decreased with the decrease of catalyst amount. Thereby the best results were obtained with 20 mol% of catalyst, providing the desired product in 85% yield and good diastereoselectivity (83:17 α:β).

Using the best reaction conditions, the influence of the glycosidic donor was studied.

Table 16. Donor influence studies



138 or **144a-b** **142** **143** or **145a-c** **75**

Entry[a]	Donor	Product	Yield[b] (%)	α:β[c]
1	Glucose (**144a**)	**145a**	70	70:30
2	Galactose (**138**)	**143**	85	83:17
3	Mannose (**144b**)	**145b**	84	89:11

[a]Performed on glycosyl phosphate **138** or **144a-b** (0.043 mmol), molecular sieves 4 Å Ms (0.043 g), L-methyl lactate **142** (0.085 mmol, 2 eq.) in $^{i}Pr_2O$ (427 µL) at 40 °C for 19 h using 20 mol% of catalyst **75**

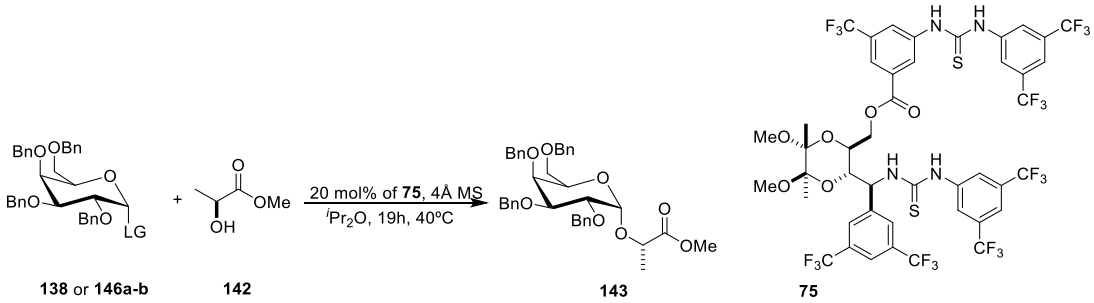
[b]Isolated Yield

[c]Determined by ^{1}H NMR

The results are presented in **Table 16** and reveal that using benzyl protected glucosyl phosphate as a donor, in the glycosylation reaction, the product was obtained with lower selectivity when compared with benzyl protected galactosyl phosphate as a donor. Jacobsen also observed a decrease in yield and selectivity when using perbenzylated-glucose (87:13 β:α) as a donor instead of perbenzylated-galactose (97:3 β:α).[133] Using benzyl protected mannosyl phosphate as a donor the desired product was obtained in good yield (84%) and good diastereoselectivity (89:11 α:β), showing that organocatalyst **75** was able to activate this donor. Though the mannose axial position at C2 already favours the formation of the α product strongly Lewis acidic conditions are required to obtain the product in high selectivity and although these conditions are generally compatible with carbohydrate substrates, they present poor tolerance toward a wide variety of several functional groups and have limited utility using complex acceptors.[137,138] Our bis-thiourea organocatalyst afforded the α-mannosyl product with excellent yield (84%) and selectivity (89:11 α:β), as obtained with Lewis acid promoters, but using mild and neutral conditions. Jacobsen's group tried to use their organocatalyst **140** in the glycosylation reaction between benzyl protected mannosyl phosphate and serine, using the same reaction conditions, and obtained the glycosylation product in 48% yield and without selectivity (1:1 α:β).[139]

The influence of the leaving group was evaluated and the obtained experimental results are in **Table 17**.

Table 17. Donor influence studies



Entry[a]	Leaving Group (LG)	Yield[b] (%)	α:β[c]
1	-Cl	23	84:16
2	$-OP(O)(OPh)_2$	85	83:17
3	$-OC(NH)(CCl_3)$	No Product	

[a]Performed on galactosyl phosphate **138** or **146a-b** (0.043 mmol), molecular sieves 4 Å Ms (0.043 g), L-methyl lactate **142** (0.085 mmol, 2 eq.) in $^{i}Pr_2O$ (427 µL) at 40 °C for 19 h using 20 mol% of catalyst **75**

[b]Isolated Yield

[c]Determined by ^{1}H NMR

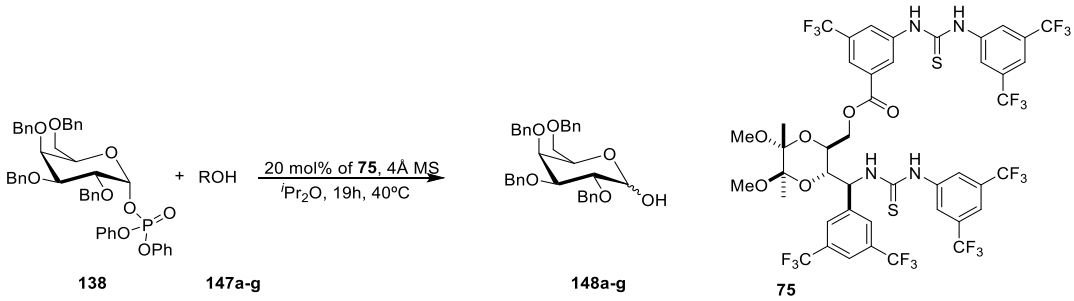
The glycosylation reaction with phosphate as a leaving group provided the desired product in higher yield (85%) in contrast with 23% yield obtained using galactosyl chloride as donor, nevertheless the diastereoselectivity remained the same. The literature suggests that with complex nucleophiles bearing multiple Lewis basic groups the activity of the catalyst was inhibited, presumably due to the unproductive association of the key H-bond donor motifs. Jacobsen concluded that the phosphate not only binds more tightly to the catalyst but it is also more labile toward substitution when bound, resulting in an improvement in catalytic efficiency.[133] With the trichloroacetimidate as leaving group the reaction

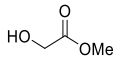
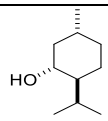
did not occur. This result can be interesting for the one-pot synthesis of di- or tri- and higher saccharides because the organocatalyst **75** is selective for certain leaving groups.

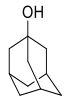
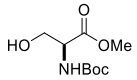
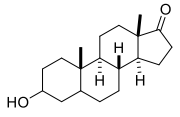
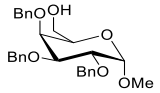
Another important aspect is whether the diphenylphosphoric acid byproduct affects the catalytic glycosylation reaction. Jacobsen showed that this effect is solvent-dependent, with solvents in which the phosphoric acid byproduct is soluble the catalytic reaction is suppressed almost completely. Therefore, the best solvents for this transformation are nonpolar solvents, such as cyclohexane and ethereal solvents.[133]

With optimal conditions in hand, the scope of the glycosylation reaction was evaluated with different acceptors, using compound **75** as the organocatalyst (**Table 18**).

Table 18. Acceptor scope



Entry[a]	Acceptor	Product	Yield[b] (%)	α:β[c]
1		**148a**	85	83:17
2		**148b**	58	41:59
3		**148c**	60	49:51

4		**148d**	41	57:43
5		**148e**	64	73:27
6		**148f**	58	50:50
7		**148g**	70	56:43

[a]Performed on galactosyl phosphate **138** (0.043 mmol), molecular sieves 4 Å Ms (0.043 g), acceptor ROH (0.085 mmol, 2 eq.) in $^{i}Pr_2O$ (427 µL) at 40 °C for 19 h using 20 mol% of catalyst **75**

[b]solated Yield

[c]Determined by ^{1}H NMR

It should be noted that once again all glycosylation reactions proceeded with moderate to excellent yield (41-85%), whilst mixtures of diastereomers were formed in all reactions. Excellent yield (85%) and α:β (83:17) selectivity were observed with methyl glycolate (**Table 18**, entry 1), which is structurally similar to methyl lactate, but it has a primary alcohol. The reaction with serine, that contains in its structure multiple Lewis basic sites, was successful, as expected, with 64% yield and a good anomeric selectivity (73:27, **Table 18**, entry 5). Catalyst **75** was able to promote the formation of 1,6-glycosidic bonds giving the product **148g** in good yield (70%) but low anomeric selectivity (α:β 56:43). In the examples studied, with acceptors that contain secondary alcohols and which are considerably larger/bulkier than methyl lactate, such as **147b**, **147c** and **147f**, the yield decreased and the product was obtained without anomeric selectivity. These results reinforce our analysis of the mechanism of the glycosylation reaction because they suggest that the transition state involving the donor, the acceptor and the catalyst is not able to accommodate and efficiently direct larger acceptor molecules.

The nucleophile **147d** provided the corresponding product **148d** with moderate yield (41%) since it presents a tertiary alcohol in its structure, less reactive than primary and secondary alcohols. However, with our catalyst slight diastereoselectivity was obtained for product α, as it was observed for the other larger acceptors. In all cases, the diastereoselectivity was determined by NMR analysis.

These results reinforce that the acceptor structure has a strong influence in glycosylation reactions and that the mechanism of action of our bis-thioureas is not an invertive nucleophilic substitution of the glycosyl phosphate.

4.3 Conclusion

Bis-thiourea **75** can act as a cocatalyst in combination with bis-(nitrophenyl)phosphoric acid catalyst in the glycosylation reaction between *O*-glycosyl trichloroacetimidate donor and isopropanol as acceptor, affording the desired product in 58% of yield and a proportion β:α 82:18.

Moreover, bis-thiourea organocatalyst **75** was successfully applied on the catalytic activation of glycosyl phosphates for stereoselective glycosylation reaction and provided the appropriate glycosylation product in moderate to excellent yields and in several cases with high α:β selectivity (83:17). It is interesting that the same organocatalyst was able to activate different leaving groups, under different glycosylation reaction conditions, affording the opposite anomeric selectivity. These results confirm that in the presence of our bis-thioureas the glycosylation reaction does not proceed via an invertive substitution mechanism, the stereochemical outcome of the glycosylation reaction is independent of the configuration of the glycosyl donor leaving group and of the nature of the glycoside. This suggests that it is the catalyst that is exclusively controlling the anomeric selectivity, by establishing a rigid transition state.

Furthermore, these neutral H-bond donor catalysts can activate organic phosphates and trichloroacetimidates as leaving groups, allowing stereoselective glycosylation reactions under mild conditions without the use of participating protecting groups, proving the versatility of our synthesised bis-thioureas organocatalysts derived from L-tartaric acid. Nevertheless, the obtained results show that our organocatalysts are not efficient with glycosyl chloride donors.

Glycosylation of glycosyl phosphates catalysed by bis-thiourea **75** involves the dissociation of the donor leaving group by bis-thiourea moiety and the rigid tartrate structure present on the catalyst has an important role as well as the 9-atoms distance between the two thioureas. 1,2-*cis* glycosides are still challenging to obtain and our catalyst is an alternative method to obtain 1,2-*cis* galactosides and glucosides. In particular, perbenzylated galactosyl donors are considerably more reactive than the corresponding glucosyl donors, thus affording lower α anomeric selectivity using traditional glycosylation methods.

Catalyst **75** was specific for the activation of phosphate donors and this feature can be explored for the orthogonal synthesis of higher saccharides with miniumum protecting groups manipulation. Although with larger and bulkier acceptors the glycosylation was obtained with poor selectivity, the structure of the synthesised organocatalysts can be quickly modified and optimised, allowing a wide range of possibilities for obtaining new efficient bis-thiourea organocatalysts for glycosylation reactions.

Acknowledgements

This work was supported by Fundação para a Ciência e Tecnologia (FCT) through a grant to M.R. (PD/BD/135494/2018) and (COVID/BD/152506/2022) and through MOSTMICRO-ITQB R&D Unit (UIDB/04612/2020, UIDP/04612/2020) and LS4FUTURE Associated Laboratory (LA/P/0087/2020) and Centro de Química de Coimbra (UIDB/00313/2020). The NMR data was acquired at CERMAX, ITQB-NOVA, Oeiras, Portugal with equipment funded by FCT, project AAC 01/SAICT/2016.

Chapter 5

Other Reactions

This chapter contains unpublished data.

The author contributed fully to this chapter, namely in the planning of the experimental work, performing the experiments and writing the manuscript.

Abstract

The synthesised organocatalysts derived from L-tartaric acid and (+)-camphoric acid were tested in the alcoholysis of styrene oxide and the phosphonation of *N*-aryl tetrahydroisoquinolines by cross-dehydrogenative coupling reaction of C(sp^3)-H. The principal objective was to obtain the asymmetric version of these reactions catalysed by our chiral organocatalysts.

Although the principal aim was not achieved, the synthesis of regioselective β-alkoxy alcohols was accomplished in 60% yield by alcoholysis of styrene oxide with methanol, proving the versatility of our organocatalysts.

The synthesis of α-aminophosphonates by phosphonation through cross-dehydrogenative coupling reaction of C(sp^3)-H reaction did not occur.

5.1 Introduction

One of our main objectives was the application of organocatalysis as a strategy for the generation of a new chiral centre. Therefore, we also decided to test our organocatalysts in organocatalytic reactions without an enantioselective version reported in the literature, to broaden the application of the new organocatalysts. We selected two reactions already catalysed by Schreiner thiourea and replaced this catalyst by our chiral organocatalysts.

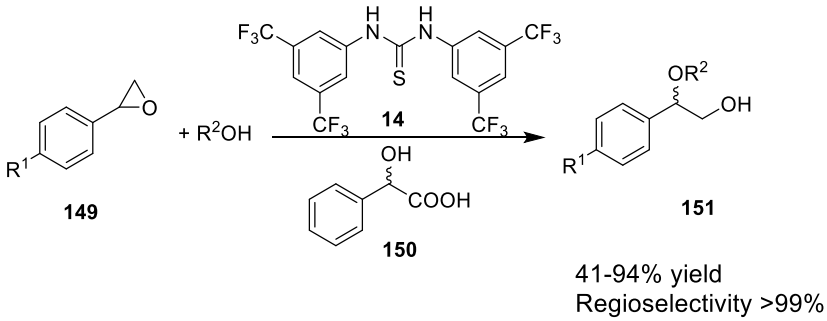
5.2 Results and Discussion

5.2.1 Alcoholysis of Styrene Oxide

In 2008, Schreiner's group based on the cooperative Brønsted acid type organocatalytic system developed a mild and efficient method for the completely regioselective alcoholysis of styrene oxides.[130]

The epoxide ring opening reaction by the addition of alcohols allows the formation of the synthetically important class of β-alkoxy alcohols. Nonetheless, alcohols possess relatively low nucleophilicity and requires the use of catalysts possessing stronger acidity or basicity to enhance reactivity for alcoholysis of epoxides.[140] Brønsted acid catalysis is the most used method for epoxide openings favouring the protonation of the basic epoxide oxygen that facilitates the ring opening with the nucleophile.[141] Lewis acids catalysis has also been used for epoxide ring openings.[142,143]

In nature enzymes can catalyse the activation of the epoxide through hydrogen bonding. Therefore, Schreiner developed a cooperative system between a thiourea catalyst and a Brønsted acid. Several acids were tested and mandelic acid provided the desired β-alkoxy alcohols in good to excellent yields and complete regioselectively (**Scheme 24**).



Scheme 24. Alcoholysis of Styrene Oxides with Mandelic Acid[131]

In a first screening, we studied two organocatalysts derived from L-tartaric acid, a mono and a bis-thiourea (**65** and **70**, respectively) to explore their influence in the reaction, and one catalyst derived from (+)-camphoric acid (**87**) **Figure 39**, in the alcoholysis of styrene oxide with methanol and mandelic acid at room temperature during 72 h.

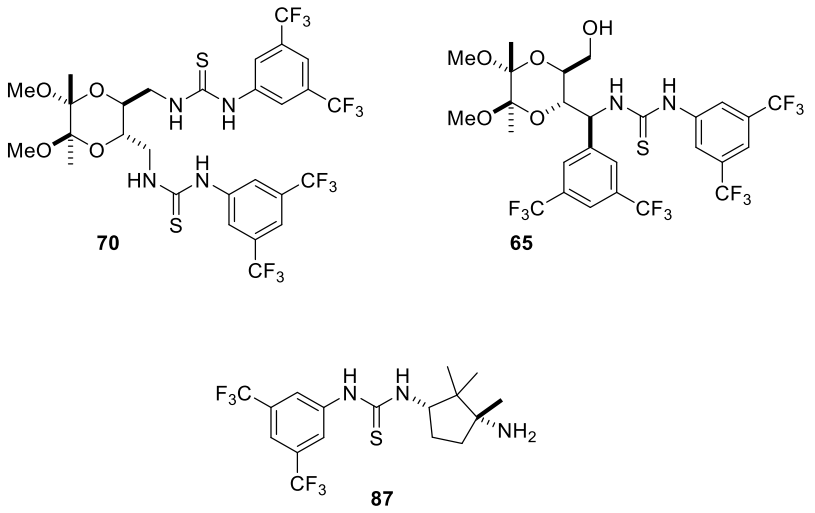
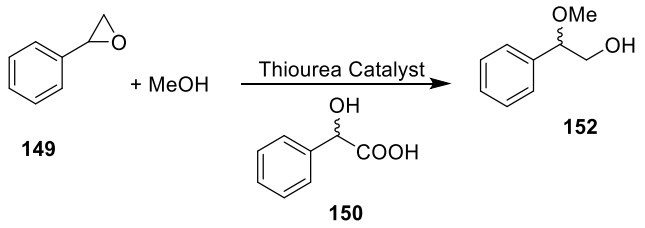


Figure 39. Organocatalysts evaluated in the alcoholysis of styrene oxide

The results are presented in **Table 19**.

Table 19. Preliminary screening of catalysts



Entry[a]	Catalyst	Yield[c] (%)	*ee*[d] (%)
1	-	No Product	
2[b]	**70**	26	*Rac*
3		60	*Rac*
4	**65**	52	*Rac*
5	**87**	5	*Rac*

[a]Performed on styrene oxide **149** (1 eq.), CH_3OH (12 eq.), mandelic acid **150** (1 mol%) at room temperature for 72 h using 1 mol% of thiourea catalyst.

[b]Reaction without Brønsted acid

[c]Isolated Yield

[d]Determined by HPLC on a chiral column AD-H

It should be noted that all tested organocatalysts afforded the product with high regioselectivity (> 99%) nevertheless, the racemic product was obtained with all our organocatalysts. The obtained results proved the importance of the thiourea catalyst for the styrene oxide alcoholysis reaction, without its presence the product was not formed (entry 1). When the reaction was performed without the presence of mandelic acid the product was obtained at a lower yield, showing the importance of the cooperative phenomena between Brønsted acids and thiourea catalysts (entry 2 vs entry 3). Comparing the use of bis-thiourea **70** and mono-thiourea **65**, the first provided the β-alkoxy alcohol in higher yield, probably due to the presence of one more coordination centre on the thiourea catalyst (entry 3 vs entry 4). Organocatalyst **87**, derived from camphoric acid, is not efficient for this reaction (entry 5 vs entries 3 and 4).

Although the application of our organocatalysts derived from L-tartaric acid in the cooperative catalysis of alcoholysis of styrene oxide has not afforded optically active products, these organocatalysts showed to be efficient for the synthesis of regioselective β-alkoxy alcohols, in particular the bis-thiourea. As our aim was the

obtention of optically active products, no further optimisations of this reaction were done, for example to increase the yield and to study the scope of the reaction.

5.2.2 Cross-Dehydrogenative Coupling of C(sp^3)-H with Diethyl Phosphite

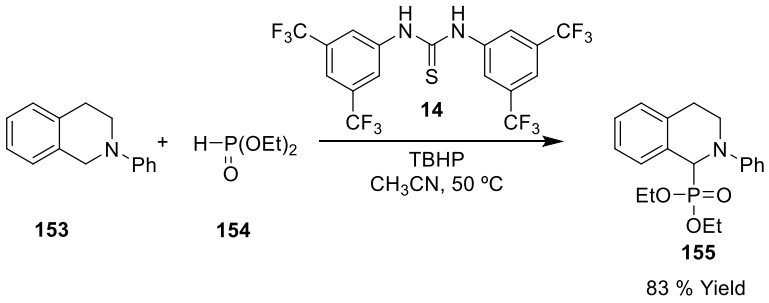
The formation of C-C bonds is a well recognised challenge in organic chemistry because of its fundamental application in the generation of molecular diversity and complexity. Li and coworkers[144,145] developed a method that resorts to the use of unfunctionalised starting materials for the direct formation of C-C bonds, that is, C-H bond activation, this type of reaction is known as cross-dehydrogenative coupling (CDC).

Among all cross-coupling reactions, C(sp^3)-H bond functionalization is considered the most challenging due to its low reactivity. Murahashi[146] and Li[147,148] were pioneering in the activation of C(sp^3)-H bonds adjacent to tertiary amines, in particular, *N*-aryl tetrahydroisoquinolines. The phosphonation of these compounds by CDC reaction allows the formation of α-aminophosphonates. These compounds are analogues of amino acids in which a carboxylic moiety is replaced by phosphonic acid or related groups (phosphonous, phosphinic, phosphine oxide, etc.).[149] They are also used as isosteric and bioisosteric analogues to natural and unnatural amino acids and have thus found wide applications in the biological and pharmacological realms, for example as antibacterial and antifungal agents.[149–151]

Commonly, in this type of reactions transition metals[152–155] are used as catalyst or visible-light mediated photocatalysis.[156–159] Recently some metal-free versions of the CDC reactions, using strong oxidants – SO_2Cl_2[160], AcOH[161], 2-chloroanthra-9,10-quinone[162], I_2[163], Eosin Y[164] or DDQ[165,166] were described. Nonetheless, these three approaches have high costs and toxicity associated, even the metal-free reactions, because these methods required the use of stoichiometric

amounts of oxidants with high molecular weight and some of these oxidants may be toxic, explosive or corrosive.[167]

Thereby, in 2016, Zhang and collaborators reported the use of Schreiner thiourea **14** combined with *tert*-butyl hydroperoxide (TBHP) as an oxidant in the cross-dehydrogenative coupling reaction of C(sp^3)-H with diethyl phosphite **154** to obtain α-aminophosphonates **155** with good results (yield up to 83%) (**Scheme 25**).[168] The scope of the reaction was extended to *N*-aryl tetrahydroisoquinolines with electron-withdrawing or -donating groups and both corresponding products were obtained in good to excellent yields (59-89%).



Scheme 25. Thiourea-Catalysed Cross-Dehydrogenative Coupling of C(sp^3)-H with Diethyl Phosphite[171]

Taking these results into consideration we decided to apply our organocatalysts derived from L-tartaric acid and (+)-camphoric acid (**Figure 40**) in the phosphonation reaction through the cross-dehydrogenative coupling of C(sp^3)-H to evaluate their efficacy on the formation of the α-aminophosphonates and also their ability to afford the enantiomerically enriched products.

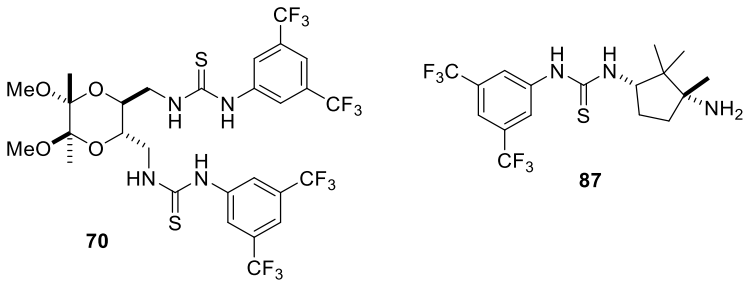
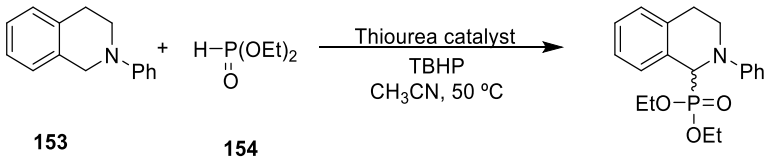


Figure 40. Organocatalysts applied in the CDC reaction

The cross-dehydrogenative coupling reaction with diethyl phosphite **154**, TBHP and thiourea organocatalyst was performed in acetonitrile at 50 °C for 12 h. The results are presented in **Table 20**.

Table 20. Screening of catalyst



153 154 155

Entry[a]	Catalyst	Yield[b] (%)	*ee*[c] (%)
1	-	55	*Rac*
2	**70**	13	*Rac*
3	**87**	20	*Rac*

[a]Performed on aryl tetrahydroisoquinoline **153** (1 eq.), diethyl phosphite **154** (3 eq.) at 50 °C for 12 h using 20 mol% of thiourea catalyst.

[b]Isolated Yield

[c]Determined by HPLC on a chiral column AD-H

From the obtained results, as expected, it was observed the formation of the product in 55% yield in the absence of catalyst (entry 1 vs entries 2 and 3), this result suggests that the TBHP alone is capable of the oxidation process.[169] With each of the two organocatalysts evaluated, the yield was lower and no chirality induction was observed.

Therefore, we did not proceed further with these studies.

5.3 Conclusion

The principal aim of this chapter was to report the first asymmetric version of the alcoholysis of styrene oxide and the phosphonation of *N*-aryl tetrahydroisoquinolines by cross-dehydrogenative coupling reaction of C(sp^3)-H using our chiral organocatalysts. Even though this objective was not achieved, the obtained results showed that the organocatalyst **70**, derived from L-tartaric acid, was efficient in the cooperative catalysis of alcoholysis of styrene oxide, afforded regioselectively β-alkoxy alcohols in 60% of yield, under unoptimised conditions.

Hence these preliminary results not only show the versatility of our organocatalysts but also open the way to expand their application. Further structure optimisation studies are required to obtain the enantiomeric version of this catalytic system, but the advantage of our organocatalysts is that they can be quickly modified inexpensively, allowing a wide range of possibilities for obtaining new efficient L-tartaric acid derived-organocatalysts.

For the cross-dehydrogenative coupling reaction of C(sp^3)-H our organocatalysts were not efficient, giving the desired α-aminophosphonates in low yield (13-20%) as racemic mixtures.

Acknowledgements

This work was supported by Fundação para a Ciência e Tecnologia (FCT) through a grant to M.R. (PD/BD/135494/2018) and (COVID/BD/152506/2022) and through MOSTMICRO-ITQB R&D Unit (UIDB/04612/2020, UIDP/04612/2020) and LS4FUTURE Associated Laboratory (LA/P/0087/2020) and Centro de Química de Coimbra (UIDB/00313/2020). The NMR data was acquired at CERMAX, ITQB-NOVA, Oeiras, Portugal with equipment funded by FCT, project AAC 01/SAICT/2016.

Chapter 6

Conclusion

The principal aim of this project was to develop organocatalysts derived from unexpensive and natural sources of chirality, and their application in different type of asymmetric reactions.

After optimisation of synthetic procedures it was possible to synthesise eight organocatalysts derived from L-tartaric acid and seven organocatalysts derived from (+)-camphoric acid in moderate to excellent global yields (up to 57%). The synthesis of a macrocyclic bis-thiourea derived from L-tartaric acid for application in glycosylation reactions also was one of the aims, unfortunately, it was not possible to obtain the desired compound but all attempts provided us the knowledge to design the synthetic sequences for the synthesis of the other organocatalysts derived from L-tartaric acid. 1,3-Diamine derived bifunctional thiourea and squaramide organocatalysts were easily prepared from (+)-camphoric acid in a few steps.

The organocatalysts derived from (+)-camphoric acid were successfully applied in the enantioselective Michael addition of 1,3-dicarbonyl compounds to *trans*-β-nitrostyrene acceptors. The organocatalyst **98** provided the chiral product in high yields (up to 98%) and good enantioselectivities (*ee* up to 74%) and, when applicable, high diastereoselectivities (*dr* up to 93:7). These results were important because they prove that, such as 1,2-diamine-derived bifunctional thiourea, 1,3-diamine-derived bifunctional thiourea and squaramide organocatalysts are capable of promoting the enantioselective Michael reaction of 1,3-dicarbonyl compounds with *trans*-β-nitrostyrene acceptors. Although the obtained results were not excellent, it was possible to conclude that the (+)-camphoric acid moiety has clearly an influence in the stereoselective outcome of the Michael reactions studied. Additionally, by changing the substituent it was possible to tune the catalyst in order to obtain either the *R* or *S* product.

The organocatalysts derived from L-tartaric acid have not provided good results in Michael and Friedel-Crafts reactions.

The organocatalysts derived from L-tartaric acid were successfully applied to stereoselective glycosylation reactions. The obtained results allowed to conclude that neutral H-bond donor catalysts can participate in stereoselective glycosylation reactions under mild conditions without the use of participating protecting groups, proving the versatility of our synthesised bis-thioureas organocatalysts derived from L-tartaric acid.

Bis-thiourea **75** can act as a cocatalyst in combination with bis-(nitrophenyl)phosphoric acid catalyst in the glycosylation reaction between *O*-glycosyl trichloroacetimidate donor and isopropanol as acceptor, affording the desired product in 58% of yield and a proportion β:α 82:18. Further studies are needed to evaluate the scope of this catalysed reaction. Bis-thiourea organocatalyst **75** was also successfully applied in the catalytic activation of glycosyl phosphates for stereoselective glycosylation reactions and provided the appropriate glycosylation product in moderate to excellent yields and in several cases with high α:β selectivity (up to 83:17). Nevertheless, further catalyst optimisation is needed for improving the yield and anomeric selectivity of the glycosylation reactions involving larger acceptors.

To prove the efficacy of our organocatalysts on induction of chirality, studies towards the first organocatalysed asymmetric version of the alcoholysis of styrene oxide reaction and the phosphonation of *N*-aryl tetrahydroisoquinolines by cross-dehydrogenative coupling reaction of C(sp^3)-H were performed.

The application of our organocatalysts on the cross-dehydrogenative coupling reaction of C(sp^3)-H was not successful, affording the desired α-aminophosphonates in low yields (13-20%) as racemic mixtures. In the

alcoholysis of styrene oxide, even though enantioselectivity was not achieved, the use of organocatalyst **70** afforded regioselectively β-alkoxy alcohols in 60% yield. Further catalyst modifications might provide the enantioselective version of this reaction.

In this thesis work, several synthetic multistep strategies were developed and optimised for the preparation of new molecules derived from readily available and inexpensive tartatic and camphoric acids. These molecules provide asymmetric centres that are important to induce stereoselectivity in other reactions and this was the rationale to incorporate these moieties in new thiourea derived organocatalysts. Additional chiral centres and functional groups were introduced in the organocatalysts, affording a range of structure variations that were then studied in several asymmetric challenging reactions. The results obtained pave the way to expand the application of the novel organocatalysts, since they can be easily modified, allowing a wide range of possibilities for obtaining new efficient organocatalysts.

Chapter 7

Experimental Procedures

7.1 Materials and Methods for Synthesis

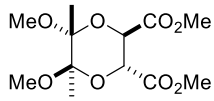
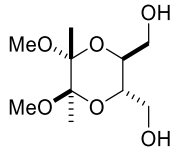
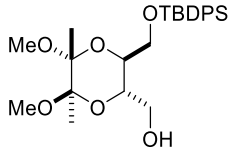
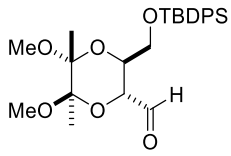
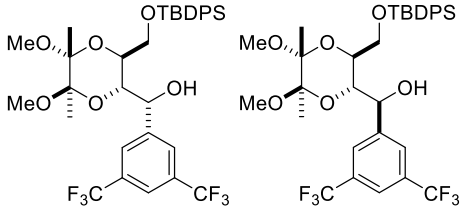
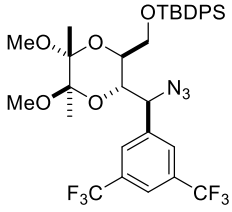
All the reactions were carried out under an inert atmosphere (argon), except when the solvents were not dried. Air sensitive materials were handled in a Braun MB 150-GI glove box. The synthetic compounds were purified using flash chromatography using Kieselgel 60, (0.032–0.063mm) and preparative TLC using Merck 60 F_{254} silica gel. Analytical TLC was performed on aluminium-backed Merck 60 F_{254} silica gel plates. Infrared (IR) spectra were obtained using a commercial ATR-FTIR spectrophotometer and are in cm^{-1}. Specific rotations were measured using a Perkin–Elmer D241 automatic polarimeter and are reported as follows: $[\alpha]_D^{20}$ (*c* g/100mL; solvent). Molecular mass was determined by ESI-MS and the mass spectra of the samples were acquired in positive mode using Q Exactive Focus. ^{1}H NMR spectra were obtained at 400 MHz in $CDCl_3$, MeOH-d_4**,** DMSO-d_6 or D_2O with chemical shift values (δ) in ppm downfield from tetramethylsilane in the case of $CDCl_3$ and using the residual solvent peak in the other cases, and ^{13}C NMR spectra were obtained at 100.61 MHz in $CDCl_3$, MeOH-d_4**,** DMSO-d_6 or D_2O. Assignments are supported by 2D correlation NMR studies. The enantiomeric excesses were determined by HPLC on a Waters 600E/U6K instrument, using a Daicel Chiralpack AD-H or IB column.

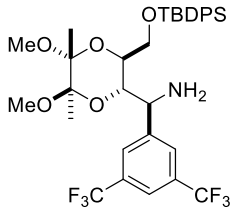
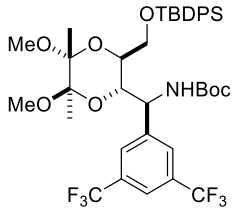
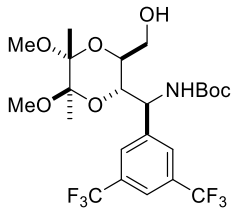
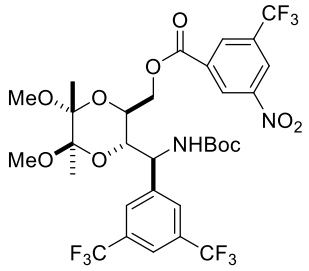
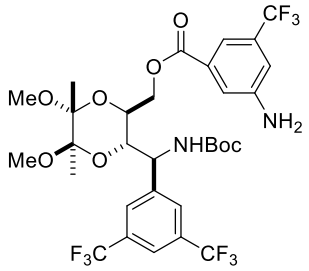
7.1.1 Solvent and Reagent Purification

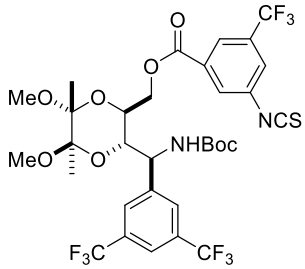
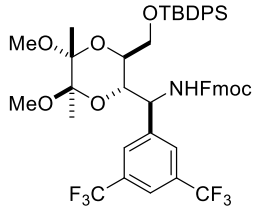
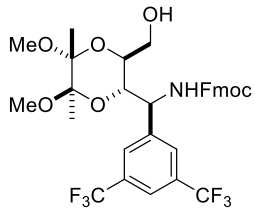
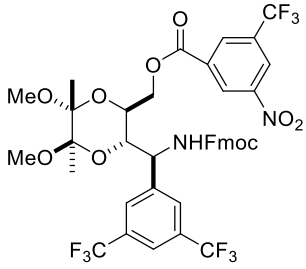
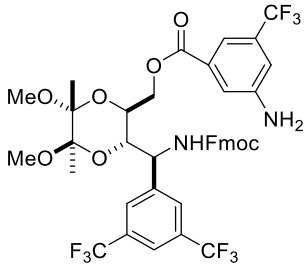
Reagents and solvents were purified and dried according to the literature.[170]

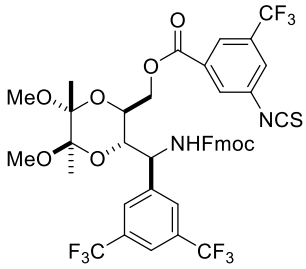
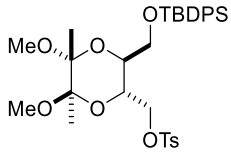
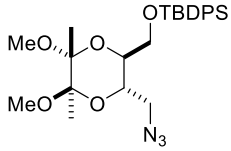
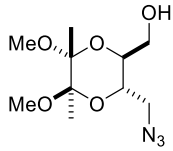
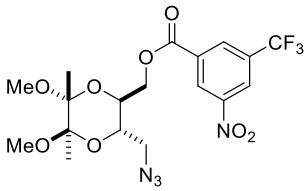
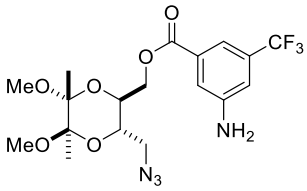
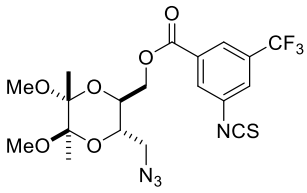
7.1.2 Graphical Index of Compounds and Experiments

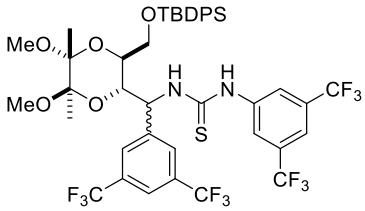
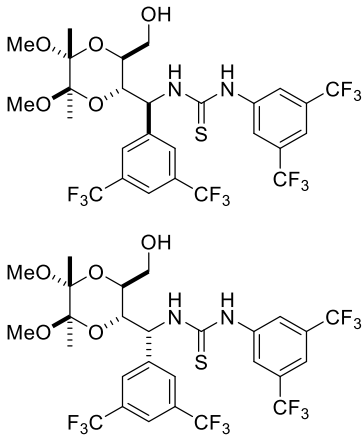
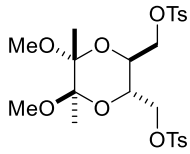
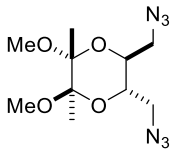
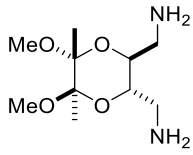
Table 21 – Graphical índex of compounds and experiments.

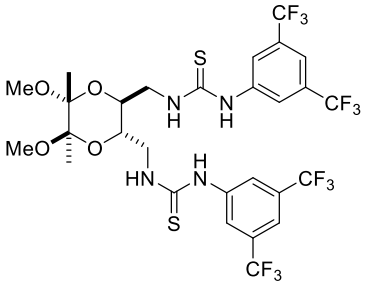
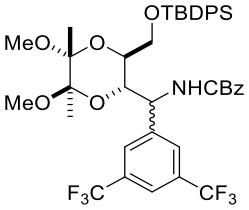
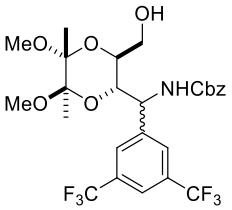
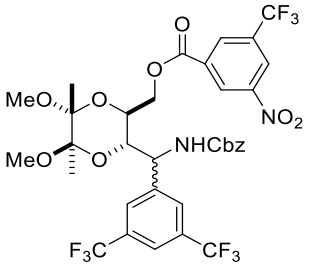
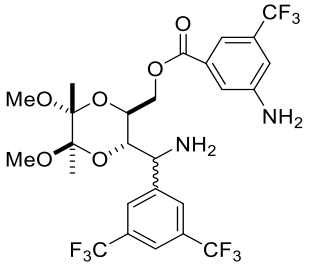
Compound number	Compound Structure	Experiment	Page
36		**1**	136
37		**2**	136
38		**3**	136
39		**4**	137
40 and **41**		**5**	137
43		**6**	138

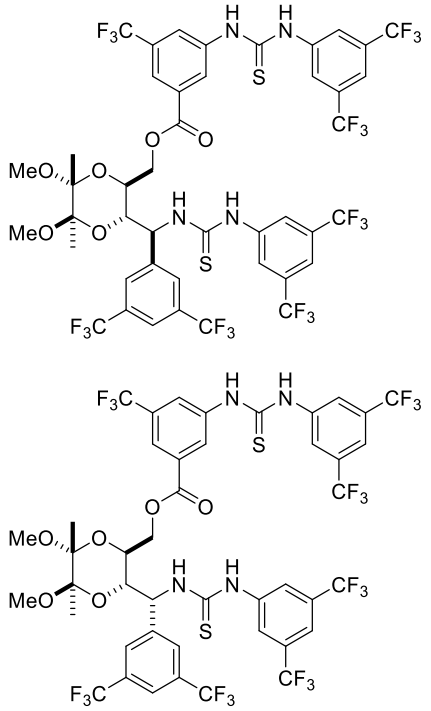
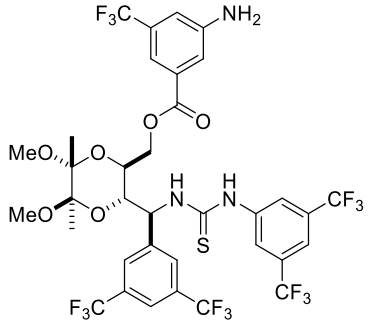
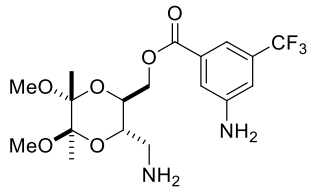
44		**7**	140
45		**8**	141
46		**9**	141
47		**10**	142
48		**11**	143

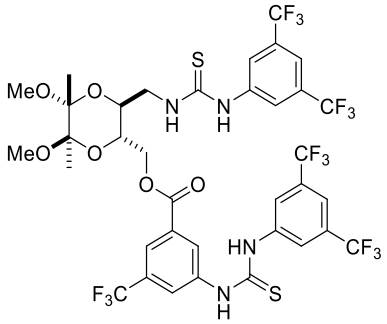
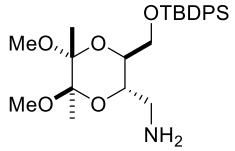
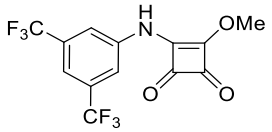
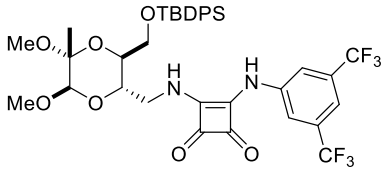
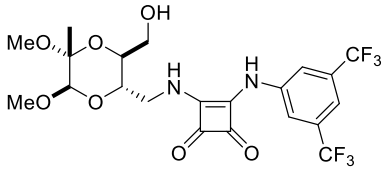
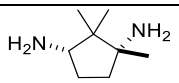
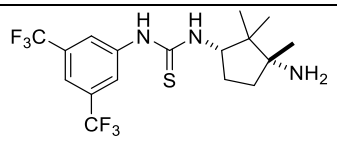
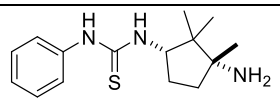
49		**12**	144
52		**13**	144
53		**14**	146
54		**15**	146
55		**16**	147

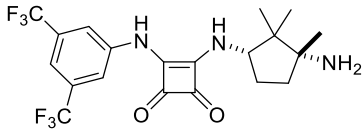
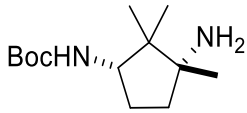
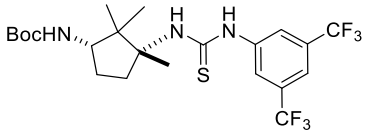
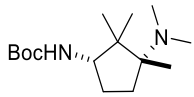
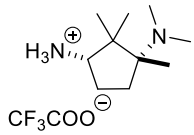
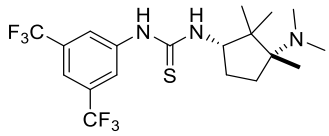
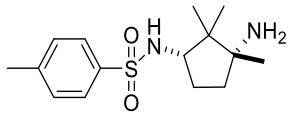
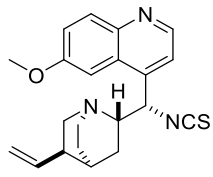
56		**17**	148
57		**18**	149
58		**19**	150
59		**20**	150
60		**21**	151
61		**22**	151
62		**23**	152

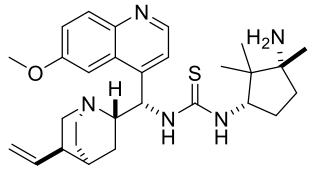
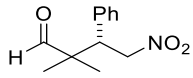
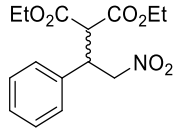
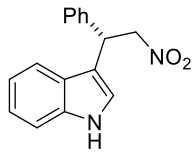
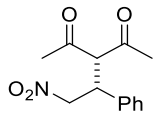
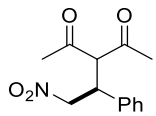
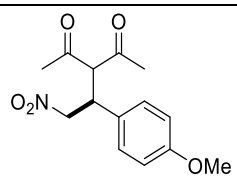
64		**24**	152
65 and **66**		**25**	153
67		**26**	154
68		**27**	155
69		**28**	155

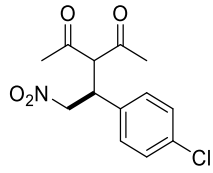
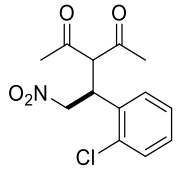
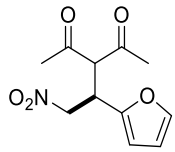
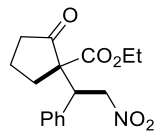
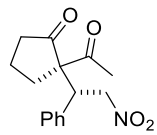
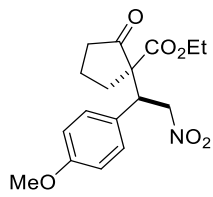
70		**29**	156
71		**30**	156
72		**31**	157
73		**32**	158
74		**33**	159

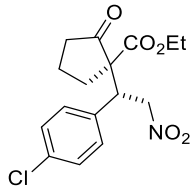
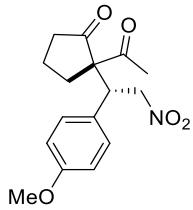
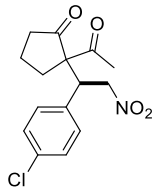
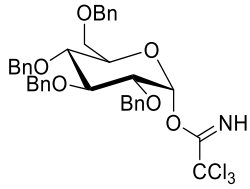
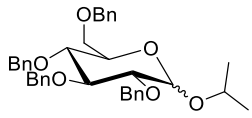
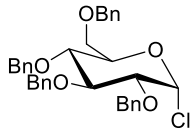
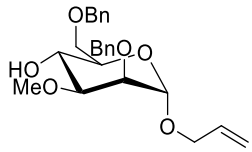
75 and **76**		**34**	160
77		**35**	161
78		**36**	162

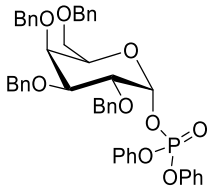
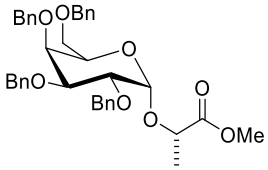
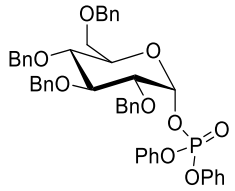
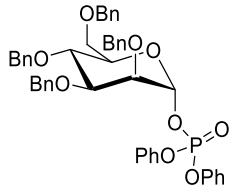
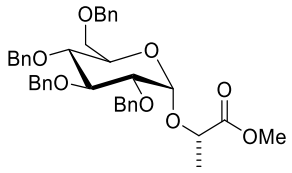
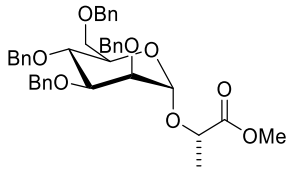
79		**37**	163
80		**38**	163
81		**39**	164
82		**40**	164
83		**41**	165
86		**42**	165
87		**44**	166
88		**45**	166

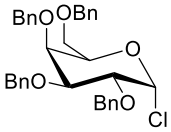
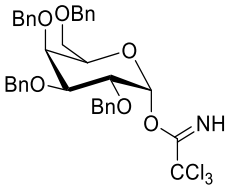
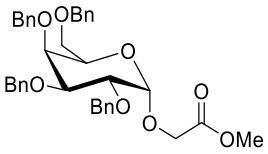
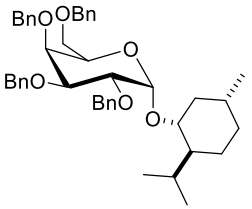
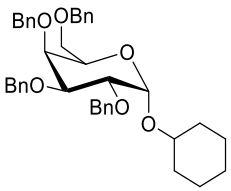
89		**46**	166
90		**47**	167
91		**48**	168
93		**49**	168
94		**50**	169
95		**51**	169
96		**52**	170
97		**53**	170

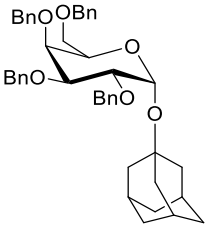
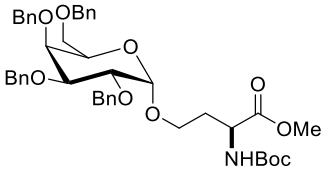
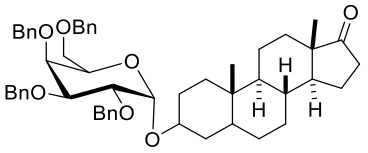
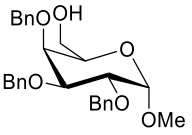
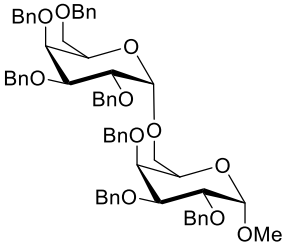
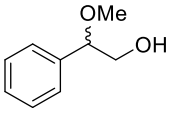
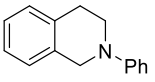
98		**54**	170
113a		**56**	171
113b		**57**	171
113c		**58**	172
113d		**60**	173
114a		**61**	173
114b		**62**	173

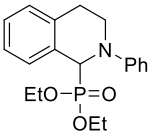
114c		**63**	174
114d		**64**	174
114e		**65**	174
116a		**66**	175
116b		**67**	175
116c		**68**	175

116d		**69**	176
116e		**70**	176
116f		**71**	177
125		**72**	177
130		**74**	178
131		**75**	178
136		**77**	179

138		**78**	179
143		**80**	180
144a		**81**	180
144b		**82**	180
145a		**83**	181
145b		**84**	181

146a		**85**	182
146b		**86**	182
148a		**87**	182
148b		**88**	183
148c		**89**	183

148d		**90**	184
148e		**91**	184
148f		**92**	185
148g		**93**	185
148g		**94**	186
152		**97**	187
153		**98**	187

155		**101**	188

7.1.3 Experimental Procedures

Experiment 1: Synthesis of (2*R*,3*R*,5*R*,6*R*)-dimethyl 5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate 36

The synthesis of compound **36** was carried out according to the procedure described in the literature.[171]

Experiment 2: Synthesis of (2*S*,3*S*,5*R*,6*R*)-2,3-bis(hydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 37

The synthesis of compound **37** was carried out according to the procedure described in the literature.[55]

Experiment 3: Synthesis of (2*S*,3*S*,5*R*,6*R*)-2-hydroxymethyl-3-((*tert*-butyldiphenylsilyl)oxymethyl)- 5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 38

To a stirred solution of **37** (2.09 g, 8.84 mmol) in THF (15 mL) was slowly added NaH (0.85 g, 35.36 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and vigorously stirred for 10 minutes. The solution was cooled again at 0 °C and TBDPSCl (2.5 mL, 9.72 mmol) was added. Then it was carefully quenched with NH_4Cl at 0 °C and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (70:30, Hexane/AcOEt) to afford product **38** (4.03 g, **96%**) as a colourless oil. $[\alpha]_D^{20}$= -81.58 (*c* 1, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 7.69-7.67 (m, 4H), 7.46-7.35 (m, 6H), 3.88-3.66 (m, 6H), 3.25 (s, 3H), 3.11 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H), 1.05 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): 135.7, 135.6, 132.9, 132.8, 129.9, 129.8, 127.8, 127.7, 98.7, 98.6, 71.6, 70.1, 64.6, 62.6, 47.9, 47.8, 26.7, 19.1, 17.6, 17.5 ppm. **FTIR** (neat): 3492 (OH) cm^{-1}. **HRMS** m/z: $[M+H_2O]^+$ calcd for $C_{26}H_{40}O_7Si$ 492.2543; Found 492.2781.

Experiment 4: Synthesis of (2*R*,3*S*,5*R*,6*R*)-2-carbaldehyde-3-((*tert*-butyldiphenylsilyl)oxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 39

To a stirred solution of oxalyl chloride (1 mL, 11.02 mmol) in CH_2Cl_2 (20 mL) was added DMSO (1.6 mL, 22.05 mmol) at -78 °C, the reaction was stirred 30 minutes at this temperature and then the compound **38** (4.03 g,8.48 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise and the solution was stirred at -78 °C during 1 h. After this time the resulting mixture was allowed to warm to rt and Et_3N (4 mL, 29.68 mmol) was added and the solution was stirred at rt for 1 h. After this time the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The compound **39** (4.01 g, **quantitative yield**) was obtained as a yellow oil. **^{1}H NMR** ($CDCl_3$): δ 9.70 (s, 1H), 7.69-7.67 (m, 4H), 7.46-7.35 (m, 6H), 4.30 (d, *J* = 8.71 Hz, 1H), 3.89-3.83 (m, 3H), 3.27 (s, 3H), 3.21 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H), 1.03 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): 198.6, 135.7, 135.6, 133.4, 133.1, 129.7, 127.7, 127.6, 98.9, 98.6, 74.3, 68.3, 63.3, 48.2, 48.0, 26.7, 19.3, 17.5, 17.4 ppm.

Experiment 5: Synthesis of (2*S*,3*S*,5*R*,6*R*)-2-(*R*)-hidroxy-((3,5-bis(trifluoromethyl)phenyl)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 40 and (2*S*,3*S*,5*R*,6*R*)-2-methanol-(*S*)-(3,5-bis(trifluoromethyl)phenyl)-3-((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 41

To a solution of compound **39** (1.72 g, 3.64 mmol) in THF (20 mL) was added (3,5-bis(trifluoromethyl)phenyl)magnesium bromide (14.6 mL) at -78 °C. The resulting mixture was allowed to warm to rt and vigorously stirred. Afterward, the reaction was neutralised with NH_4Cl sat. aq. solution at -78 °C and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product as a mixture of two diastereomers was purified by

flash column chromatography on silica gel (80:20, Hexane/AcOEt) to afford the products **40 (major diastereomer)** and **41 (minor diastereomer)** (*dr* 1.7:1, 3.52 g, **87%**) as a yellow oil.

Compound 40: $[\alpha]_D^{20}$= -61.11 (*c* 0.95, CH_2Cl_2).**^{1}H NMR** ($CDCl_3$): δ 7.92 (s, 2H), 7.78-7.68 (m, 5H), 7.46-7.37 (m, 6H), 5.10 (s, 1H), 4.10-4.02 (m, 2H), 3.82 (ddd, *J* = 21.84, *J* = 11.36 Hz, *J* = 3.36 Hz, 2H), 3.17 (s, 3H), 2.71 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.08 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 144.8, 135.8, 135.5, 133.0, 132.6, 131.1 (q, *J* = 33.30 Hz), 129.9, 129.8, 127.8, 127.7, 126.6 (d, *J* = 3.19 Hz), 123.4 (q, *J* = 272.71 Hz), 121.0 (q, *J* = 3.69 Hz), 99.2, 98.8, 73.1, 71.1, 68.5, 64.5, 47.9, 47.4, 26.7, 19.2, 17.4, 17.2 ppm. **HRMS**: m/z: $[M+Na]^+$ calcd for $C_{34}H_{40}F_6NaO_6Si$ 709.2391; Found 709.2376. **FTIR** (Neat): 3395 (O-H) cm^{-1}.

Compound 41: $[\alpha]_D^{20}$= -40.77 (*c* 1, CH_2Cl_2).**^{1}H NMR** ($CDCl_3$): δ 8.05 (s, 2H), 7.79 (s, 1H), 7.74-7.69 (m, 4H), 7.50-7.39 (m, 6H), 5.74 (d, *J* = 2.48 Hz, 1H), 4.92 (dd, *J* = 8.71 Hz , *J* = 2.42 Hz, 1H), 4.14-4.04 (m, 1H), 3.82 (ddd, *J* = 8.79 Hz , *J* = 8.79 Hz, *J* = 2.74 Hz, 1H), 3.75 (dd, *J* = 11.07 Hz , *J* = 2.60 Hz, 1H), 3.60 (t, *J* = 8.85 Hz, 1H), 2.97 (s, 3H), 2.54 (s, 3H), 1.10 (s, 3H), 1.08 (s, 9H), 1.05 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 144.1, 135.6, 135.5, 131.8, 131.6, 131.1 (q, *J* = 33.44 Hz), 130.3, 130.2, 128.2 (d, *J* = 3.23 Hz), 128.1, 128.0, 123.4 (q, *J* = 273.71 Hz), 121.1 (q, *J* = 4.00 Hz), 98.9, 98.8, 73.1, 71.1, 68.5, 64.5, 47.9, 47.4, 26.7, 19.2, 17.3, 17.2 ppm. **FTIR** (Neat): 3378 (O-H), 1277 (C-O) cm^{-1}. **HRMS**: m/z: $[M+Na]^+$ calcd for $C_{34}H_{40}F_6NaO_6Si$ 709.2391; Found 709.2386.

Experiment 6: Synthesis of (2*S*,3*S*,5*R*,6*R*)-2-(*S*)-azido((3,5-bis(trifluoromethyl)phenyl)methyl)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 43

To a solution of DIAD (1.17 mL, 5.92 mmol) and PPh_3 (1.55 g, 5.92 mmol) in THF (10 mL) was added a solution of compound **40** (2.03 g, 2.96 mmol) and DPPA (1.28 mL, 5.92 mmol) in THF (10 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with H_2O and

extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (85:15, Hexane/AcOEt) to afford the product **43 (major diastereomer)** (1.89 g, **90%**) as a yellow oil. $[\alpha]_D^{20}$= -53.24 (*c* 0.85, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.07 (s, 2H), 7.85 (s, 1H), 7.61 (dd, *J* = 8.12 Hz, *J* = 1.22 Hz, 2H), 7.57 (dd, *J* = 8.18 Hz, *J* = Hz, 2H), 7.42 (td, *J* = 7.33 Hz, *J* = Hz, 2H), 7.37-7.34 (m, 4H), 4.61 (d, *J* = 3.39 Hz, 1H), 4.32 (dd, *J* = 10.16 Hz, *J* = 3.39 Hz, 1H), 3.76 (dd, *J* = 11.23 Hz, *J* = 5.71 Hz, 1H), 3.66 (dd, *J* = 11.22 Hz, *J* = 3.85 Hz, 1H), 3.54-3.49 (m, 1H), 3.29 (s, 3H), 3.03 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H), 1.03 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 138.2, 135.7, 135.5, 133.0, 132.7, 131.5 (q, *J* = 33.50 Hz), 129.9 (d, *J* = 2.13 Hz), 129.8, 129.7, 127.8, 127.7, 124.7 (q, *J* = 272.81 Hz), 122.2 (q, *J* = 3.67 Hz), 98.8, 98.6, 72.4, 68.5, 64.8, 62.6, 48.2, 47.7, 26.8, 19.1, 17.2, 17.1 ppm. **FTIR** (Neat): 2115 (N=N=N) cm^{-1}. **HRMS**: m/z: $[M+Na]^+$ calcd for $C_{34}H_{39}F_6N_3NaO_5Si$ 734.2450; Found 734.2455.

The experimental procedure for compound **43' (minor diastereomer)** (0.18 g, **77%**) was the same and it was obtained as a yellow oil. $[\alpha]_D^{20}$= - 110.3 (*c* 1, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 7.95 (s, 2H), 7.86 (s, 1H), 7.76 (dd, *J* = 8.40 Hz, *J* = 1.44 Hz, 2H), 7.73 (dd, *J* = 8.02 Hz, *J* = 1.58 Hz, 2H), 7.48-7.38 (m, 6H), 5.01 (d, *J* = 1.47 Hz, 1H), 4.07-4.02 (m, 1H), 3.97-3.87 (m, 3H), 3.21 (s, 3H), 2.58 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.11 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 140.2, 135.9, 135.6, 133.2, 132.8, 131.7 (q, *J* = 33.44 Hz), 130.0, 129.9, 128.4 (d, *J* = 2.88 Hz), 127.9, 127.8, 123.2 (q, *J* = 272.74 Hz), 122.0 (q, *J* = 3.73 Hz), 99.4, 98.9, 72.1, 68.8, 64.5, 63.2, 48.0, 47.2, 26.8, 19.3, 17.3, 17.2 ppm. **FTIR** (Neat): 2109 (N=N=N), 1277 (C-O) cm^{-1}. **HRMS**: m/z: $[M-N_3]^-$ calcd for $C_{34}H_{42}F_6O_5Si$ 684.2706; Found 684.2568.

Experiment 7: Synthesis of (2*S*,3*S*,5*R*,6*R*)-2-(*S*)-methanamine-(3,5-bis(trifluoromethyl)phenyl)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 44

To a solution of compound **43** (1.98 g, 2.78 mmol) in THF:H_2O (8:2) (30 mL) was added PPh_3 (1.46 g, 5.56 mmol). The solution was refluxed for 2h, at the end of this time the reaction was quenched with sat. aq. $NaHCO_3$ and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (70:30, Hex/AcOEt) to afford the product **44** (1.82 g, **95%**) as a colourless oil. $[\alpha]_D^{20}$= - 81.47 (*c* 0.68, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 7.99 (s, 2H), 7.76 (s, 1H), 7.66-7.61 (m, 4H), 7.44-7.33 (m, 6H), 4.19 (d, *J* = 3.92 Hz, 1H), 4.09 (dd, *J* = 10.11 Hz, *J* = 4.21 Hz, 1H), 3.78 (dd, *J* = 11.49 Hz, *J* = 5.18 Hz, 1H), 3.68 (dd, *J* = 11.33 Hz, *J* = 3.91 Hz, 1H), 3.47-3.43 (m, 1H), 3.16 (s, 3H), 2.99 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.03 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 145.5, 135.7, 135.5, 133.2, 132.8, 131.1 (q, *J* = 33.29 Hz), 129.8, 128.9 (d, *J* = 2.65 Hz), 127.7, 127.6, 123.4 (q, *J* = 272.95 Hz), 121.0 (q, *J* = 3.56 Hz), 98.6, 98.5, 73.1, 69.9 64.8, 55.5, 48.0, 47.6, 26.8, 19.2, 17.3, 17.2 ppm. **FTIR** (Neat): 2952 (N-H), 1277 (C-O) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{34}H_{42}F_6NO_5Si$ 686.2730; Found 686.2731.

The experimental procedure for compound **44' (minor diastereomer)** (1.70 g, **94%**) was the same and it was obtained as a colourless oil. **^{1}H NMR** ($CDCl_3$): δ 7.85 (s, 2H), 7.77-7.71 (m, 5H), 7.46-7.37 (m, 6H), 4.37 (s, 1H), 4.06-4.01 (m, 1H), 3.94 (dd, *J* = 11.24 Hz, *J* = 3.38 Hz, 1H), 3.89-3.83 (m, 2H), 3.20 (s, 3H), 2.52 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.09 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 146.8, 135.9, 135.6, 133.3, 132.9, 131.1 (q, *J* = 33.07 Hz), 129.9, 127.8, 127.7, 127.5 (d, *J* = 3.00 Hz), 123.5 (q, *J* = 272.44 Hz), 120.6 (q, *J* = 3.70 Hz), 99.1, 98.9, 73.3, 69.2, 64.4, 54.4, 47.9, 47.1, 26.76, 19.2, 17.4, 17.3 ppm. **FTIR** (Neat): 2993 (N-H), 1277 (C-O) cm^{-1} **HRMS**: m/z: $[M+H]^+$ calcd for $C_{34}H_{42}F_6NO_5Si$ 686.2734; Found 686.2731.

Experiment 8: Synthesis of *tert*-butyl ((*S*)-(3,5-bis(trifluoromethyl)phenyl)((2*S*,3*S*,5*R*,6*R*)-3-(((*tert* butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)carbamate 45

To a solution of compound **44** (0.15 g, 0.22 mmol) in CH_2Cl_2 (5 mL) was added Boc_2O (0.08 mL, 0.33 mmol) and Et_3N (0.10 mL, 0.66 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. Then the solution was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (80:20, Hexane/AcOEt) to afford the product **45** (0.16 g, **94%**) as a colourless oil. **^{1}H NMR** ($CDCl_3$): δ 8.05 (s, 2H), 7.78 (s, 1H), 7.68 (dd, *J* = 18.67 Hz, *J* = 6.86 Hz, 4H), 7.44-7.33 (m, 6H), 5.88 (d, *J* = 8.14 Hz, 1H), 4.10 (t, *J* = 6.31 Hz, 1H), 4.20-4.16 (m, 1H), 3.82-3.69 (m, 2H), 3.49 (d, *J* = 9.38 Hz, 1H), 3.07 (s, 3H), 3.01 (s, 3H), 1.41 (s, 9H), 1.27 (s, 3H), 1.24 (s, 3H), 1.04 (s, 9H) ppm.

The experimental procedure for compound **45' (minor diastereomer)** (0.58 g, **54%**) was the same and it was obtained as a colourless oil**. ^{1}H NMR** ($CDCl_3$): δ 7.85-7.67 (m, 7H), 7.44-7.31 (m, 6H), 5.87 (d, *J* = 8.48 Hz, 1H), 5.14 (d, *J* = 8.64 Hz, 1H), 4.22 (d, *J* = 9.66 Hz, 1H), 3.99 (dd, *J* = 11.69 Hz, *J* = 3.33 Hz, 1H), 3.94-3.78 (m, 2H), 3.19 (s, 3H), 2.60 (s, 3H), 1.45 (s, 9H), 1.25 (s, 3H), 1.21 (s, 3H), 1.08 (s, 9H) ppm.

Experiment 9: Synthesis of *tert*-butyl ((*S*)-(3,5-bis(trifluoromethyl)phenyl)((2*S*,3*S*,5*R*,6*R*)-3-(hydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)carbamate 46

To a solution of compound **45** (0.18 g, 0.23 mmol) in THF (5 mL) was added TBAF (0.30 mL, 0.25 mmol). The reaction mixture was stirred for 1 h, then it was quenched with H_2O and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was

purified by flash column chromatography on silica gel (70:30, Hexane/AcOEt) to afford the product **46** (0.091 g, **73%**) as a white solid. **^{1}H NMR** ($CDCl_3$): δ 8.08-8.01 (m, 2H), 7.80 (s, 1H), 5.00 (d, *J* = 8.71 Hz, 1H), 4.89-4.86 (m, 1H), 4.15-4.10 (m, 1H), 3.65 (d, *J* = 4.39 Hz, 2H), 3.35 (s, 1H), 3.22 (s, 3H), 3.05 (s, 3H), 1.41 (s, 9H), 1.34 (s, 3H), 1.28 (s, 3H) ppm.

The experimental procedure for compound **46' (minor diastereomer)** (0.031 g, **63%**) was the same and it was obtained as a white solid**. ^{1}H NMR** ($CDCl_3$): δ 7.84-7.77 (m, 3H), 5.78 (d, *J* = 8.95 Hz, 1H), 5.00 (d, *J* = 8.82 Hz, 1H), 4.01 (d, *J* = 9.46 Hz, 1H), 3.85-3.80 (m, 3H), 3.28 (s, 3H), 2.62 (s, 3H), 1.46 (s, 9H), 1.26 (s, 3H), 1.21 (s, 3H) ppm.

Experiment 10: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-((*S*)-(3,5-bis(trifluoromethyl)phenyl)((tert-butoxycarbonyl)amino)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-nitro-5-(trifluoromethyl)benzoate 47

To a solution of compound **46** (0.084 g, 0.15 mmol) in CH_2Cl_2 (5 mL) was added 3-nitro-5-(trifluoromethyl)benzoic acid (0.053 g, 0.23 mmol). Then the mixture was stirred at 0 °C and EDC.HCl (0.043 g, 0.23 mmol) and DMAP (0.027 g, 0.23 mmol) were added. The resulting mixture was allowed to warm to rt and stirred until all starting material was consumed. Afterwards, the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (80:20, Hexane/AcOEt) to afford the product **47** (0.096 g, **82%**) as a colourless oil. **^{1}H NMR** ($CDCl_3$): δ 8.99 (s, 1H), 8.68 (s, 1H), 8.60 (s, 1H), 8.12 (s, 2H), 7.82 (s, 1H), 5.48 (d, *J* = 8.97 Hz, 1H), 4.97 (dd, *J* = 9.09 Hz, *J* = 2.16 Hz, 1H), 4.53 (d, *J* = 12.38 Hz, 1H), 4.36 (dd, *J* = 12.15 Hz, *J* = 5.33 Hz, 1H), 4.30 (dd, *J* = 10.52 Hz, *J* = 2.37 Hz, 1H), 3.62 (s br, 1H), 3.34 (s, 3H), 3.07 (s, 3H), 1.40 (s, 12H), 1.30 (s, 3H) ppm.

The experimental procedure for compound **47' (minor diastereomer)** (0.032 g, **74%**) was the same and it was obtained as a colourless oil. **^{1}H NMR** ($CDCl_3$): δ 9.06 (t, *J* = 1.68 Hz, 1H), 8.70 (s, 1H), 8.65 (s, 1H), 7.79 (s, 3H), 5.75 (d, *J* = 9.29 Hz, 1H), 5.08 (d, *J* = 9.18 Hz, 1H), 4.72 (dd, *J* = 11.99 Hz, *J* = 4.86 Hz, 1H), 4.64 (dd, *J* = 12.21 Hz, *J* = 3.46 Hz, 1H), 4.19-4.15 (m, 1H), 3.97 (d, *J* = 9.74 Hz, 1H), 3.34 (s, 3H), 2.64 (s, 3H), 1.41 (s, 9H), 1.27 (s, 3H), 1.23 (s, 3H) ppm..

Experiment 11: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-((*S*)-(3,5-bis(trifluoromethyl)phenyl)((tert-butoxycarbonyl)amino)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-amino-5-(trifluoromethyl)benzoate 48

Compound **47** (0.10 g, 0.13 mmol) in EtOH (5 mL) was hydrogenated at 50 psi in the presence of Pd/C 10% (0.016 g) overnight. Then the reaction mixture was filtered and the solvent was evaporated to afford product **48** (0.10 g, **87%**) as a colourless oil. **^{1}H NMR** ($CDCl_3$): δ 8.10 (s, 2H), 7.78 (s, 1H), 7.58 (s, 2H), 7.5 (s, 1H), 5.56 (d, *J* = 9.33 Hz, 1H), 5.15 (dd, *J* = 9.37 Hz, *J* = 9.37 Hz, 1H), 5.56 (d, *J* = 4.59 Hz, 1H), 4.25-4.21 (m, 2H), 3.59-3.54 (m, 1H), 3.32 (s, 3H), 3.04 (s, 3H), 1.43 (s, 9H), 1.38 (s, 3H), 1.29 (s, 3H) ppm.

The experimental procedure for compound **48'** (0.032 g, **99%**) **(minor diastereomer)** was the same and it was obtained as a colourless**. ^{1}H NMR** ($CDCl_3$): δ 7.78 (s, 3H), 7.66 (s, 1H), 7.62 (s, 1H), 7.04 (s, 1H), 5.82 (d, *J* = 8.70 Hz, 1H), 5.17 (d, *J* = 8.77 Hz, 1H), 4.70 (dd, *J* = 12.15 Hz, *J* = 4.03 Hz, 1H), 4.37 (dd, *J* = 12.01 Hz, *J* = 5.41 Hz, 1H), 4.16 (s, 1H), 3.90 (d, *J* = 9.84 Hz, 1H), 3.32 (s, 3H), 2.59 (s, 3H), 1.43 (s, 9H), 1.27 (s, 3H), 1.22 (s, 3H) ppm.

Experiment 12: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-((*S*)-(3,5-bis(trifluoromethyl)phenyl)((tert-butoxycarbonyl)amino)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-isothiocyanato-5-(trifluoromethyl)benzoate 49

To a solution of compound **48** (0.08 g, 0.10 mmol) in CH_2Cl_2 (3 mL) was added TCDI (0.04 g, 0.20 mmol) and imidazole (0.004 g, 0.05 mmol). Afterwards, the resulting mixture was neutralised with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (70:30, Hexane/AcOEt) to afford the product **49** (0.62 g, **78%**) as a colourless oil. **^{1}H NMR** ($CDCl_3$): δ 8.12 (d, *J* = 8.27 Hz, 3H), 8.01 (s, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 5.47 (d, *J* = 9.09 Hz, 1H), 4.98 (dd, *J* = 9.32 Hz, *J* = 2.56 Hz, 1H), 4.78 (dd, *J* = 12.12 Hz, *J* = 2.10 Hz, 1H), 4.31 (dd, *J* = 12.23 Hz, *J* = 5.24 Hz, 1H), 4.24 (dd, *J* = 10.37 Hz, *J* = 2.92 Hz, 1H), 3.58 (s br, 1H), 3.32 (s, 3H), 3.05 (s, 3H), 1.42 (s, 9H), 1.39 (s, 3H), 1.29 (s, 3H) ppm.

The experimental procedure for compound **49'** (0.022 g, **55%**) **(minor diastereomer)** was the same and it was obtained as a colourless oil**. ^{1}H NMR** ($CDCl_3$): δ 8.20 (s, 1H), 8.08 (s, 1H), 7.78 (s, 3H), 7.65 (s, 1H), 5.74 (d, *J* = 9.14 Hz, 1H), 5.07 (d, *J* = 9.25 Hz, 1H), 4.69 (dd, *J* = 12.17 Hz, *J* = 4.78 Hz, 1H), 4.55 (dd, *J* = 12.22 Hz, *J* = 3.57 Hz, 1H), 4.15-4.10 (m, 1H), 3.93 (d, *J* = 10.03 Hz, 1H), 3.32 (s, 3H), 2.61 (s, 3H), 1.42 (s, 9H), 1.27 (s, 3H), 1.22 (s, 3H) ppm.

Experiment 13: Synthesis of (9*H*-fluoren-9-yl)methyl ((*S*)-(3,5-bis(trifluoromethyl)phenyl)((2*S*,3*S*,5*R*,6*R*)-3-(((*tert* butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)carbamate 52

To a solution of compound **44** (0.25 g, 0.56 mmol) in dioxane (10 mL) was added an aqueous solution of $NaHCO_3$ 1M (1.4 mL) at 0 °C. The resulting mixture was

stirred for 10 min. Then Fmoc-Osu (0.21 g, 0.61 mmol) dissolved in dioxane (10 mL) was added. The solution was stirred at rt overnight. After this time it was acidified with citric acid 10% until pH 4 and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (80:20, Hexane/AcOEt) to afford the product **52** (0.20 g, **92%**) as a white solid. **^{1}H NMR** ($CDCl_3$): δ 8.08 (s, 2H), 7.79 (s, 1H), 7.74 (d, *J* = 7.64 Hz, 2H), 7.64 (dd, *J* = 19.17 Hz, *J* = 7.06 Hz, 4H), 7.51 (d, *J* = 7.29 Hz, 2H), 7.42-7.32 (m, 8H), 7.23 (d, *J* = 7.73 Hz, 2H), 6.02 (d, *J* = 8.98 Hz, 1H), 5.14 (q, *J* = 4.37 Hz, 1H), 4.43 (d, *J* = 7.03 Hz, 2H), 4.22-4.18 (m, 2H), 3.73 (d, *J* = 4.09 Hz, 2H), 3.46 (td, *J* = 7.53 Hz, *J* = 4.36 Hz, 1H), 3.13 (s, 3H), 3.01 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.03 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 155.3, 143.7, 143.6, 141.8, 141.3, 135.8, 135.5, 133.0, 132.6, 131.3 (q, *J* = 33.20 Hz), 129.8, 129.4, 127.7, 127.6, 127.0, 124.9, 124.8, 123.3 (q, *J* = 272.47 Hz), 121.5 (q, *J* = 3.76 Hz), 120.0, 98.8, 98.5, 71.2, 69.1, 66.9, 64.7, 53.8, 47.9, 47.6, 47.2, 26.7, 19.2, 17.3, 17.2 ppm.

The experimental procedure for compound **52' (minor diastereomer)** (0.135 g, **90%**) was the same and it was obtained as a white solid. **Mp** 54-56 °C. $[\alpha]_D^{20}$= -50.75 (*c* 1.19, CH_2Cl_2).**^{1}H NMR** ($CDCl_3$): δ 7.87 (s, 2H), 7.81 (d, *J* = 7.45 Hz, 3H), 7.75-7.69 (m, 4H), 7.59 (t, *J* = 6.89 Hz, 2H), 7.44-7.19 (m, 10H), 6.15 (d, *J* = 8.45 Hz, 1H), 5.17 (d, *J* = 8.83 Hz, 1H), 4.59 (dd, *J* = 11.12 Hz, *J* = 6.62 Hz, 1H), 4.43 (dd, *J* = 10.87 Hz, *J* = 6.24 Hz, 1H), 4.26-4.20 (m, 2H), 3.91 (dd, *J* = 11.86 Hz, *J* = 3.18 Hz, 1H), 3.82-3.78 (m, 1H), 3.67 (dt, *J* = 9.74 Hz, *J* = 2.87 Hz, 1H), 3.17 (s, 3H), 2.62 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.08 (s, 9H) ppm.

^{13}C NMR ($CDCl_3$): δ 155.9, 143.8, 143.7, 143.6, 141.4, 136.1, 135.7, 133.4, 133.0, 131.5 (q, *J* = 33.36 Hz), 129.9, 129.7, 127.8, 127.7, 127.6, 127.5, 127.3, 127.1, 127.0, 125.0, 124.9, 123.4 (q, *J* = 272.82 Hz), 121.2 (q, *J* = 3.68 Hz), 120.1, 120.0, 99.1, 98.9, 71.2, 69.0, 66.6, 64.3, 53.8, 47.9, 47.5, 47.3, 26.7, 19.4, 17.4, 17.3 ppm. **FTIR** (Neat): 1726 (C=O), 1277 (C-O) cm^{-1}. **HRMS**: m/z: $[M+Na]^+$ calcd for $C_{49}H_{51}F_6NNaO_7Si$ 930.3227; Found 930.3231.

Experiment 14: Synthesis of (9*H*-fluoren-9-yl)methyl ((*S*)-(3,5-bis(trifluoromethyl)phenyl)((2*S*,3*S*,5*R*,6*R*)-3-(hydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)carbamate 53

To a solution of compound **52** (0.27, 0.30 mmol) in THF (5 mL) was added $Et_3N.3HF$ (0.24 mL, 1.50 mmol). The resulting mixture was stirred at rt for 5 days. Then was quenched with H_2O and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (50:50, Hexane/AcOEt) to afford the product **53 (minor diastereomer)** (0.14 g, **71%**) as a white solid. **Mp** 207-209 °C. $[\alpha]_D^{20}$= -72.26 (*c* 1, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 7.82 (s, 2H), 7.77 (d, *J* = 8.01 Hz, 3H), 7.60 (d, *J* = 7.69 Hz, 2H), 7.44-7.36 (m, 2H), 7.31 (t, *J* = 7.44, 2H), 6.03 (d, *J* = 9.15 Hz, 1H), 5.03 (d, *J* = 9.05 Hz, 1H), 4.62-4.58 (m, 1H), 4.47 (dd, *J* = 11.17 Hz, *J* = 6.16 Hz, 1H), 4.23 (t, *J* = 6.29 Hz, 1H), 4.00 (d, *J* = 9.90 Hz, 1H), 3.79 (td, *J* = 11.79 Hz, *J* = 3.19 Hz, 2H), 3.69 (dt, *J* = 9.70 Hz, *J* = 3.65 Hz, 1H), 3.23 (s, 3H), 2.64 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 155.9, 143.7, 143.6, 143.1, 141.4, 141.3, 131.5 (q, *J* = 33.44 Hz), 127.8, 127.7, 127.3 (d, *J* = 2.68 Hz), 127.1, 127.0, 125.0, 124.8, 123.3 (q, *J* = 273.75 Hz), 121.3 (q, *J* = 3.74 Hz), 120.1, 120.0, 99.1, 98.9, 70.6, 68.8, 66.6, 62.0, 53.6, 48.1, 47.5, 47.4, 17.4, 17.3 ppm. **FTIR** (Neat): 3278 (O-H), 1721 (C=O), 1280 (C-O) cm^{-1}. **HRMS**: m/z: $[M+Na]^+$ calcd for $C_{33}H_{33}F_6NNaO_7$ 692.2052; Found 692.2053**.**

Experiment 15: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-((*S*)-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)(3,5-bis(trifluoromethyl)phenyl)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-nitro-5-(trifluoromethyl)benzoate 54

To a solution of compound **53** (0.32 g, 0.47 mmol) in CH_2Cl_2 (30 mL) was added 3-nitro-5-(trifluoromethyl)benzoic acid (0.22 g, 0.94 mmol). Then the mixture was

stirred at 0 °C and EDC.HCl (0.18 g, 0.94 mmol) and DMAP (0.11 g, 0.94 mmol) were added. The resulting mixture was allowed to warm to rt and stirred until all the starting material was consumed. Afterwards the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (80:20, Hexane/AcOEt) to afford the product **54 (minor diastereomer)** (0.26 g, **61%**) as a white solid. **Mp** 179-181 °C. $[\alpha]_D^{20}$= - 61.48 (*c* 0.4, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.97 (s, 1H), 8.62 (s, 1H), 8.59 (s, 1H), 7.80 (s, 3H), 7.75 (q, *J* = 3.74 Hz, 2H), 7.55 (q, *J* = 3.63 Hz, 2H), 7.39 (q, *J* = 7.49 Hz, 2H), 7.30 (d, *J* = 7.44 Hz, 2H), 6.01 (d, *J* = 9.12 Hz, 1H), 5.12 (d, *J* = 9.12 Hz, 1H), 4.60 (d, *J* = 2.85 Hz, 2H), 4.54 (dd, *J* = 10.25 Hz, *J* = 6.50 Hz, 1H), 4.38 (dd, *J* = 11.31 Hz, *J* = 6.60 Hz, 1H), 4.14 (t, *J* = 6.45 Hz) 4.08 (td, *J* = 9.96 Hz, *J* = 4.12 Hz, 1H), 3.94 (d, *J* = 10.00 Hz, 1H), 3.31 (s, 3H), 2.65 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H) ppm. **FTIR** (Neat): 1720 (C=O), 1535 (N-O) cm^{-1}. **HRMS**: m/z: $[M+Na]^+$ calcd for $C_{41}H_{35}F_9N_2NaO_{10}$ 909.2047; Found 909.2040.

Experiment 16: ((2*S*,3*S*,5*R*,6*R*)-3-((*S*)-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)(3,5-bis(trifluoromethyl)phenyl)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-amino-5-(trifluoromethyl)benzoate 55

To a solution of compound **54** (0.13 g, 0.14 mmol) in AcOEt was added $SnCl_2.2H_2O$ (0.16 g, 0.72 mmol). The resulting mixture was stirred at 50°C overnight. Then it was filtered, washed with satd. aq. $NaHCO_3$ solution and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (70:30, Hexane/AcOEt) to afford the product **55 (minor diastereomer)** (0.1 g, **80%**) as a yellow pale solid. **^{1}H NMR** ($CDCl_3$): δ 7.80 (d, *J* = 6.39 Hz, 3H), 7.75 (dd, *J* = 7.77 Hz, *J* = 2.44 Hz, 2H), 7.64 (s, 1H), 7.57-7.52 (m, 3H), 7.41-7.36 (m, 3H), 7.30-7.21 (m, 2H), 6.16 (d, *J* = 8.65 Hz,

1H), 5.21 (d, *J* = 8.70 Hz, 1H), 4.63 (dd, *J* = 12.12 Hz, *J* = 3.96 Hz, 1H), 4.55 (dd, *J* = 10.68 Hz, *J* = 6.48 Hz, 1H), 4.42-4.32 (m, 2H), 4.19 (t, *J* = 6.60 Hz), 4.06-4.01 (m, 1H), 3.87 (d, *J* = 9.68 Hz, 1H), 3.30 (s, 3H), 2.61 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 165.2, 156.0, 147.5, 143.6, 143.1, 141.4, 131.7 (q, *J* = 32.71 Hz), 131.6 (q, *J* = 33.49 Hz), 127.9, 127.8, 121.2 (d, *J* = 2.72 Hz), 127.1, 124.9, 124.8, 123.7 (q, *J* = 271.78 Hz), 123.2 (q, *J* = 272.94 Hz), 121.5 (q, *J* = 3.70 Hz), 120.0 (d, *J* = 2,64 Hz), 115.9 (q, *J* = 4.09 Hz), 115.2 (d, *J* = 3.58 Hz), 99.2, 99.0, 72.5, 66.8, 66.6, 64.6, 53.8, 48.2, 47.5, 47.2, 17.3, 17.2 ppm. **FTIR** (Neat): 3396 (NH_2), 1706 (C=O ester), 1618 (C=O amide) cm^{-1}.

Experiment 17: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-((*S*)-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)(3,5-bis(trifluoromethyl)phenyl)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-isothiocyanato-5-(trifluoromethyl)benzoate 56

To a solution of compound **55** (0.18 g, 0.211 mmol) in CH_2Cl_2 (5 mL) TCDI (0.09 g, 0.53 mmol) and imidazole (0.014 g, 0.21 mmol) were added. Afterwards, the resulting mixture was neutralised with satd. aq. NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (70:30, Hex/AcOEt) to afford the product **56 (minor diastereomer)** (0.15 g, **78%**) as a white solid. **Mp** 124-126 °C. $[\alpha]_D^{20}$= -56.23 (*c* 0.67, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.15 (s, 1H), 7.95 (s, 1H), 7.80 (s, 3H), 7.77 (dd, *J* = 7.87 Hz, *J* = 4.48 Hz, 2H), 7.57-7.54 (m, 3H), 7.39 (q, *J* = 7.67 Hz, 2H), 7.29 (d, *J* = 7.25 Hz, 2H), 6.06 (d, *J* = 9.08 Hz, 1H), 5.13 (d, *J* = 9.10 Hz, 1H), 4.63-4.49 (m, 3H), 4.42-4.36 (m, 1H), 4.13 (t, *J* = 6.39 Hz, 1H), 4.09-4.06 (m, 1H), 3.92 (d, *J* = 9.65 Hz, 1H), 3.30 (s, 3H), 2.64 (s, 2H), 1.27 (s, 3H), 1.24 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 163.8, 155.9, 143.6, 143.6, 142.9, 141.4, 141.3, 139.7, 133.3, 132.6 (q, *J* = 34.46 Hz), 132.3, 131.6 (q, *J* = 33.39 Hz), 129.9, 127.8 (d, *J* = 2.03 Hz), 127.2, 127.0, 127.0, 124.9, 124.8, 124.7 (q, *J* = 3.50 Hz) , 124.4,

124.2, 123.3 (q, *J* = 271.94 Hz), 122.7 (q, *J* = 273.40 Hz), 121.5 (q, *J* = 3.38 Hz), 120.1, 99.3, 99.1, 71.6, 66.9, 66.8, 65.0, 53.6, 48.2, 47.6, 47.2, 17.3,17.2 ppm. **FTIR** (Neat): 3350 (N-H), 2010 (N=C=S), 1713 (C=O), 1276 (C-O) cm^{-1}. **HRMS**: m/z: $[M+Na]^+$calcd for $C_{42}H_{35}F_9N_2NaO_8S$ 921.1860; Found 921.1863.

Experiment 18: ((2*S*,3*S*,5*R*,6*R*)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate 57

To a solution of compound **38** (1.66 g, 3.49 mmol) in CH_2Cl_2 (20 mL) was added tosyl chloride (1.66 g, 8.73 mmol), Et_3N (1.20 mL, 8.73 mmol) and DMAP (cat. amount) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. Then the solution was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (80:20, Hexane/AcOEt) to afford the product **57** (2.15 g, **98%**) as a colourless oil. **^{1}H NMR** ($CDCl_3$): δ 7.78 (s, 1H), 7.76 (s, 1H), 7.67-7.61 (m, 4H), 7.46-7.34 (m, 6H), 7.28 (s, 1H), 7.25 (s, 1H), 4.48 (dd, *J* = 10.85 Hz, *J* = 2.47 Hz, 1H), 4.15-4.06 (m, 1H), 3.99 (td, *J* = 7.38 Hz, *J* = 2.49 Hz, 1H), 3.69-3.63 (m, 2H), 3.61-3.55 (m, 1H), 3.19 (s, 3H), 3.09 (s, 3H), 2.42 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.10 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 144.6, 135.6, 135.6, 133.1, 133.1, 132.9, 129.8, 129.7, 128.0, 127.8, 127.7, 98.8, 98.6, 69.4, 69.3, 69.0, 64.1, 47.9, 47.8, 26.7, 21.6, 19.1, 17.3, 17.3 ppm. **FTIR** (Neat): 1366 (S=O) cm^{-1}. **HRMS**: m/z: $[M+H_2O]^+$ calcd for $C_{33}H_{46}O_9SSi$ 646.2632; Found 646.2860.

Experiment 19: Synthesis of (((2*S*,3*S*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methoxy)(tert-butyl)diphenylsilane 58

To a solution of compound **57** (2.14 g, 3.40 mmol) in DMF (20 mL) NaN_3 (0.33 g, 5.10 mmol) was added. The resulted mixture was stirred at 70 °C overnight. Then the solution was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The compound **58** (1.68 g, **quantitative yield**) was obtained as a colourless oil. **^{1}H NMR** ($CDCl_3$): δ 7.68-7.65 (m, 4H), 7.45-7.36 (m, 6H), 4.00-3.93 (m, 1H), 3.71-3.66 (m, 3H), 3.44-3.43 (m, 2H), 3.30 (s, 3H), 3.16 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H), 1.04 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 135.7, 135.6, 133.2, 133.0, 129.8, 127.8, 127.7, 98.8, 98.8, 71.0, 69.7, 64.3, 50.9, 48.0, 47.9, 26.7, 19.2, 17.4, 17.3 ppm. **FTIR** (Neat): 2097 (N=N=N) cm^{-1}. **HRMS**: m/z: $[M+H_2O]^+$ calcd for $C_{26}H_{39}N_3O_6Si$ 517.2608; Found 517.2838.

Experiment 20: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanol 59

To a solution of compound **58** (0.85 g, 1.70 mmol) in THF (5 mL) was added TBAF (2.60 mL, 2.55 mmol). The reaction mixture stirred for 1 h, then was quenched with H_2O and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (50:50 Hexane/AcOEt) to afford the product **59** (0.40 g, **90%**) as a white solid. **Mp** 59-61 °C. **^{1}H NMR** ($CDCl_3$): δ 3.99-3.94 (m, 1H), 3.77-3.73 (m, 1H), 3.71-3.66 (m, 1H), 3.63-3.57 (m, 1H), 3.41-3.36 (m, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 2.06 (t, *J* = 6.26 Hz, 1H), 1.33 (s, 3H), 1.31 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 99.1, 98.9, 69.5, 68.5, 62.1, 50.9, 48.1, 48.0, 17.5 ppm. **FTIR** (Neat): 3250 (O-H), 2089 (N=N=N) cm^{-1}.

Experiment 21: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-nitro-5-(trifluoromethyl)benzoate 60

To a solution of compound **59** (0.40 g, 1.52 mmol) in CH_2Cl_2 (10 mL) 3-nitro-5-(trifluoromethyl)benzoic acid (0.54 g, 2.28 mmol) was added. Then the mixture was stirred at 0 °C and EDC.HCl (0.44 g, 2.28 mmol) and DMAP (0.28 g, 2.28 mmol) were added. The resulting mixture was allowed to warm to rt and stirred until all starting material has been consumed. Afterwards the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (80:20, Hexane/AcOEt) to afford the product **60** (0.70 g, **96%**) as colourless oil. **^{1}H NMR** ($CDCl_3$): δ 9.04 (s, 1H), 8.70 (s, 1H), 8.63 (s, 1H), 4.50-4.42 (m, 2H), 4.15-4.10 (m, 1H), 4.02-3.98 (m, 1H), 3.46 (dd, *J* = 13.34 Hz, *J* = 6.15 Hz, 1H), 3.37 (d, *J* = 3.61 Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 162.8, 148.5, 132.9 (q, *J* = 34.87 Hz), 132.9, 131.9 (q, *J* = 3.52 Hz), 127.6, 124.7 (q, *J* = 3.61 Hz), 122.4 (q, *J* = 273.66 Hz), 99.2, 99.1, 68.6, 67.3, 65.1, 51.0, 48.1, 48.0, 17.4, 17.3 ppm. **FTIR** (Neat): 2102 (N=N=N), 1736 (C=O), 1548 (N-O) cm^{-1}. **HRMS**: m/z: $[M+Na]^+$ calcd for $C_{18}H_{21}F_3N_4NaO_8$ 502.1238; Found 502.3742.

Experiment 22: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-amino-5-(trifluoromethyl)benzoate 61

To a solution of compound **60** (0.10 g, 0.22 mmol) in dioxane:H_2O (3:1) (12 mL) NH_4Cl (0.088 g, 1.65 mmol) and Zn (0.11 g, 1.65 mmol) were added. The resulting mixture was stirred at rt. Afterwards, it was filtered and extracted with AcOEt and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (70:30, Hexane/AcOEt) to afford the product **61** (0.04 g, **39%**) as a yellow oil. $[\alpha]_D^{20}$= - 108.46 (*c* 0.95, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 7.74 (d, *J* = 17.14 Hz, 1H), 7.39 (s, 1H), 7.16 (s, 1H), 6.52 (s, 1H), 4.40-4.32 (m, 2H), 4.10-4.05 (m,

1H), 4.00-3.95 (m, 1H), 3.44 (dd, *J* = 13.40 Hz, *J* = 6.44 Hz 1H), 3.36 (d, *J* = 3.09 Hz, 1H), 3.33 (s, 3H), 3.30 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H) ppm. **HRMS**: m/z: [M+H$^+$] calcd for $C_{18}H_{24}N_4F_3O_6$ 449.1570; Found 449.1338.

Experiment 23: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-isothiocyanato-5-(trifluoromethyl)benzoate 62

To a solution of compound **61** (0.04 g, 0.08 mmol) in CH_2Cl_2 was added TCDI (0.03 g, 0.17 mmol) and imidazole (0.003 g, 0.042 mmol). Afterwards, the resulting mixture was neutralised with satd. aq. NH_4Cl sol. and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by preparative TLC (70:30, Hexane/AcOEt) to afford the product **62** (0.006 g, **15%**) as colourless oil. **^{1}H NMR** ($CDCl_3$): δ 8.16 (s, 1H), 8.03 (s, 1H), 7.64 (s, 1H), 4.39 (d, *J* = 4.50 Hz, 2H), 4.09-4.05 (m, 1H), 3.98-3.93 (m, 1H), 3.43 (dd, *J* = 13.02 Hz, *J* = 6.23 Hz, 1H), 3.36 (d, *J* = 3.15 Hz, 1H), 3.32 (s, 3H), 3.30 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H) ppm.

Experiment 24: Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((3,5-bis(trifluoromethyl)phenyl)((2*S*,3*S*,5*R*,6*R*)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)thiourea 64

To a solution of compound **44** (0.14 g, 0.20 mmol) in CH_2Cl_2 (10 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (54 µL, 0.30 mmol). The resulting mixture was stirred for 1 h and then it was evaporated. The crude product was purified by flash column chromatography on silica gel (90:10, Hexane/AcOEt) to afford the product **64** (0.19 g, **97%**) as a white solid. **^{1}H NMR** ($CDCl_3$): δ 8.30 (s, 1H), 8.15 (s, 2H), 7.81 (s, 1H), 7.77 (s, 1H), 7.70 (s, 2H), 7.64 (dt, *J* = 8.01 Hz, *J* = 1.61 Hz, 4H), 7.43-7.38 (m, 2H), 7.34 (q, *J* = 7.16 Hz, 4H), 6.00 (s br, 1H), 4.29

(dd, *J* = 10.07 Hz, *J* = 4.07 Hz, 1H), 3.76 (dd, *J* = 11.40 Hz, *J* = 4.78 Hz, 1H), 3.67 (dd, *J* = 11.35Hz, *J* = 3.88 Hz, 1H), 3.40-3.34 (m, 1H), 2.96 (s, 6H), 1.21 (s, 3H), 1.18 (s, 3H), 1.06 (s, 9H) ppm. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{43}H_{45}F_{12}N_2O_5SSi$ 957.2621; Found 957.2515.

The experimental procedure for compound **64' (minor diastereomer)** (0.25 g, **91%**) was the same and this compound was obtained as a white solid. **Mp** 47-49 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -11.66 (*c* 0.52, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.82 (s, 1H), 7.97 (s, 2H), 7.89 (s, 2H), 7.85 (d, *J* = 7.51 Hz, 1H), 7.79 (d, *J* = 6.94 Hz, 2H), 7.74 (d, *J* = 6.51 Hz, 2H), 7.70 (s, 1H), 7.43-7.34 (m, 6H), 6.00 (d, *J* = 7.52 Hz, 1H), 4.42 (d, *J* = 9.88 Hz, 1H), 4.16-4.06 (m, 1H), 3.85 (d, *J* = 11.80 Hz, 1H), 3.65 (d, *J* = 9.25 Hz, 1H), 3.14 (s, 3H), 2.75 (s, 3H), 1.28 (s, 3H), 1.17 (s, 3H), 1.08 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 181.2, 142.6, 139.4, 136.0, 135.6, 133.2, 132.9 (q, *J* = 34.01 Hz), 131.6 (q, *J* = 33.42 Hz), 129.8, 129.7, 127.8, 127.6, 123.6, 122.9 (q, *J* = 272.65 Hz), 1225, 122.3 (q, *J* = 272.95 Hz), 121.5 (q, *J* = 3.40 Hz), 119.1 (q, *J* = 3.80 Hz), 99.3, 98.8, 71.1, 69.0, 64.2, 56.5, 48.1, 47.6, 26.6, 19.4, 17.4, 17.2 ppm. **FTIR** (Neat): 1276 (C-O), 1126 (C=S) cm^{-1}.

Experiment 25: Synthesis of (3,5-bis(trifluoromethyl)phenyl)-3-((*S*) or (*R*)-(3,5-bis(trifluoromethyl)phenyl)((2*S*,3*S*,5*R*,6*R*)-3-(hydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)thiourea 65 and 66

To a solution of compound **64** (0.32 g, 0.33 mmol) in THF (10 mL) was added TBAF (0.37 mL, 0.40 mmol). The reaction mixture was stirred for 1 h, then it was quenched with H_2O and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (60:40, Hexane/AcOEt) to afford the product **65** (0.22 g, **91%**) as a white solid. **Mp** 167-169 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= -98.18 (*c* 1, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.53 (s, 1H), 8.11 (s, 2H), 7.83 (s, 1H), 7.76 (s, 3H), 7.30 (d, *J* = 7.98 Hz, 1H), 5.78 (t, *J* = 6.04 Hz, 1H), 4.21 (q, *J* = 5.06 Hz, 1H), 3.71-3.63 (m, 2H), 3.35 (dt, *J* = 10.04 Hz, *J* = 3.73 Hz, 1H), 3.03 (s, 3H),

2.93 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 179.8, 139.9, 138.4, 133.3 (q, *J* = 34.18 Hz), 131.5 (q, *J* = 33.33 Hz), 129.7 (d, *J* = 2.75 Hz), 124.6 (d, *J* = 3.61 Hz), 122.9 (q, *J* = 274.24 Hz), 122.6 (q, *J* = 273.09 Hz), 122.1 (q, *J* = 3.65 Hz), 120.1 (q, *J* = 3.54 Hz), 99.2, 98.8, 69.2, 69.0, 62.0, 57.1, 47.9, 17.2, 17.0 ppm. **FTIR** (Neat): 3330 (N-H), 3302 (O-H), 1275 (C-O), 1123 (C=S) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{27}H_{27}F_{12}N_2O_5S$ 719.1444; Found 719.1444**.**

The experimental procedure for compound **66 (minor diastereomer)** (0.19 g, **99%**) was the same and this compound was obtained as a white solid. **Mp** 175-177 °C. $[\alpha]_D^{20}$= -56.8 (*c* 1, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.49 (s, 1H), 7.91 (s, 2H), 7.88 (s, 2H), 7.83 (s, 1H), 7.75 (s, 1H) 7.66 (d, *J* = 8.21 Hz, 1H), 5.94 (d, *J* = 8.32 Hz, 1H), 4.12 (d, *J* = 10.18 Hz, 1H), 3.92 (t, *J* = 4.70 Hz, 2H), 3.70 (dt, *J* = 7.22 Hz, *J* = 3.56 Hz, 1H), 3.19 (s, 3H), 2.76 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 181.1, 142.0, 139.0, 132.8 (q, *J* = 33.85 Hz), 131.7 (q, *J* = 33.15 Hz), 127.6 (d, *J* = 2.89 Hz), 124.3 (q, *J* = 273.28 Hz), 124.0 (d, *J* = 3.13 Hz), 123.2 (q, *J* = 272.96 Hz), 121.7 (q, *J* = 3.69 Hz), 119.5 (q, *J* = 3.64 Hz), 99.2, 98.9, 70.7, 68.8, 62.2, 56.5, 48.3, 47.9, 17.3, 17.2 ppm. **FTIR** (Neat): 3340 (N-H), 3304 (O-H), 1277 (C-O), 1121 (C=S) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{27}H_{27}F_{12}N_2O_5S$ 719.1440; Found 719.1444).

Experiment 26: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene)-bis(4-methylbenzenesulfonate) 67

To a solution of compound **37** (0.55 g, 2.32 mmol) in CH_2Cl_2 (15 mL) was added tosyl chloride (2.21 g, 11.6 mmol), Et_3N (1.60 mL, 11.6 mmol) and DMAP (cat. amount) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. Then the solution was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (70:30, Hexane/AcOEt) to afford the product **67** (1.00 g, **79%**) as a white solid. **Mp** 110-112 °C. **^{1}H NMR** ($CDCl_3$): δ 7.79 (d, *J* = 8.26 Hz, 4H), 7.35 (d, *J* =

8.16 Hz, 4H), 4.05-4.03 (m, 4H), 3.81-3.78 (m, 2H), 3.13 (s, 6H), 2.46 (s, 6H), 1.17 (s, 6H) ppm. **^{13}C NMR** ($CDCl_3$): δ 145.0, 132.6, 129.9, 128.0, 98.9, 68.7, 66.9, 48.0, 21.6, 17.2 ppm. **FTIR** (Neat): 1353 (S=O) cm^{-1}. **HRMS**: m/z: $[M+NH_4]^+$ calcd for $C_{24}H_{36}NO_{10}S_2$ 562.1775; Found 562.1777**.**

Experiment 27: Synthesis of (2*R*,3*R*,5*S*,6*S*)-5,6-bis(azidomethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane 68

To a solution of compound **67** (1.00 g, 1.84 mmol) in DMF (15 mL) was added NaN_3 (0.35 g, 5.52 mmol). The reaction mixture was stirred at 70 °C overnight. Then the solution was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The compound **68** (0.49 g, **93%**) was obtained as a white solid**. Mp** 61-63 °C. $[\alpha]_D^{20}$= -103.10 (*c* 0.36, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 3.88-3.86 (m, 2H), 3.38-3.33 (m, 2H), 3.31 (s, 6H), 3.23 (d, *J* = 2.64 Hz, 1H), 3.19 (d, *J* = 2.59 Hz, 1H), 1.32 (s, 6H) ppm. **^{13}C NMR** ($CDCl_3$): δ 99.2, 69.1, 50.9, 48.2, 17.4 ppm. **FTIR** (Neat): 2096 (N=N=N) cm^{-1}. **HRMS**: m/z: $[M+Na]^+$ calcd for $C_{10}H_{18}F_6N_6NaO_4$ 309.1282; Found 309.0978.

Experiment 28: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanamine 69

Compound **68** (0.49 g, 1.72 mmol) in EtOH (10 mL) was hydrogenated at 50 psi in the presence of Pd/C 10% (0.05 g) overnight. Then the reaction mixture was filtered, washed with CH_3OH and the solvent was evaporated to afford product **69** (0.40 g, **quantitative yield**) as a white solid. **Mp** 85-87 °C. **^{1}H NMR** ($CDCl_3$): δ 3.60-3.58 (m, 2H), 3.28 (s, 6H), 2.76 (d, *J* = 5.36 Hz, 4H), 1.62 (br s, 2H), 1.32 (s, 6H) ppm. **^{13}C NMR** ($CDCl_3$): δ 98.6, 71.1, 47.9, 42.6, 17.6 ppm. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{10}H_{23}N_2O_4$ 235.1613; Found 235.1650.

Experiment 29: Synthesis of (((2*S*,3*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene))bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) 70

To a solution of compound **69** (0.40 g, 1.72 mmol) in CH_2Cl_2 (10 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.90 mL, 5.16 mmol). The resulting mixture was stirred for 1 h and then was evaporated. The crude product was purified by flash column chromatography on silica gel (60:40, Hexane/AcOEt) to afford the product **70** (1.16 g, **91%**) as a white solid. **Mp** 102-104 °C. $[\alpha]_D^{20}$= -64.58 (*c* 1, CH_3OH). **^{1}H NMR** (CD_3OD): δ 8.22 (s, 4H), 7.63 (s, 2H), 4.01-3.94 (m, 4H), 3.83-3.79 (m, 2H), 3.31 (s, 6H), 1.34 (s, 6H) ppm. **^{13}C NMR** (CD_3OD): δ 181.7, 141.61, 131.3 (q, *J* = 33.38 Hz), 123.3 (q, *J* = 271.93 Hz), 122.0, 116.5 (q, *J* = 3.56 Hz), 98.8, 67.9, 47.1, 44.6, 16.5 ppm. **FTIR** (Neat): 3338 (N-H), 1122 (C=S) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{28}H_{29}F_{12}N_4O_4S_2$ 777.1433; Found 777.1435.

Experiment 30: Synthesis of benzyl-(3,5-bis(trifluoromethyl)phenyl)((2*S*,3*S*,5*R*,6*R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)carbamate 71

To a solution of compound **44** (1.58 g, 2.30 mmol) in CH_2Cl_2 (15 mL) was added CbzCl (1.31 mL, 9.21 mmol) dropwise and Et_3N (2.55 mL, 18.40 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. The solution was washed with satd. aq. $NaHCO_3$ sol. and H_2O and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (70:30, Hexane/AcOEt) to afford the product **71 (major diastereomer)** (1.17 g, **90%**) as a colourless oil. $[\alpha]_D^{20}$= -55.46 (*c* 0.6, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.08 (s, 2H), 7.79 (s, 1H), 7.65 (dd, *J* = 20.49 Hz, *J* = 7.18 Hz, 4H), 7.43-7.32 (m, 11H), 6.10

(d, *J* = 8.83 Hz, 1H), 5.17-5.06 (m, 3H), 4.2 (dd, *J* = 10.24 Hz, *J* = 4.44 Hz, 1H), 3.73 (d, *J* = 3.73 Hz, 2H), 3.46-3.41 (m, 1H), 3.10 (s, 3H), 2.99 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 1.04 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 155.4, 142.0, 136.2, 135.8, 135.6, 133.0, 132.6, 131.2 (q, *J* = 33.29 Hz), 129.8, 129.4 (d, *J* = 2.48 Hz), 128.6, 128.3, 128.2, 127.8, 127.7, 123.4 (q, *J* = 271.99 Hz), 121.5 (q, *J* = 3.80 Hz), 98.8, 98.5, 71.0, 69.2, 67.2, 64.8, 54.1, 48.0, 47.6, 26.7, 19.2, 17.3, 17.2 ppm. **FTIR** (Neat): 2953 (N-H), 1277 (C-O) cm^{-1}. **HRMS**: m/z: $[M+Na]^+$ calcd for $C_{42}H_{47}F_6NNaO_7Si$ 842.2906; Found 842.2918.

The experimental procedure for compound **71' (minor diastereomer)** (0.62 g, **92%**) was the same and this compound was obtained as a colourless oil**. ^{1}H NMR** ($CDCl_3$): δ 7.85 (s, 2H), 7.79 (d, *J* = 7.07 Hz, 2H), 7.73 (d, *J* = 7.39 Hz, 3H), 7.45-7.36 (m, 11H), 6.15 (d, *J* = 8.21 Hz, 1H), 5.18-5.06 (m, 3H), 4.20 (d, *J* = 9.38 Hz, 1H), 3.98 (dd, *J* = 11.62 Hz, *J* = 2.88 Hz, 1H), 3.91-3.77 (m, 2H), 3.14 (s, 3H), 2.60 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.08 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 155.9, 143.9, 136.0, 135.6, 133.4, 132.9, 131.4 (q, *J* = 33.84 Hz), 129.8, 129.7, 128.7, 128.5, 128.3, 127.8, 127.6, 127.2 (d, *J* = 2.99 Hz), 123.3 (q, *J* = 272.74 Hz), 121.2 (q, *J* = 3.68 Hz), 99.1, 98.8, 71.4, 68.8, 67.3, 64.3, 53.9, 47.9, 47.2, 26.6, 19.3, 17.4, 17.2.

Experiment 31: Synthesis of benzyl-(3,5-bis(trifluoromethyl)phenyl)((2*S*,3*S*,5*R*,6*R*)-3-(hydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl)carbamate 72

To a solution of compound **71** (0.52 g, 0.63 mmol) in THF (15 mL) was added TBAF (0.7 0 mL, 0.69 mmol). The reaction mixture stirred for 1 h, then it was quenched with H_2O and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (60:40, Hexane/AcOEt) to afford the product **72 (major diastereomer)** (0.36 g, **98%**) as a white solid. **^{1}H NMR** ($CDCl_3$): δ 8.08 (s, 2H), 7.81 (s, 1H), 7.33 (s, 5H), 5.93 (d, *J* = 8.82 Hz, 1H),

5.11-5.02 (m, 2H), 4.94 (dd, *J* = 8.85 Hz, *J* = 4.13 Hz, 1H), 4.15 (dd, *J* = 10.26 Hz, *J* = 4.13 Hz, 1H), 3.63 (s, 2H), 3.32-3.28 (m, 1H), 3.19 (s, 3H), 3.03 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 155.4, 141.1, 135.9, 131.4 (q, *J* = 33.39 Hz), 129.5 (d, *J* = 2.93 Hz), 128.6, 128.4, 128.3, 123.3 (q, *J* = 272.80 Hz), 121.8 (q, *J* = 3.85 Hz), 99.0, 98.7, 69.8, 68.8, 67.3, 61.9, 53.9, 48.3, 47.8, 17.3, 17.2 ppm.

The experimental procedure for compound **72' (minor diastereomer)** (0.40 g, **93%**) was the same and this compound was obtained as a white solid. **Mp** 143-145 °C. $[\alpha]_D^{20}$= - 73.15 (*c* 0.7, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 7.83 (s, 2H), 7.78 (s, 1H), 7.39-7.65 (m, 5H), 6.08 (d, *J* = 8.80 Hz, 1H), 5.12 (d, *J* = 3.54 Hz, 2H), 5.08-5.04 (m, 1H), 4.00 (d, *J* = 8.91 Hz, 1H), 3.88-3.80 (m, 3H), 3.22 (s, 3H), 2.62 (s, 3H), 1.24 (s, 3H), 1.19 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 156.0, 143.2, 135.9, 131.5 (q, *J* = 33.70 Hz), 128.7, 128.5, 128.4, 127.2 (d, *J* = 2.86 Hz), 123.3 (q, *J* = 273.06 Hz), 121.3 (q, *J* = 3.51 Hz), 99.2, 98.9, 70.7, 68.8, 67.5, 53.7, 48.1, 47.5, 17.4, 17.2 ppm. **FTIR** (Neat): 3450 (OH), 3250 (N-H), 1718 (C=O) cm^{-1}. **HRMS** m/z: $[M-H]^-$ calcd for $C_{26}H_{28}F_6NO_7$ 580.1770; Found 580.1780.

Experiment 32: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-(((benzyloxy)carbonyl)amino)(3,5-bis(trifluoromethyl)phenyl)methyl-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-nitro-5-(trifluoromethyl)benzoate 73

To a solution of compound **72** (0.39 g, 0.67 mmol) in CH_2Cl_2 (10 mL) was added 3-nitro-5-(trifluoromethyl)benzoic acid (0.24 g, 1.01 mmol). Then the mixture was stirred at 0 °C and EDC.HCl (0.19 g, 1.01 mmol) and DMAP (0.12 g, 1.01 mmol) were added. The resulting mixture was allowed to warm to rt and stirred until all the starting material was consumed. Afterward, the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (70:30, Hexane/AcOEt) to afford the

product **73 (major diastereomer)** (0.53 g, **99%**) as a white solid. **Mp** 55-57 °C. $[\alpha]_D^{20}$= - 61.38 (*c* 0.68, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.99 (s, 1H), 8.69 (s, 1H), 8.59 (s, 1H), 8.12 (s, 2H), 7.83 (s, 1H), 7.32 (s, 5H), 5.81 (d, *J* = 9.03 Hz, 1H), 5.11-5.00 (m, 3H), 4.52 (dd, *J* = 11.97 Hz, *J* = 2.81 Hz, 1H), 4.34 (dd, *J* = 12.22 Hz, *J* = 5.42 Hz, 1H), 4.28 (dd, *J* = 10.56 Hz, *J* = 3.25 Hz, 1H), 3.58-3.53 (m, 1H), 3.28 (s, 3H), 3.04 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 162.8, 155.4, 148.5, 140.1, 135.8, 132.8 (q, *J* = 35.36 Hz), 132.0 (q, *J* = 3.67 Hz), 131.7 (q, *J* = 33.36 Hz), 129.5 (d, *J* = 2.45 Hz), 128.6, 128.5, 128.4, 127.6, 124.7 (d, *J* = 3.79 Hz), 123.1 (q, *J* = 273.25 Hz), 122.2 (q, *J* = 3.63 Hz), 99.1, 98.9, 69.6, 67.5, 66.5, 64.7, 53.7, 48.3, 47.8, 17.3, 17.2 ppm. **FTIR** (Neat): 2953 (N-H), 1724 (C=O), 1548 (N-O), 1277 (C-O) cm^{-1}. **HRMS** $[M\text{-}Cbz]^-$ calcd for $C_{26}H_{26}F_9N_2O_8$ 665.1540; Found 665.1543.

The experimental procedure for compound **73' (minor diastereomer)** (0.49 g, **96%**) was the same and the compound was obtained as a white solid**. ^{1}H NMR** ($CDCl_3$): δ 9.05 (s, 1H), 8.70 (s, 1H), 8.65 (s, 1H), 7.80 (s, 3H), 7.35 (s, 5H), 6.07 (d, *J* = 8.94 Hz, 1H), 5.12-5.04 (m, 3H), 4.68 (dd, *J* = 12.14 Hz, *J* = 4.79 Hz, 1H), 4.61 (dd, *J* = 12.11 Hz, *J* = 3.75 Hz, 1H), 4.18-4.13 (m, 1H), 3.94 (d, *J* = 9.80 Hz, 1H), 3.29 (s, 3H), 2.63 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H) ppm.

Experiment 33: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-amino(3,5-bis(trifluoromethyl)phenyl)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-amino-5-(trifluoromethyl)benzoate 74

Compound **73** (0.95 g, 0.76 mmol) in AcOEt (5 mL) was hydrogenated at 50 psi in the presence of Pd/C 10% (0.08 g) for 50 minutes. Then the reaction mixture was filtered with CH_3OH and the solvent was evaporated to afford product **74 (major diastereomer)** (0.37 g, **61%**) as a white solid. **Mp** 48-50 °C. $[\alpha]_D^{20}$= -122 (*c* 0.5, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 7.98 (s, 2H), 7.76 (s, 1H), 7.60 (s, 1H), 7.42 (s, 1H), 7.06 (s, 1H), 4.45 (dd, , *J* = 12.12 Hz, *J* = 3.21 Hz, 1H), 4.29 (dd, *J* = 11.97 Hz, *J* = 5.79 Hz, 1H), 4.11-4.08 (m, 2H), 3.99 (s, 2H), 3.67-3.62 (m,1H), 3.27 (s,

3H), 3.07 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 165.2, 147.1, 145.2, 132.0 (q, *J* = 32.45 Hz), 131.5, 131.4 (q, *J* = 33.31 Hz), 128.5 (d, *J* = 2.71 Hz), 123.6 (q, *J* = 272.78 Hz), 123.3 (q, *J* = 272.41 Hz), 121.3 (q, *J* = 3.66 Hz), 118.6, 116.0 (q, *J* = 3.89 Hz), 115.4 (q, *J* = 3.65 Hz), 98.9, 98.6, 71.5, 67.7, 64.4, 55.9, 48.1, 47.7, 17.3, 17.2 ppm. **FTIR** (Neat): 3375 (N-H), 1278 (C-O) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{26}H_{28}F_9N_2O_6$ 635.1798; Found 635.1792.

The experimental procedure for compound **74' (minor diastereomer)** (0.31 g, **84%**) was the same and the compound was obtained as a white solid. **^{1}H NMR** (CD_3OD): δ 8.03 (s, 2H), 7.84 (s, 1H), 7.55 (s, 1H), 7.52 (s, 1H), 7.15 (s, 1H), 4.68 (dd, *J* = 12.34 Hz, *J* = 5.13 Hz, 1H), 4.51 (dd, *J* = 12.44 Hz, *J* = 2.68 Hz, 1H), 4.39-4.34 (m, 2H), 3.83 (dd, *J* = 10.10 Hz, *J* = 2.68 Hz, 1H), 3.33 (s, 3H), 2.57 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H) ppm.

Experiment 34: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-((*S*) or -(*R*)-(3,5-bis(trifluoromethyl)phenyl)(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-5-(trifluoromethyl)benzoate 75 and 76

To a solution of compound **74** (0.36 g, 0.57 mmol) in CH_2Cl_2 (5 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.04 mL, 5.69 mmol). The resulting mixture was stirred for 1 h and then it was evaporated. The crude product was purified by flash column chromatography on silica gel (80:20, Hexane/AcOEt) to afford the product **75 (major diastereomer)** (0.554 g, **83%**) as a yellow pale solid. **Mp** 109-111 °C. $[\alpha]_D^{20}$= - 55.10 (*c* 1.2, CH_2Cl_2).**^{1}H NMR** ($CDCl_3$): δ 8.55-8.51 (m, 1H), 8.35-8.29 (m, 3H), 8.14 (s, 1H), 8.12 (s, 2H), 8.00 (s, 1H), 7.93 (s, 2H), 7.82 (s, 1H), 7.79 (s, 1H), 7.72 (s, 1H), 7.67 (s, 2H), 7.04 (d, *J* = 8.11 Hz, 1H), 5.99 (dd, *J* = 8.41 Hz, *J* = 3.36 Hz, 1H), 4.46 (dd, *J* = 12.09 Hz, *J* = 4.53 Hz, 1H), 4.39 (dd, *J* = 12.20 Hz, *J* = 4.47 Hz, 1H), 4.33 (dd, *J* = 10.37 Hz, *J* = 3.55 Hz, 1H), 3.53-3.48 (m, 1H), 3.05 (s, 3H), 3.01 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H) ppm. **^{13}C**

NMR ($CDCl_3$): δ 180.2, 179.4, 163.9, 138.9, 138.8, 138.2, 137.9, 133.6 (q, *J* = 34.39 Hz), 132.5 (q, *J* = 34.06 Hz), 131.8 (q, *J* = 33.32 Hz), 131.7, 129.8 (d, *J* = .31 Hz), 128.7, 125.9 (q, *J* = 3.66 Hz), 124.7 (d, *J* = 3.51 Hz), 124.6 (q, *J* = 2.14 Hz), 124.4 (d, *J* = 3.51 Hz), 123.0 (q, *J* = 273.12 Hz), 122.8 (q, *J* = 274.29 Hz), 122.5 (q, *J* = 3.79 Hz), 120.4 (q, *J* = 4.01 Hz), 120.0 (q, *J* = 3.67 Hz), 99.2, 98.9, 69.9, 66.1, 64.3, 56.9, 48.1, 47.9, 17.1, 17.0 ppm. **FTIR** (Neat): 1730 (C=O), 1275 (C-O), 1123 (C=S) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{41}H_{25}F_{21}N_4NaS_2$ 1199.1391; Found 1199.1385.

The experimental procedure for compound **76 (minor diastereomer)** (0.463 g, **69%**) was the same and this compound was obtained as a white solid. **Mp** 105-107 °C. $[\alpha]_D^{20}$= -32.84 (*c* 0.88, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.72 (s, 1H), 8.67 (s, 1H), 8.28 (s, 1H), 8.20 (s, 1H), 8.13 (s, 1H), 8.09 (s, 1H), 8.01 (d, *J* = 7.35 Hz, 1H), 7.83 (d, *J* = 7.76 Hz, 7H), 7.68 (s, 1H), 7.64 (s, 1H), 5.85 (d, *J* = 7.24 Hz, 1H), 4.75 (dd, *J* = 12.21 Hz, *J* = 3.52 Hz, 1H), 4.46 (dd, *J* = 12.23 Hz, *J* = 5.35 Hz, 1H), 4.02-3.93 (m, 2H), 3.27 (s, 3H), 2.69 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 181.1, 179.9, 164.2, 141.9, 138.8, 138.7, 133.0-131.3 (m), 131.1, 127.8, 127.6 (d, *J* = 2.30 Hz), 125.3 (q, *J* = 2.25 Hz), 124.7 (d, *J* = 3.22 Hz), 124.1 (d, *J* = 3.76 Hz), 123.9 (q, *J* = 3.70 Hz), 123.1 (q, *J* = 271.89 Hz), 122.9 (q, *J* = 273.63 Hz), 122.6 (q, *J* = 272.31 Hz), 121.8 (q, *J* = 2.20 Hz), 119.9-119.7 (m), 99.5, 99.1, 72.8, 66.8, 65.1, 56.9, 48.5, 47.9, 17.2, 17.0 ppm. **FTIR** (Neat): 1726 (C=O), 1275 (C-O), 1124 (C=S) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{44}H_{34}F_{21}N_4O_6S_2$ 1177.1575; Found 1177.1579.

Experiment 35: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-((*S*)-(3,5-bis(trifluoromethyl)phenyl)(3-(3,5-bis(trifluoromethyl)phenyl)thioureia)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-amino-5-(trifluoromethyl)benzoate 77

The experimental procedure was the same of the one followed for the obtention of compounds **75** and **76**.

Mp 91-93 °C. $[\alpha]_D^{20}$**=** -79.28 (*c* 1.2, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.42 (s, 1H), 8.14 (s, 2H), 7.81 (s, 1H), 7.78 (s, 1H), 7.71 (s, 2H), 7.64 (d, *J* = 9.61 Hz, 2H), 7.16 (d, *J* = 7.16 Hz, 2H), 5.98 (dd, *J* = 8.65 Hz, *J* = 3.30 Hz, 1H), 4.44 (dd, *J* = 12.05 Hz, *J* = 4.88 Hz, 1H), 4.34 (dd, *J* = 12.17 Hz, *J* = 4.58 Hz, 1H), 4.26 (dd, *J* = 10.24 Hz, *J* = 3.76 Hz, 1H), 3.53-3.48 (m, 1H), 3.03 (s, 3H), 3.02 (s, 3H), 1.25 (s, 3H), 1.22 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 179.6, 165.1, 139.1, 138.1, 133.5 (q, *J* = 33.98 Hz), 132.7-131.2 (m), 129.8 (d, *J* = 3.28 Hz), 124.6 (d, *J* = 2.80 Hz) 123.5 (q, *J* = 271.98 Hz), 123.1 (q, *J* =272.40 Hz), 122.5 (q, *J* = 273.24 Hz), 122.3 (q, *J* = 3.76 Hz), 120.3 (q, *J* = 3.51 Hz), 119.6 (q, *J* = 3.14 Hz), 117.2 (q, *J* = 2.38 Hz), 116.5 (q, *J* = 2.86 Hz), 99.1, 98.7, 70.1, 66.3, 64.0, 57.0, 48.0, 47.8, 17.1, 17.0 ppm. **FTIR** (Neat): 3410 (N-H), 1707 (C=O), 1275 (C-O), 1124 (C=S) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{35}H_{30}F_{15}N_4O_6S$ 906.1649; Found 906.1680.

Experiment 36: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-(aminomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methyl 3-amino-5-(trifluoromethyl)benzoate 78

Compound **60** (0.20 g, 0.42 mmol) in AcOEt (10 mL) was hydrogenated at 50 psi in the presence of Pd/C 10% (0.02 g) overnight. Then the reaction mixture was filtered and washed with CH_3OH and the solvent was evaporated to afford product **78** (0.033 g, **19%**) as colourless oil. **^{1}H NMR** ($CDCl_3$): δ 7.62 (s, 1H), 7.47 (s, 1H), 7.05 (s, 1H), 4.40-4.32 (m, 2H), 3.98 (q, *J* = 4.88 Hz, 1H), 3.80-3.75 (m, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 2.95-2.84 (m, 2H), 1.32 (s, 6H) ppm. **^{13}C NMR** ($CDCl_3$): δ 165.3, 147.3, 132.0 (q, *J* = 32.70 Hz), 131.6, 123.7 (q, *J* = 272.83 Hz), 118.5, 115.9 (q, *J* = 4.05 Hz), 115.3 (q, *J* = 3.68 Hz), 98.9, 98.7, 70.1, 68.0, 64.5, 48.0, 47.9, 424.4, 17.6, 17.5 ppm

Experiment 37: Synthesis of [(2*S*,5*R*,6*R*)-3-[({[3,5-bis(trifluoromethyl)phenyl]carbamothioyl}amino)methyl]- 5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl]methyl 3-({[3,5-bis(trifluoromethyl)phenyl]carbamothioyl}amino)-5-(trifluoromethyl)benzoate 79

To a solution of compound **78** (0.056 g, 0.13 mmol) in CH_2Cl_2 (5 mL) was added 3.5-bis(trifluoromethyl)phenyl isothiocyanate (0.06 mL, 0.33 mmol). The resulting mixture was stirred for 1 h and then it was evaporated. The crude product was purified by flash column chromatography on silica gel (50:50, Hexane/AcOEt) to afford the product **79** (0.043 g, **47%**) as an orange solid. **Mp** 103-105 °C. $[\alpha]_D^{20}$= -117.04 (*c* 0.26, CH_2Cl_2).**^{1}H NMR** (CD_3OD): δ 8.58 (s, 1H), 8.23 (s, 2H), 8.19 (s, 2H), 8.12 (s, 2H), 7.70 (s, 1H), 7.61 (s, 1H), 4.61-4.50 (m, 3H), 4.25 (s, 1H), 4.01-3.97 (m, 1H), 3.77-3.71 (m, 1H), 3.32 (s, 3H), 3.31 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H) ppm. **^{13}C NMR** (CD_3OD): δ 181.7, 181.1, 164.6, 141.6, 141.3, 140.4, 131.4 (q, *J* = 33.39 Hz), 131.3, 131.2 (q, *J* = 33.50 Hz), 130.9 (q, *J* = 33.05 Hz), 128.1, 124.4 (q, *J* = 3.69 Hz), 123.4 (d, *J* = 3.54 Hz), 123.3 (q, *J* = 271.89 Hz), 122.2 (q, *J* = 2.26 Hz), 121.9 (q, *J* = 271.95 Hz) 117.3 (q, *J* = 3.93 Hz), 116.5 (q, *J* = 2.32 Hz), 98.9, 98.8, 67.9, 67.1, 64.5, 47.1, 44.4, 16.5, 16.4 ppm. **FTIR** (Neat): 3265 (N-H), 1728 (C=O), 1275 (C-O), 1120 (C=S) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{44}H_{33}F_{21}N_4O_6S_2$ 965.1479; Found 965.1505.

Experiment 38: Synthesis of ((2*S*,3*S*,5*R*,6*R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)methanamine 80

To a solution of compound **58** (0.72 g, 1.44 mmol) in THF:H_2O (8:2) (20 mL) was added PPh_3 (0.75 g, 2.88 mmol). The solution was refluxed for 2 h, at the end of this time the reaction was quenched with satd. aq. $NaHCO_3$ sol. and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and

evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (95:5 CH_2Cl_2/CH_3OH) to afford the product **80** (0.60 g, **88%**) as a colourless oil. $[\alpha]_D^{20}$= - 86.09 (*c* 0.73, CH_2Cl_2).**^{1}H NMR** ($CDCl_3$): δ 7.70-7.66 (m, 4H), 7.44-7.35 (m, 6H), 3.75-3.63 (m, 4H), 3.25 (s, 3H), 3.18 (s, 3H), 2.96 (dd, *J* = 13.35 Hz, *J* = 2.76 Hz, 1H), 2.86-2.80 (m, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.05 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 135.7, 135.6, 133.4, 133.2, 129.7, 127.7, 127.6, 98.6, 98.5, 72.2, 70.6, 64.5, 47.8, 47.7, 42.8, 26.8, 19.2, 17.6, 17.5 ppm. **FTIR** (Neat): 2931 (N-H) cm^{-1}. **HRMS**: m/z: $[M+H]^+$calcd for $C_{26}H_{40}NO_5Si$ 474.2672; Found 474.2670.

Experiment 39: 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione 81

The synthesis of compound **81** was carried out according to the procedure described in the literature.[60]

Experiment 40: Synthesis of 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((((2*S*,3*S*,5*R*,6*R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dimethoxy-5-methyl-1,4-dioxan-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione 82

To a solution of compound **80** (0.57 g, 1.21 mmol) in CH_2Cl_2 (10 ml) was added 3-(3,5-bis(trifluoromethyl)phenylamino)-4-methoxycyclobut-3-ene-1,2-dione **81** (0.45 g, 1.33 mmol). The resulting mixture was stirred for 48 h at rt. The solvent was removed and the crude product was purified by flash column chromatography on silica gel (70:30 Hexane/AcOEt) to afford the product **82** (0.75 g, **79%**) as a yellow solid. $[\alpha]_D^{20}$= - 42.56 (*c* 0.95, CH_3OH). **^{1}H NMR** (DMSO-d_6): δ 11.22 (s, 1H), 10.33 (t, *J* = 5.95 Hz, 1H), 8.42 (s, 2H), 7.74-7.66 (m, 5H), 7.46-7.39 (m, 6H), 4.01-3.94 (m, 2H), 3.82-3.73 (m, 3H), 3.60 (dt, *J* = 9.62 Hz, *J* = 3.86 Hz, 1H), 3.16 (s, 3H), 3.13 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 0.98 (s, 9H) ppm. **^{13}C NMR** (DMSO-d_6): δ 184.5, 172.7, 141.3, 135.8, 135.6, 133.4, 133.2, 131.7 (q, *J* = 32.85 Hz), 130.2, 128.2, 128.1, 123.6 (q, *J* = 273.59 Hz), 119.2 (d, *J* = 3.97 Hz), 115.7

(q, *J* = 3.33 Hz), 98.7, 98.6, 70.6, 68.5, 63.8, 47.8, 47.7, 45.2, 26.9, 19.3, 17.8, 17.7 ppm.

Experiment 41: Synthesis of 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((((2*S*,3*S*,5*R*,6*R*)-3-(hydroxymethyl)-5,6-dimethoxy-5-methyl-1,4-dioxan-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione 83

To a solution of compound **82** (0.56 g, 0.71 mmol) in THF (10 mL) was added TBAF (1.00 mL, 1.07 mmol). The reaction mixture stirred for 1 h, then it was quenched with H_2O and extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (100 % AcOEt) to afford the product **83** (0.33 g, **85%**) as a yellow solid. **Mp** 221-223 °C. $[\alpha]_D^{20}$= -50.95 (*c* 1, CH_3OH).**^{1}H NMR** (DMSO-d_6): δ 10.34 (s, 1H), 8.08 (s, 2H), 7.81 (s, 1H), 7.66 (s, 1H), 4.83 (s br, 1H), 3.94 (d, *J* = 11.36 Hz, 1H), 3.74 (d, *J* = 7.59 Hz, 2H), 3.53-3.50 (m, 3H), 3.17 (s, 3H), 3.15 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H) ppm. **^{13}C NMR** (DMSO-d_6): δ 185.0, 181.0, 170.4, 162.9, 141.6, 131.8 (q, *J* = 32.49 Hz), 123.6 (q, *J* = 272.47 Hz), 118.5 (d, *J* = 2.76 Hz), 115.1 (q, *J* = 3.65 Hz), 98.7, 98.6, 70.3, 69.6, 61.2, 47.7, 44.8, 17.9 ppm. **FTIR** (Neat): 3340 (N-H), 2950 (O-H), 1275 (C-O), 1664 (C=C), 1564 (C=O) cm^{-1}. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{22}H_{24}F_6N_2O_7$ 543.1521; Found 543.1552.

Experiment 42: Synthesis of (1*R*,3*S*)-1,3-diamino-1,2,2-trimethylcyclopentane 86

The synthesis of compound **86** was carried out according to the procedure described in the literature.[61]

Experiment 43: General procedure for the synthesis of compounds 87 and 88

To a stirred solution of diamine **86** (0.13 g, 0.928 mmol) in dry CH_2Cl_2 (5 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate or phenyl isothiocyanate

(0.49 mmol), dropwise, dissolved in CH_2Cl_2. The resulting mixture was stirred for 0.5 h and then evaporated.

Experiment 44: Synthesis of *N*-((1*S*,3*R*)-3-amino-2,2,3-trimethylcyclopentyl)-1-(3,5-bis(trifluoromethyl)phenylthiourea 87

The crude product was washed with Et_2O to afford the product **87** (0.17 g, **63%**) as a white solid. **Mp** 180-183 °C. $[\alpha]_D^{20}$= + 39.42 (*c* 1, CH_3OH). **^{1}H NMR** (DMSO-d_6): δ 10.39 (bs, 1H), 8.31 (s, 2H), 7.70 (s, 1H), 4.62 (dd, *J* = 8.43 Hz, *J* = 2.41 Hz, 1H), 2.20-2.11 (m, 1H), 1.72-1.47 (m, 3H), 1.07 (s, 3H), 0.87 (s, 6H) ppm. **^{13}C NMR** (DMSO-d_6): δ 178.9, 142.6, 130.6 (q, *J* = 32.87 Hz), 123.7 (q, *J* = 272.50 Hz), 121.8 (d, *J* = 2.77 Hz), 116.1 (q, *J* = 3.10 Hz), 63.9, 61.7, 47.8, 37.6, 29.1, 25.7, 24.9, 17.4 ppm. **HRMS:** m/z: $[M+H]^+$ calcd for $C_{17}H_{22}F_6N_3S$ 414.1394; Found 414.1429. **FTIR** (Neat): 3179 (N-H), 3152 (N-H primary amine), 1122 (C=S) cm^{-1}.

Experiment 45: Synthesis of *N*-((1*S*,3*R*)-3-amino-2,2,3-trimethylcyclopentyl)-1-phenylthiourea 88

The crude product was washed with Et_2O to afford the product **88** (0.107 g, **51%**) as a white solid. **Mp** 174-177 °C. $[\alpha]_D^{20}$= + 79.00 (*c* 0.95, CH_3OH). **^{1}H NMR** (DMSO-d_6): δ 9.56 (s, 1H), 7.33-7.31 (m, 4H), 7.14-7.07 (m, 1H), 4.61 (d, *J* = 6.80 Hz, 1H), 2.16-2.07 (m, 1H), 1.66-1.38 (m, 3H), 1.02 (s, 3H), 0.85 (s, 6H) ppm. **^{13}C NMR** (DMSO-d_6): δ 178.5, 139.0, 129.4, 124.7, 123.8, 64.6, 61.5, 47.8, 37.5, 29.5, 25.8, 25.0, 17.6 ppm. **HRMS:** m/z: $[M+H]^+$ calcd for $C_{15}H_{24}N_3S$ 278.1685. Found 278.1682. **FTIR** (Neat): 3147 (N-H), 2956 (N-H primary amine), 1243 (C=S) cm^{-1}.

Experiment 46: Synthesis of *N*-((1*S*,3*R*)-3-amino-2,2,3-trimethylcyclopentyl)-4-((3,5-bis-(trifluoromethyl)pheny) amino) cyclobut-3-ene-1,2-dione 89

To a stirred solution of diamine **86** (0.13 g, 0.93 mmol) in CH_2Cl_2 (5 mL) was added 3-(3,5-bis(trifluoromethyl)phenylamino)-4-methoxycyclobut-3-ene-1,2-dione **81** (0.25 g, 0.75 mmol) portion-wise. The resulting mixture was stirred for 48 h at rt. The solvent was removed and the crude product was purified by flash column chromatography on silica gel (90:10, CH_2Cl_2/CH_3OH) to afford the product **89** (0.185 g, **55%**) as a yellow pale solid. **Mp** 138-142 °C. $[\alpha]_D^{20}$= +9.89 (*c* 1, CH_3OH). **^{1}H NMR** (DMSO-d_6): δ 8.09 (s, 2H), 7.63 (s, 1H), 4.33 (dd, *J* = 9.20 Hz, *J* = 5.63 Hz, 1H), 2.23-2.14 (m, 1H), 1.81-1.62 (m, 3H), 1.10 (s, 3H), 0.87 (s, 6H) ppm. **^{13}C NMR** (DMSO-d_6): δ 184.9, 180.6, 169.6, 162.7, 142.1, 131.7 (q, *J* = 33.08 Hz), 123.7 (q, *J* = 273.22 Hz), 118.5 (d, *J* = 3.98 Hz) , 114.80 (q, *J* = 3.33 Hz), 63.4, 61.7, 47.5, 36.5, 28.5, 25.1, 22.8, 17.5 ppm. **HRMS**: m/z: $[M+H]^+$ calcd for $C_{20}H_{22}F_6N_3O_2$ 450.1616; Found 450.1607. **FTIR** (Neat): 3312 (N-H primary amine), 3180 (N-H), 1794 (C=O), 1684 (C=C), 1172 (C=S) cm^{-1}.

Experiment 47: Synthesis of *N*-((1*S*,3*R*)-3-amino-2,2,3-trimethylcyclopentyl)-*tert*-butyl carbamate 90

To a solution of diamine **86** (1.10 g, 7.75 mmol) in THF:H_2O (2:1) (18 mL) was added Na_2CO_3 (0.41 g, 3.87 mmol). Then the mixture was stirred at 0 °C and Boc_2O (0.89 mL, 3.87 mmol) was added. The resulting mixture was allowed to warm to rt and stirred overnight. After this time the THF was evaporated and the obtained mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (90:10, AcOEt/CH_3OH) to afford the product **90** (0.81 g, **86%**) as a colourless oil. **^{1}H NMR** ($CDCl_3$): δ 6.05 (d, *J* = 9.19 Hz, 1H), 3.81 (ddd, *J* = 10.16 Hz, *J* = 10.16 Hz, *J* = 3.60 Hz, 1H), 2.24-2.14 (m, 1H), 1.75-1.66 (m, 1H), 1.59-1.50 (m, 2H), 1.42 (s, 9H), 1.10 (s,

3H), 0.88 (s, 6H) ppm. **^{13}C NMR** ($CDCl_3$): δ 155.8, 78.4, 60.1, 47.0, 37.9, 28.9, 28.5, 24.3, 16.6 ppm. **HRMS:** m/z: $[M+H]^+$ calcd for $C_{13}H_{27}N_2O_2$ 243.2067; Found 243.2065.

Experiment 48: Synthesis of *N*-((1*S*,3*R*)-3-(3-(3,5-bis(trifluoromethyl)phenyl)thioureia)-2,2,3-trimethylcyclopentyl)-*tert*-butyl carbamate 91

To a solution of compound **90** (0.11 g, 0.46 mmol) in CH_2Cl_2 (5 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (92.3 µL, 0.50 mmol). The resulting mixture was stirred for 1 h and then it was evaporated. The crude product was purified by flash column chromatography on silica gel (98:2, CH_2Cl_2/CH_3OH) to afford the product **91** (0.21 g, **90%**) as a white solid. **Mp** 99-101 °C. $[\alpha]_D^{20}$= +33.43 (*c* 1, CH_2Cl_2). **^{1}H NMR** (DMSO-d_6): δ 10.10 (s, 1H), 8.29 (s, 2H), 7.71 (s, 1H), 7.54 (s, 1H), 6.71 (d, *J* = 8.81 Hz, 1H), 3.81 (q, *J* = 9.53 Hz, 1H), 2.45-2.38 (m, 1H), 2.12 (ddd, *J* = 13.26, Hz, *J* = 13.26, Hz, *J* = 5.04 Hz, 1H), 1.91-1.78 (m, 2H), 1.51 (s, 3H), 1.40 (s, 9H), 0.92 (s, 3H), 0.84 (s, 3H) ppm. **^{13}C NMR** (DMSO-d_6): 179.7, 156.0, 142.4, 130.5 (q, *J* = 32.75 Hz), 123.7 (q, *J* = 272.46 Hz), 122.3, 116.3 (q, *J* = 3.93 Hz), 77.9, 65.8, 56.5, 48.3, 34.7, 28.7, 26.2, 21.1, 20.9, 17.8 ppm; **HRMS:** m/z: $[M-H]^+$ calcd for $C_{22}H_{28}F_6N_3O_2S$ 512.1812; Found 512.1810.

Experiment 49: Synthesis of *N*-((1*S*,3*R*)-3-(dimethylamino)-2,2,3-trimethylcyclopentyl)-*tert*-butyl carbamate 93

To a solution of compound **90** (0.234 g, 0.97 mmol) in acetonitrile (10 mL) was added K_2CO_3 (0.27 g, 1.93 mmol) and CH_3I (0.30 mL, 4.83 mmol). The mixture was heated at 50 °C on a sealed tube until the consumption of initial reagent was observed. After this period, the solvent was evaporated and the obtained mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (80:2, Et_2O/ Et_3N) to afford the product **93**

(0.21 g, **80%**) as a white solid. **^{1}H NMR** ($CDCl_3$): δ 4.53 (d, *J* = 10.21 Hz, 1H), 3.90 (q, *J* = 9.76 Hz), 2.20 (s, 6H), 2.07-1.97 (m, 1H), 1.86-1.78 (m, 1H), 1.54 (dt, *J* = 11.36 Hz, *J* = 3.36 Hz, 1H), 1.44 (s, 9H), 1.34-1.24 (m, 1H), 1.01 (s, 3H), 0.94 (s, 3H), 0.89 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 155.8, 78.9, 66.4, 58.6, 47.0, 40.0, 36.6, 28.4, 26.7, 22.5, 16.9, 11.0 ppm.

Experiment 50: trifluoroacetate (1*S*,3*R*)-3-(dimethylamino)-2,2,3-trimethylcyclopentan-1-aminium salt 94

To a solution of compound **93** (0.20 g, 0.77 mmol) in CH_2Cl_2 (5 mL) was added TFA (9.6 mL) dissolved in CH_2Cl_2 (9.6 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred 1 h and then it was evaporated. The product **94** (0.19 g, **quantitative yield**) was obtained as a trifluoroacetate salt. **^{1}H NMR** (D_2O): δ 3.54 (t, *J* = 9.36 Hz, 1H), 2.82 (s, 3H), 2.76 (s, 3H), 2.22-1.99 (m, 3H), 1.76-1.66 (m, 1H), 1.32 (s, 3H), 1.19 (s, 3H), 1.09 (s, 3H) ppm. **^{13}C NMR** (D_2O): 120.6, 116.2 (q, *J* = 290.92 Hz), 73.6, 58.9, 45.7, 40.7, 38.8, 33.6, 22.4, 20.6, 15.5, 13.8 ppm.

Experiment 51: Synthesis of *N*-((1*S*,3*R*)-3-(dimethylamino)-2,2,3-trimethylcyclopentyl)-3-3,5-bis(trifluoromethyl)phenyl) thiourea 95

To a solution of compound **94** (0.03 g, 0.14 mmol) in CH_2Cl_2 (2 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (27.4 µL, 0.15 mmol) and K_2CO_3 (0.04 g, 0.27 mmol) at 0 °C. The resulting mixture was monitored by TLC until the consumption of starting material. Then the solid was filtered and washed with CH_2Cl_2 and the filtrate was evaporated. The crude product was purified by preparative TLC (80:20, CH_2Cl_2/CH_3OH) to afford the product **95** (0.03 g, 50%) as a yellow solid. **Mp** 187 °C (degradation). $[\alpha]_D^{20}$= + 2.60 (*c* 0.39, CH_3OH). **^{1}H NMR** ($CDCl_3$): δ 10.31 (s, 1H), 8.45 (d, *J* = 9.55 Hz, 1H), 8.28 (s, 2H), 7.55 (s, 1H), 5.21 (q, *J* = 9.84 Hz, 1H), 2.86 (s, 6H), 2.44 (ddd, *J* = 13.41 Hz, *J* = 13.41 Hz, *J* = 4.85 Hz, 1H), 2.28-2.19 (m, 1H), 1.97-1.87 (m, 1H), 1.77-1.66 (m, 1H),

1.48 (s, 3H), 1.39 (s, 3H), 1.23 (s, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 182.36, 141.33, 131.25 (q, *J* = 33.34 Hz), 123.31 (q, *J* = 273.58 Hz), 122.84 (d, *J* = 3.68 Hz), 117.25 (q, *J* = 3.81 Hz), 74.38, 60.17, 48.08, 34.09, 24.74, 22.02, 18.76, 16.26 ppm. **HRMS:** m/z: $[M+H]^+$ calcd for $C_{19}H_{26}N_3F_6S$ 442.1746; Found 442.1746. **FTIR** (Neat): 3255 (N-H), 1167 (C=S) cm^{-1}.

Experiment 52: Synthesis of *N*-((1*S*,3*R*)-3-amino2,2,3-trimethylciclopentyl)-4-methylbenzenesulfonamide 96

The synthesis of compound **96** was carried out according to the procedure described in the literature.[63]

Experiment 53: Synthesis of 9-deoxyepiquinine isothiocyanate 96

The synthesis of compound **97** was carried out according to the procedure described in the literature.[40]

Experiment 54: Synthesis of *N*-((1*S*,3*R*)-3-amino-2,2,3-trimethylcyclopentyl)-3-((*R*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea 98

To a solution of diamine **86** (0.028 g, 0.20 mmol) in CH_2Cl_2 (2 mL) was added isothiocyanate **97** (0.058 mL, 0.159 mmol), dropwise, dissolved in CH_2Cl_2. The resulting mixture was stirred overnight and then evaporated. The crude product was purified by flash column chromatography on silica gel (80:20, CH_2Cl_2/CH_3OH) to afford the product **98** (0.039 g, **73%**) as a pale yellow solid. **Mp** 136-139 °C. $[\alpha]_D^{20}$= -89.8 (*c* 1, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$): δ 8.73 (d, *J* = 4.62 Hz, 1H), 8.03 (d, *J* = 9.29 Hz, 1H), 7.71 (br s, 3H), 7.47 (br s, 1H), 7.40 (dd, *J* = 9.24 Hz, *J* = 2.40 Hz, 1H), 5.63 (ddd, *J* = 17.44 Hz, *J* = 17.44 Hz, *J* = 2.98 Hz, 1H), 4.99-4.92 (m, 2H), 3.99 (s, 3H), 3.29 (dd, *J* = 14.51 Hz, *J* = 10.07 Hz, 1H), 3.21-3.12 (m, 2H), 2.87-2.73 (m, 2H), 2.34 (br s, 1H), 2.04 (br s, 1H), 1.73-1.52 (m, 7H), 1.38 (t, *J* = 10.97 Hz, 2H), 1.13-1.07 (m, 2H), 0.91-0.76 (m, 9H) ppm. **^{13}C NMR** ($CDCl_3$): δ 180.0, 157.8, 147.6, 144.8, 140.6, 131.7, 121.9, 114.9, 102.0,

66.0, 61.5, 55.8, 55.5, 47.2, 40.9, 39.3, 37.7, 29.3, 27.6, 27.4, 25.9, 25.5, 24.8,16.6 ppm. **HRMS:** m/z: $[M+H]^+$ calcd for $C_{29}H_{42}N_5OS$ 50.3105; Found 508.3108. **FTIR** (Neat): 3286 (N-H), 2946 (N-H primary amine), 1170 (C=S) cm^{-1}.

Experiment 55: General procedure for the preparation of racemic mixtures

To a solution of the nitroalkene acceptor (0.14 mmol), Schreiner thiourea (6 mol%) and Et_3N (6 mol%), in dry CH_2Cl_2 (0.37 mL), under argon and at the designated temperature, the Michael addition donnor was added (0.28 mmol) and the resulting reaction mixture was stirred for 24 h. The reaction was evaporated and the crude product was purified by preparative TLC. The diastereoisomeric ratio was determined by ^1H NMR analysis and the enantiomeric excess of the products was determined by HPLC analysis.

Experiment 56: Synthesis of (*S*)-2,2-Dimethyl-4-nitro-3-phenyl-butanal 113a

A mixture of of *trans*-β-nitrostyrene (0.17 mmol), catalyst (20 mol%), DMAP (0.02 mmol), isobutyraldehyde (0.47 mmol) and $CHCl_3$ (0.3 mL) was stirred at rt. When the reaction was complete (TLC) the solvent was removed under vacuum. The residue was purified by preparative TLC (80:20 Hexane/AcOEt) to afford the desired product **113a** as a yellow oil and the spectroscopic analysis of the product matched the literature data.[101] The enantiomeric excess was determined by HPLC with Chiralpack AD-H column at 205 nm (Hexane/^{i}PrOH = 99/1, 0.5 mL/min $t_{R(minor)}$ = 38.0 min, $t_{R(major)}$ = 39.9 min).

Experiment 57: Synthesis of (*R*) and (*S*)-ethyl 2-carboethoxy-4-nitro -3-phenylbutyrate 113b

Under an argon atmosphere, to a stirred solution of *trans*-β-nitrostyrene (0.20 mmol) and diethyl malonate (0.39 mmol) in dry toluene (0.40 mL) was added catalyst (10 mol%). After being stirred for 48 h, the reaction mixture was

concentrated *in vacuo*. The residue was purified by preparative TLC (80:20 Hexane/AcOEt) to afford the desired product **113b** as a yellow pale solid and the spectroscopic analysis of the product matched the literature data.[32] The enantiomeric excess was determined by HPLC with Chiralpack AD-H column at 205 nm (Hexane/^{i}PrOH = 90/10, 1 mL/min t_R = 10.9 min, t_R = 14.5 min).

Experiment 58: Synthesis of (S)-3-(2-nitro-1-phenyl-ethyl)-1*H*-indole 113c

Under an argon atmosphere, to a stirred solution of *trans*-β-nitrostyrene (0.20 mmol) and catalyst (20 mol%) in dry CH_2Cl_2 (200 µl) and 1*H*-indole (0.30 mmol) was added in one portion. After being stirred for 72 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (80:20 Hexane/AcOEt) to afford the desired product **113c** as a colourless oil and the spectroscopic analysis of the product matched the literature data.[111] The enantiomeric excess was determined by HPLC with Chiralpack AD-H column at 205 nm (Hexane/^{i}PrOH = 90/10, 0.75 mL/min $t_{R(minor)}$ = 44.4 min, $t_{R(major)}$ = 49.4 min).

Experiment 59: General procedure for Michael addition reactions of 1,3-dicarbonyl nucleophiles to nitroalkene acceptors

To a solution of the nitroalkene acceptor (0.14 mmol) and the synthesised organocatalysts (5 mol%), in anhydrous solvent (0.37 mL), under argon and at the designated temperature, the 1,3-dicarbonyl nucleophile was added (0.28 mmol) and the resulting reaction mixture was stirred until the consumption of the nitroalkene acceptor (2–24 h). The reaction was evaporated and then the crude product was purified by preparative TLC (60:40 or 70:30, Hexane/AcOEt). The diastereoisomeric ratio was determined by ^{1}H NMR analysis and the enantiomeric excess of the products was determined by HPLC analysis.

Experiment 60: Synthesis of (*R*)-3-(2-nitro-1-phenylethyl) pentane-2,4-dione 113d

The title compound was prepared from *trans*-β-nitrostyrene and acetylacetone according to the representative procedure. Product **113d** was obtained as a white solid in 80% of yield and the spectroscopic analysis of the product matched the literature data.[67] The enantiomeric excess (*ee* 68%) was determined by HPLC with Chiralpack AD-H column at 205 nm (Hexane/^{i}PrOH = 90/10, 1 mL/min $t_{R(minor)}$ = 10.9 min, $t_{R(major)}$ = 14.5 min).

Experiment 61: Synthesis of (*S*)-3-(2-nitro-1-phenylethyl) pentane-2,4-dione 114a

The title compound was prepared from *trans*-β-nitrostyrene and acetylacetone according to the representative procedure. Product **114a** was obtained as a white solid and the spectroscopic analysis of the product matched the literature data.[67] The enantiomeric excess was determined by HPLC with Chiralpack AD-H column at 205 nm (Hxane/^{i}PrOH = 90/10, 1 mL/min $t_{R(major)}$ = 10.9 min, $t_{R(minor)}$ = 14.5 min).

Experiment 62: Synthesis of (*S*)-3-(1-(4-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione 114b

The title compound was prepared from *trans*-4-methoxy-β-nitrostyrene and acetylacetone according to the representative procedure. Product **114b** was obtained as a yellow solid in 97% of yield and the spectroscopic analysis of the product matched the literature data.[67] The enantiomeric excess (*ee* 66%) was determined by HPLC with Chiralpack AD-H column at 205 nm (Hexane/^{i}PrOH = 90/10, 1 mL/min $t_{R(major)}$ = 14.9 min, $t_{R(minor)}$ = 22.8 min).

Experiment 63: Synthesis of (*S*)-3-(1-(4-chlorophenyl)-2-nitroethyl)pentane-2,4-dione 114c

The title compound was prepared from *trans*-4-chloro-β-nitrostyrene and acetylacetone according to the representative procedure. Product **114c** was obtained as a white solid in 68% of yield and the spectroscopic analysis of the product matched the literature data.[67] The enantiomeric excess (*ee* 65%) was determined by HPLC with Chiralpack AD-H column at 205 nm (Hexane/^{i}PrOH = 80/20, 1 mL/min $t_{R(major)}$ = 8.5 min, $t_{R(minor)}$ = 20.2 min).

Experiment 64: Synthesis of (*S*)-3-(1-(2-chlorophenyl)-2-nitroethyl)pentane-2,4-dione 114d

The title compound was prepared from *trans*-2-chloro-β-nitrostyrene and acetylacetone according to the representative procedure. Product **114d** was obtained as a yellow pale solid in 88% of yield and the spectroscopic analysis of the product matched the literature data.[67] The enantiomeric excess (*ee* 73%) was determined by HPLC with Chiralpack AD-H column at 205 nm (Hexane/^{i}PrOH = 99/1, 1 mL/min $t_{R(major)}$ = 31.7 min, $t_{R(minor)}$ = 40.1 min).

Experiment 65: Synthesis of (*S*)-3-(1-(furan-2-yl)-2-nitroethyl)pentane-2,4-dione 114e

The title compound was prepared from *trans*-2-(2-nitrovinyl)furan and acetylacetone according to the representative procedure. Product **114e** was obtained as a yellow oil in 91% of yield and the spectroscopic analysis of the product matched the literature data.[67] The enantiomeric excess (*ee* 56%) was determined by HPLC with Chiralpack AD-H column at 210 nm (Hexane/^{i}PrOH = 90/10, 1 mL/min $t_{R(major)}$ = 11.0 min, $t_{R(minor)}$ = 12.9 min).

Experiment 66: Synthesis of (*S*)-1-((R)-2-nitro-1-phenylethyl)-2-oxocyclopentane-1-carboxylate and (*R*)-1-((*R*)-2-nitro-1-phenylethyl)-2-oxocyclopentane-1-carboxylate 116a

The title compound was prepared from *trans*-β-nitrostyrene and ethyl-2-oxocycloethylester according to the representative procedure. Product **116a** was obtained as a colourless oil in 62% of yield and the spectroscopic analysis of the product matched the literature data.[67] The enantiomeric excess was determined by HPLC with Chiralpack IB column at 205 nm (Hexane/^{i}PrOH = 90/10, 1 mL/min major diastereomer $t_{R(major)}$ = 7.9 min, $t_{R(minor)}$ = 9.9 min – *ee* 74% and minor diastereomer $t_{R(major)}$ = 7.1 min, $t_{R(minor)}$ = 8.6 min – *ee* 36%).

Experiment 67: Synthesis of (*R*)-2-acetyl-2-((*R*)-2-nitro-1-phenylethyl)cyclopentan-1-one and (*S*)-2- acetyl-2-((*R*)-2-nitro-1-phenylethyl)cyclopentan-1-one 116b

The title compound was prepared from *trans*-β-nitrostyrene and 2-acetylcyclopentanone according to the representative procedure. Product **116b** was obtained as a yellow oil in 93% of yield and the spectroscopic analysis of the product matched the literature data.[67] The enantiomeric excess was determined by HPLC with Chiralpack IB column at 205 nm (Hexane/^{i}PrOH = 80/20, 1 mL/min major diastereomer $t_{R(major)}$ = 8.6 min, $t_{R(minor)}$ = 23.0 min – *ee* 63% and minor diastereomer $t_{R(major)}$ = 10.1 min, $t_{R(minor)}$ = 12.8 min – *ee* 69%).

Experiment 68: Synthesis of (*S*)-ethyl 1-((*S*)1-(4-methoxyphenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate and (*R*)-ethyl 1-((*S*)1-(4-methoxyphenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate 116c

The title compound was prepared from *trans*-4-methoxy-β-nitrostyrene and ethyl-2-oxocycloethylester according to the representative procedure. Product **116c** was obtained as a colourless oil in 92% of yield and the spectroscopic analysis of the product matched the literature data.[47] The enantiomeric excess was

determined by HPLC with Chiralpack AD-H column at 210 nm (Hexane/EtOH = 95/5, 1 mL/min major diastereomer $t_{R(major)}$ = 28.5 min, $t_{R(minor)}$ = 48.9 min – *ee* 73% and minor diastereomer $t_{R(major)}$ = 14.5 min, $t_{R(minor)}$ = 22.3 min – *ee* 25%).

Experiment 69: Synthesis of (*S*)-ethyl 1-((*R*)1-(4-chlorophenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate and (*R*)-ethyl 1-((*R*)1-(4-chlorophenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate 116d

The title compound was prepared from *trans*-4-chloro-β-nitrostyrene and ethyl-2-oxocycloethylester according to the representative procedure. Product **116d** was obtained as a yellow oil in 98% of yield and the spectroscopic analysis of the product matched the literature data.[113] The enantiomeric excess was determined by HPLC with Chiralpack IB column at 205 nm (Hexane/^{i}PrOH = 90/10, 1 mL/min major diastereomer $t_{R(major)}$ = 9.8 min, $t_{R(minor)}$ = 14.2 min – *ee* 71% and minor diastereomer $t_{R(major)}$ = 8.3 min, $t_{R(minor)}$ = 11.6 min – *ee* 23%).

Experiment 70: Synthesis of (*S*)-2-acetyl-2-((*R*)1-(4-methoxyphenyl)-2-nitroethyl)cyclopentan-1-one and (*R*)-2-acetyl-2-((*S*)1-(4-methoxyphenyl)-2-nitroethyl)cyclopentan-1-one 116e

The title compound was prepared from *trans*-4-methoxy-β-nitrostyrene and 2-acetylcyclopentanone according to the representative procedure. Product **116e** was obtained as a yellow oil in 97% of yield and the spectroscopic analysis of the product matched the literature data.[114] The enantiomeric excess was determined by HPLC with Chiralpack AD-H column at 205 nm (Hexane/^{i}PrOH = 90/10, 0.5 mL/min major diastereomer $t_{R(major)}$ = 23.1 min, $t_{R(minor)}$ = 25.2 min – *ee* 58% and minor diastereomer $t_{R(minor)}$ = 29.7 min, $t_{R(major)}$ = 40.8 min – *ee* 47%).

Experiment 71: Synthesis of 2-acetyl-2-((*S*)1-(4-chlorophenyl)-2-nitroethyl)cyclopentan-1-one 116f

The title compound was prepared from *trans*-4-chloro-β-nitrostyrene and 2-acetylcyclopentanone according to the representative procedure. Product **116f** was obtained as a colourless oil in 85% of yield. $[\alpha]_D^{20}$= +10.53 (*c* 0.3, CH_2Cl_2). **Major diastereomer: ^{1}H NMR** ($CDCl_3$): δ 7.29-7.27 (m, 2H), 7.22 (d, *J* = 8.37 Hz, 2H), 4.83 (dd, *J* = 11.56 Hz, *J* = 10.59 Hz, 1H), 4.52 (dd, *J* = 13.67 Hz, *J* = 3.80 Hz, 1H), 4.33 (dd, *J* = 11.56 Hz, *J* = 3.94 Hz, 1H), 2.59-2.33 (m, 2H), 2.30 (s, 3H), 1.99-1.70 (m, 4H) ppm. **^{13}C NMR** ($CDCl_3$): δ 213.1, 202.5, 134.5, 132.6, 130.9, 129.1, 75.5, 71.1, 45.7, 38.6, 27.5, 26.6, 19.4 ppm. **Minor diastereomer: ^{1}H NMR** ($CDCl_3$): δ 7.58-7.43 (m, 2H), 7.13 (d, *J* = 8.34 Hz, 2H), 5.00 (dd, *J* = 11.13 Hz, *J* = 9.21 Hz, 1H), 4.58 (dd, *J* = 13.21 Hz, *J* = 3.81 Hz, 1H), 4.58 (dd, *J* = 13.50 Hz, *J* = 3.83 Hz, 1H), 2.28-2.21 (m, 2H), 2.19 (s, 3H), 1.99-1.70 (m, 4H) ppm.**^{13}C NMR** ($CDCl_3$): δ 216.7, 202.9, 134.7, 133.9, 130.1, 129.1, 76.7, 70.1, 46.5, 39.3, 31.0, 26.8, 19.4 ppm. **HRMS:** m/z: $[M+H]^+$ calcd for $C_{15}H_{17}ClNO_4$ 310.0846; Found 310.0081

The enantiomeric excess was determined by HPLC with Chiralpack IB column at 210 nm (Hexane/EtOH = 95/5, 2 mL/min major diastereomer $t_{R(major)}$ = 8.2 min, $t_{R(minor)}$ = 35.1 min – *ee* 36% and minor diastereomer $t_{R(major)}$ = 9.1 min, $t_{R(minor)}$ = 17.4 min – *ee* 41%).

Experiment 72: Synthesis of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetamidate 125

The synthesis of compound **125** was carried out according to the procedure described in the literature.[172]

Experiment 73: General procedure for cooperative catalysis with *O*-glycosyl trichloroacetimidates as glycosyl donors

Glycosyl donor (0.05 mmol), acceptor (0.05 mmol) and cocatalyst (15 mol%) were dissolved in CH_2Cl_2 (1.0 mL) and stirred at room temperature for 5 min, acid catalyst (15 mol%) was then added. The reaction mixture was stirred at the same temperature until TLC indicated the complete consumption of the starting material, then the reaction was quenched with satd. aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography with Hexane/AcOEt to afford the desired glycosides. The α/β ratios of the newly formed glycosidic bonds were determined by the ^{1}H NMR integration of representative peaks.

Experiment 74: Synthesis of isopropyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside 130

The title compound was prepared from 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetamidate **126** and isopropanol according to the representative procedure. Product **130** was obtained as a white solid and the spectroscopic analysis of the product matched the literature data.[173] The anomeric selectivity was calculated from the peak area ratio of isopropyl CH α (1.43 ppm) and isopropyl CH β (1.52 ppm) in the crude ^{1}H NMR spectrum.

Experiment 75: Synthesis of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride 131

The synthesis of compound **131** was carried out according to the procedure described in the literature.[174]

Experiment 76: General procedure for thiourea catalysed glycosylation reactions

A round bottom flask was charged with glycosyl chloride (0.05 mmol) and catalyst (5-10 mol%). The flask was refilled with argon and a solution of acceptor (0.09 mmol) in toluene (1 mL) was added via syringe. Base (0.09 mmol) was added and the resulting mixture was stirred at room temperature for 48 h. The crude product was purified by flash column chromatography with Hexane/AcOEt to afford the desired products. The α/β ratios of the newly formed glycosidic bonds were determined by the ^{1}H NMR integration of representative peaks.

Experiment 77: Synthesis of allyl-2,6-*O*-benzyl-3-*O*-methyl-α-D-mannopyranoside 136

The compound **136** was already synthesised in our laboratory group.

Experiment 78: Synthesis of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl phosphate 138

The synthesis of compound **138** was carried out according to the procedure described in the literature.[175]

Experiment 79: General procedure for catalytic activation of glycosyl phosphates for stereoselective glycosylation reactions

A flame-dried 5 mL sealed tube with a stirring bar was charged with glycosyl donor (0.043 mmol), flame-dried 4-Å molecular sieves (43 mg), thiourea catalyst (20 mol%) and acceptor (0.085 mmol); diisopropyl ether (427 µL) was added to the reaction. The mixture was then heated with stirring at 40 °C in an oil bath for 19 h, over which time the mixture thickened. After 19 h, the mixture was cooled to room temperature, diluted with diethyl ether and filtered to remove the molecular sieves. This solution was concentrated and the crude product was purified by preparative TLC. The diastereoisomeric ratio was determined by ^{1}H NMR analysis.

Experiment 80: Synthesis of methyl (2*R*)-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl) propanoate 143

The title compound was prepared from 2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl phosphate and L-methyl lactate according to the representative procedure. Product **143** was obtained as a colourless oil in 85% yield. The anomeric selectivity (α:β 83:17) was calculated from the peak area ratio of -OCH_3 α (3.74 ppm) and -OCH_3 β (3.68 ppm) in the crude ^{1}H NMR spectrum.**^{1}H NMR** ($CDCl_3$): δ 7.43-7.26 (m, 26H), 5.13 (d, *J* = 3.67 Hz, 1H, H-1 α), 4.96 (s, 2H), 4.93 (d, *J* = 9.18 Hz, 1H), 4.88 (s, 1H), 4.84 (s, 3H), 4.76-4.71 (m, 3H), 4.59-4.53 (m, 2H), 4.48 (d, *J* =11.76, 1H, H-1 β), 4.43-4.36 (m, 3H), 4.07 (dd, *J* = 10.19 Hz, *J* = 3.60 Hz, 1H), 4.01-3.87 (m, 4H), 3.74 (s, 3H, α), 3.68 (s, 3H, β), 3.49-3.45 (m, 1H), 1.48 (d, *J* = 7.01 Hz, 3H, α), 1.44 (d, *J* = 6.84 Hz, 3H, β) ppm. **^{13}C NMR** ($CDCl_3$): δ 170.4, 138.8, 138.7, 138.5, 138.4, 138.3, 137.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 103.2, 96.3, 81.8, 79.2, 78.7, 75.9, 75.1, 74.9, 74.7, 74.5, 73.6, 73.5, 73.4, 73.2, 72.9, 69.9, 68.9, 68.7, 65.5, 63.3, 51.9, 51.8, 18.5, 18.1 ppm.

Experiment 81: Synthesis of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl phosphate 144a

The synthesis of compound **144a** was carried out according to the procedure described in the literature.[175]

Experiment 82: Synthesis of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl phosphate 144b

The synthesis of compound **144b** was carried out according to procedures described in the literature.[175–178]

Experiment 83: Synthesis of methyl (2*R*)-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl) propanoate 145a

The title compound was prepared from 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl phosphate and L-methyl lactate according to the representative procedure. Product **145a** was obtained as a colourless oil in 70% yield. The anomeric selectivity (α:β 70:30) was calculated from the peak area ratio of -CH_3α (1.43 ppm) and -CH_3β (1.52 ppm) in the crude ^{1}H NMR spectrum. **α anomer ^{1}H NMR** ($CDCl_3$): δ 7.35-7.13 (m, 20H), 4.98 (d, *J* = 10.94 Hz, 1H), 4.84-4.78 (m, 3H), 4.73 (d, *J* = 6.66 Hz, 1H), 4.60 (dd, *J* = 12.12 Hz, *J* = 6.21 Hz, 2H), 4.46 (dd, *J* = 12.16 Hz, *J* = 11.28 Hz, 2H), 4.08 (q, *J* = 6.88 Hz, 1H), 4.01 (t, *J* = 9.34 Hz, 2H), 3.75-3.71 (m, 1H), 3.68 (d, *J* = 9.53 Hz, 1H) 3.65 (s, 3H), 3.56 (dd, *J* = 5.95 Hz, *J* = 3.83 Hz, 1H), 3.51 (dd, *J* = 8.79 Hz, *J* = 1.84 Hz, 1H), 1.43 (d, *J* = 6.80 Hz, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 172.9, 138.8, 138.2, 138.2, 137.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 97.5, 81.8, 79.7, 77.4, 75.8, 75.1, 73.6, 73.5, 73.4, 70.5, 68.0, 52.1, 17.8 ppm. **β anomer ^{1}H NMR** ($CDCl_3$): 7.42-7.40 (m, 2H), 7.33-7.26 (m, 16H), 7.16-7.14 (m, 2H), 5.14 (d, *J* = 10.85 Hz, 1H), 4.93 (d, *J* = 10.99 Hz, 1H), 4.78 (dd, *J* = 23.90 Hz, *J* = 10.99 Hz, 2H), 4.71 (d, *J* = 10.85 Hz, 1H), 4.60 (d, *J* = 12.22 Hz, 1H), 4.55-4.49 (m, 4H), 3.71 (s, 3H), 3.69 (d, *J* = 2.03 Hz, 1H), 3.68-3.65 (m, 1H), 3.64-3.60 (m, 1H), 3.57 (d, *J* = 8.86 Hz, 1H), 3.49 (t, *J* = 8.17 Hz, 1H),3.42 (ddd, *J* = 9.25 Hz, *J* = 4.57 Hz, *J* = 2.13 Hz, 1H), 1.52 (d, *J* = 6.88 Hz, 3H) ppm. **^{13}C NMR** ($CDCl_3$): δ 173.0, 138.6, 138.5, 138.0, 137.9, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 102.4, 84.4, 81.8, 77.4, 75.8, 75.1, 74.7, 74.6, 73.4, 72.6, 68.6, 52.1, 19.3 ppm.

Experiment 84: Synthesis of methyl (2*R*)-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl) propanoate 145b

The title compound was prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl phosphate and L-methyl lactate according to the representative

procedure. Product **145b** was obtained as a colourless oil in 84% yield. The anomeric selectivity (α:β 89:11) was calculated from the peak area ratio of -OCH_3α (3.69 ppm) and -OCH_3β (3.60 ppm) in the crude ^{1}H NMR spectrum.**^{1}H NMR** ($CDCl_3$): δ 7.38-7.25 (m, 19H), 7.16-7.10 (m, 4H), 5.23 (d, *J* = 1.02 Hz, 1H, H-1 β), 5.04 (d, *J* = 1.24 Hz, 1H, H-1 α), 4.87 (d, *J* = 10.47 Hz, 1H, H-2 α), 4.72 (s, 2H), 4.64 (s, 1H), 4.61 (s, 1H), 4.59 (d *J* = 1.43 Hz, 1H), 4.53-4.47 (m, 3H), 4.38 (d, *J* = 6.78 Hz, 1H), 4.02-3.92 (m, 3H), 3.81-3.71 (m, 3H), 3.69 (s, 3H, α), 3.60 (s, 3H, β), 1.38 (d, *J* = 7.07 Hz, 3H, α), 1.25 (d, *J* = 5.59 Hz, 3H, β) ppm. **^{13}C NMR** ($CDCl_3$): δ 173.06, 138.4, 138.2, 138.1, 138.0, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 96.9, 79.8, 75.3, 74.7, 74.3, 73.4, 72.7, 72.3, 71.9, 70.0, 69.0, 52.0, 18.5 ppm.

Experiment 85: Synthesis of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride 146a

The title compound **146a** was carried out according to the procedure described in the literature.[179]

Experiment 86: Synthesis of 2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl trichloroacetamidate 146b

The title compound **146b** was carried out according to the procedure described in the literature.[172]

Experiment 87: Synthesis of Synthesis of methyl 2-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl) propanoate 148a

The title compound was prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl phosphate and methyl glicolate according to the representative procedure. Product **148a** was obtained as a colourless oil in 58% yield. The anomeric selectivity (α:β 83:17) was calculated from the peak area ratio of -CH_3α (3.73 ppm) and CH_3β (3.74 ppm) in the crude ^{1}H NMR spectrum.**^{1}H NMR** ($CDCl_3$):

δ 7.44-7.27 (m, 22H), 5.09 (d, *J* = 3.68 Hz, 1H, H-1 α), 4.95 (d, *J* = 11.58 Hz, 1H), 4.89 (d, *J* = 11.72 Hz, 1H), 4.83 (d, *J* = 12.84 Hz, 1H), 4.80-4.76 (m, 1H), 4.62 (d, *J* = 11.73 Hz, 1H), 4.57 (d, *J* = 11.47 Hz, 1H), 4.49-4.37 (m,3H), 4.30 (d, *J* = 16.59 Hz, 1H), 4,15 (d, *J* = 16.80 Hz, 1H), 4.09 (dd, *J* = 9.83 Hz, *J* = 3.63 Hz, 1H), 4.00-3.95 (m, 3H), 3.74 (s, 3H, β), 3.73 (s, 3H, α), 3.57-3.44 (m, 3H) ppm.**^{13}C NMR** ($CDCl_3$): δ 170.4, 138.8, 138.5, 138.3, 137.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 103.3, 97.0, 81.8, 79.2, 78.6, 75.9, 75.1, 74.9, 74.8, 74.5, 73.6, 73.5, 73.4, 73.2, 72.9, 69.9, 68.9, 68.7, 65.5, 63.3, 51.9 ppm.

Experiment 88: Synthesis of *O*-1-L-menthyl-2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranoside 148b

The title compound was prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl phosphate and L-menthol according to the representative procedure. Product **148b** was obtained as a colourless oil in 58% yield and the spectroscopic analysis of the product matched the literature data.[180] The anomeric selectivity (α:β 41:59) was calculated from the peak area ratio of -CH_3α (0.75 ppm) and -CH_3β (0.69 ppm) in the crude ^{1}H NMR spectrum.

Experiment 89: Synthesis of *O*-1-cyclohexyl-2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranoside 148c

The title compound was prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl phosphate and cyclohexanol according to the representative procedure. Product **148c** was obtained as a colourless oil in 60% yield and the spectroscopic analysis of the product matched the literature data.[181] The anomeric selectivity (α:β 49:51) was calculated from the peak area ratio of H-1α (5.00 ppm) and H-4β (3.86 ppm) in the crude ^{1}H NMR spectrum.

Experiment 90: Synthesis of 1-*O*-adamantanyl-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside 1498d

The title compound was prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl phosphate and adamantanol according to the representative procedure. Product **148d** was obtained as a colourless oil in 41% yield and the spectroscopic analysis of the product matched the literature data.[182] The anomeric selectivity (α:β 57:43) was calculated from the peak area ratio of H-1α (5.30 ppm) and H-1β (4.62 ppm) in the crude ^{1}H NMR spectrum.

Experiment 91: Synthesis of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-*N*-Boc-L-ser-methyl ester 148e

The title compound was prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl phosphate and *N*-Boc-L-ser-methyl ester according to the representative procedure. Product **148e** was obtained as a colourless oil in 64% yield. The anomeric selectivity (α:β 73:27) was calculated from the peak area ratio of -OCH_3α (3.64 ppm) and -OCH_3β (3.71 ppm) in the ^{1}H NMR crude spectrum.**^{1}H NMR** ($CDCl_3$): δ 7.40-7.26 (m, 25H), 5.78 (d, *J* = 8.56 Hz, 1H, H-1 α), 5.50 (d, *J* = 8.30 Hz, 1H, H-1 β) 4.92 (d, *J* = 11.52 Hz, 1H), 4.85-468 (m, 5H), 4.63-4.50 (m, 4H), 4.46-4.27 (m, 4H), 4.10 (dd, *J* = 11.29 Hz, *J* = 3.39 Hz, 1H), 4.02 (dd, *J* = 10.24 Hz, *J* = 3.68 Hz, 1H), 3.96-3.88 (m, 2H), 3.86 (dd, *J* = 10.08 Hz, *J* = 2.72 Hz, 1H), 3.81-3.75 (m, 2H), 3.71 (s, 3H, β), 3.64 (s, 3H, α), 3.57-3.49 (m, 4H), 1.42 (s, 9H, α), 1.40 (s, 9H, β) ppm. **^{13}C NMR** ($CDCl_3$): δ 170.9, 170.7, 138.7, 138.6, 138.5, 138.4, 138.4, 138.3, 137.9, 137.8, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 104.4, 99.3, 82.1, 79.9, 79.1, 78.7, 76.4, 75.3, 74.8, 74.7, 74.6, 73.6, 73.5, 73.4, 73.3, 73.2, 73.1, 73.0, 70.2, 70.1, 69.7, 68.7, 68.6, 54.2, 54.1, 54.0, 52.5, 52.3, 28.3 ppm.

Experiment 92: Synthesis of 2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl-epiandrosterone 148f

The title compound was prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl phosphate and epiandrosterone according to the representative procedure. Product **148f** was obtained as a colourless oil in 58% yield. The anomeric selectivity (α:β 50:50) was calculated from the peak area ratio of H-1α (4.98 ppm) and H-4β (3.86 ppm) in the crude ^{1}H NMR spectrum.**^{1}H NMR** ($CDCl_3$): δ 7.39-7.27 (m, 40H), 4.98 (d, *J* = 3.81 Hz, 1H, H-1 α), 4.96-4.90 (m, 4H), 4.85 (d, *J* = 11.79 Hz, 2H), 4.77-4.68 (m, 8H), 4.65-4.55 (m, 6H), 4.53-4.49 (m, 1H), 4.46 (d, *J* = 5.47 Hz, 1H, H-1 β), 4.42 (d, *J* = 3.77 Hz, 1H), 4.39-4.28 (m, 4H), 4.05-4.02 (m, 2H), 4.00 (d, *J* = 3.54 Hz, 1H), 3.95-3.90 (m, 3H), 3.86 (d, *J* = 2.51 Hz, 1H), 3.80-3.76 (m, 1H), 3.58-3.48 (m, 9H), 3.08-3.00 (m, 2H), 2.95 (dd, *J* = 12.76 Hz, *J* = 4.77 Hz, 1H), 2.43 (dd, *J* = 19.33 Hz, *J* = 8.64 Hz, 1H), 2.11-2.01 (m, 2H), 1.95-1.90 (m, 3H), 1.75-1.65 (m, 5H), 1.54-1.45 (m, 8H), 1.35-1.20 (m, 18H), 0.85 (s, 3H, α), 0.82 (s, 3H, β), 0.69-0.62 (m, 2H) ppm.**^{13}C NMR** ($CDCl_3$): δ 139.0, 138.9, 138.8, 138.7, 138.6, 138.6, 138.5, 138.4, 138.3, 138., 137.8, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 127.5, 127.5, 127.4, 127.3, 127.3, 127.1, 102.1, 99.8, 82.4, 82.3, 79.7, 79.2, 78.9 78.8, 78.6, 76.5, 76.1, 75.2, 75.1, 74.8, 74.7, 74.6, 74.4, 73.5, 73.5, 73.4, 73.2, 73.2, 73.2, 73.1, 72.9, 72.6, 69.7, 69.3, 69.0, 68.5, 68.2, 54.5, 54.4, 51.4, 47.8, 45.1, 44.7, 36.9, 36.8, 35.9, 35.8, 35.0, 34.6, 31.5, 30.9, 29.5, 28.4, 21.8, 20.5, 13.8, 12.2 ppm.

Experiment 93: Synthesis of methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside 148g

The synthesis of this compound was carried out according to the procedure described in the literature.[183-184]

Experiment 94: Synthesis of methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-galactopyranoside 148g

The title compound was prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl phosphate and methyl-2,3,4-Tri-*O*-benzyl-galactose-α-D-galactopyranoside according to the representative procedure. Product **148g** was obtained as a colourless oil in 70% yield and the spectroscopic analysis of the product matched the literature data.[182] The anomeric selectivity (α:β 56:43) was calculated from the peak area ratio of H-1α (4.99 ppm) and H-1β (4.31 ppm) in the crude ^{1}H NMR spectrum.

Experiment 95: General procedure for the preparation of racemic mixtures of styrene oxides with mandelic acid

To a solution of styrene oxide (0.17 mmol) in dry methanol (0.5 mL) was added DDQ (0.2 mmol) and the resulting mixture was stirred at rt. After the completion of the reaction (monitored by TLC) the solvent was evaporated, the obtained solid was washed several times with hexane and filtered. The enantiomeric excess of the products was determined by chiral HPLC analysis.

Experiment 96: General Procedure for alcoholysis of styrene oxides with mandelic acid

A round bottom flask was charged with mandelic acid (0.002 mmol) and thiourea organocatalysts **65**, **70** or **87** (0.002 mmol, 1 mol%). After addition of styrene oxide (0.17 mmol) and dry methanol (1.99 mmol) the reaction solution was vigorously stirred at room temperature. The full conversation was observed by TLC and the excess of methanol was evaporated. The crude was analysed by ^{1}H NMR and the enantiomeric excess was determined by HPLC analysis.

Experiment 97: Synthesis of 2-methoxy-2-phenyl-ethanol 152

The title compound was prepared according to the representative procedure. Product **152** was obtained as a yellow oil and the spectroscopic analysis of the product matched the literature data.[130] The enantiomeric excess was determined by HPLC with Chiralpack AD-H column at 210 nm (hexane/^{i}PrOH = 97/3, 0.5 mL/min t_R = 21.2 min, t_R = 25.1 min).

Experiment 98: Synthesis of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline 153

The synthesis of compound **153** was carried out according to the procedure described in the literature.[147]

Experiment 99: General procedure for the preparation of racemic mixtures for cross-dehydrogenative coupling reaction

Diethyl phosphonate (0.6 mmol) and TBHP (0.6 mmol, 5.5 M in decane) were successively added to a mixture of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (0.2 mmol) and Schreiner thiourea (20 mol%, 0.04 mmol) in CH_3CN (600 µL). Then, the mixture was stirred at 50°C for 12 h. Upon completion of the reaction, as monitored by TLC analysis the mixture was directly purified by column chromatography (80:20 Hexane/AcOEt) to afford desired product **155** and the enantiomeric excess of the products was determined by chiral HPLC analysis.

Experiment 100: General procedure for cross-dehydrogenative coupling reaction

Diethyl phosphonate (0.6 mmol) and TBHP (0.6 mmol, 5.5 M in decane) were successively added to a mixture of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (0.2 mmol) and organocatalyst **70** or **87** (20 mol%, 0.04 mmol) in CH_3CN (600 µL). Then, the mixture was stirred at 50 °C for 12 h. Upon completion of the reaction, as monitored by TLC analysis the mixture was directly purified by column

chromatography (80:20 Hexane/AcOEt) to afford desired coupling product **156** and the enantiomeric excess of the products was determined by HPLC analysis.

Experiment 101: Synthesis of diethyl (2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate 155

The title compound was prepared according to the representative procedure. Product **156** was obtained as a colourless oil and the spectroscopic analysis of the product matched the literature data.[168] The enantiomeric excess (*rac*) was determined by HPLC with Chiralpack AD-H column at 210 nm (Hexane/^{i}PrOH = 95/5, 1 mL/min t_R = 17.1 min, t_R = 18.4 min).

Chapter 8

Bibliography

(1) Inaki, M.; Liu, J.; Matsuno, K. Cell Chirality: Its Origin and Roles in Left-Right Asymmetric Development. *Philos. Trans. R. Soc. B Biol. Sci.* **2016**, *371*.

(2) Rocha Gonsalves, A. M. d'A; Serra, M. E. S.; Eusébio, M. E. *Estereoquímica*; Imprensa Universidade de Coimbra, 2011.

(3) Vittorio Caprio, J. M. J. W. *Catalysis in Asymmetric Synthesis*, 2nd ed.; Wiley, 2009.

(4) Lin, G. Q.; Li, Y. M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; Wiley: New York, 2001.

(5) Feringa, B.; Delden, R. Absolute Asymmetric Synthesis: The Origin, Control, and Amplification of Chirality. *Angew. Chem. Int. Ed.* **1999**, *38*, 3418–3438.

(6) Kagan, H. B.; Gopalaiah, K. Early History of Asymmetric Synthesis: Who Are the Scientists Who Set up the Basic Principles and the First Experiments? *New J. Chem.* **2011**, *35*, 1933–1937.

(7) Mulzer, J. *2.1 Introductory Remarks: Chiral Pool Syntheses and Diastereoselective Reactions*; Elsevier Ltd., 2012; Vol. 2.

(8) Kiitiro Utimoto, Sadao Kato, Michio Tanaka, Yukihisa Hoshino, Sadao Fujikura, and H. N. Synthesis of Naturally Occurring (R)-(+)-Muscopyridine. *Heterocycl. Commun.* **1982**, *18*, 149–152.

(9) Dipak K. Mandal. *Stereochemistry and Organic Reactions*, 1st ed.; Elsevier, 2021.

(10) Pridgen, L. N.; Mokhallalati, M. K.; McGuire, M. A. A Stereospecific Synthesis of Both Enantiomers of 2-(1'-Amino-2'-Methylpropyl)Imidazole, a Key Synthon in the Synthesis of SB 203386; a Potent Protease Inhibitor. *Tetrahedron Lett.* **1997**, *38*, 1275–1278.

(11) Jiao, T.; Tu, J.; Li, G.; Xu, F. Chemical Cu-Catalyzed Asymmetric Henry Reaction Promoted by Chiral Camphor Schiff Bases. *J. Mol. Catal. A. Chem.* **2016**, *416*, 56–62.

(12) Rosenthaler, L. Durch Enzyme Bewirkte Asymmetrische Synthesen, Eidgenössischen Technischen Hochschule in Zürich, 1908, Vol. 14.

(13) Tsutomu Katsuki, K. B. S. The First Practical Method for Asymmetric Epoxidation. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

(14) Rita Ventura, M. Asymmetric Syntheses Based on Organocatalysis. *Mini. Rev. Org. Chem.* **2014**, *11*, 154–163.

(15) MacMillan, D. W. C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455*, 304–308.

(16) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels - Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

(17) Lelais, G.; MacMillan, D. W. C. *Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation*; 2006.

(18) Sigman, M. S.; Jacobsen, E. N. Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

(19) Corey, E. J.; Grogan, M. J. Enantioselective Synthesis of α-Amino Nitriles from N-Benzhydryl Imines and HCN with a Chiral Bicyclic Guanidine as Catalyst. *Org. Lett.* **1999**, *1*, 157–160.

(20) Wenzel, A. G.; Jacobsen, E. N. Asymmetric Catalytic Mannich Reactions Catalyzed by Urea Derivatives: Enantioselective Synthesis of β-Aryl-β-Amino Acids. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

(21) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. Enantioselective Pictet - Spengler-Type Cyclizations of Hydroxylactams : H-Bond Donor Catalysis by Anion Binding. *J. Am.Chem.Soc* **2007**, *129*, 13404–13405.

(22) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. Enantioselective Thiourea-Catalyzed Additions to Oxocarbenium Ions. *J. Am.Chem.Soc* **2008**, *130*,

7198–7199.

(23) Curran, D. P.; Kuo, L. H. Acceleration of a Dipolar Claisen Rearrangement by Hydrogen Bonding to a Soluble Diaryl Urea. *Tetrahedron Lett.* **1995**, *36*, 6647–6650.

(24) Kuo, L. H.; Curran, D. P. Altering the Stereochemistry of Allylation Reactions of Cyclic α-Sulfinyl Radicals with Diarylureas. *J. Org. Chem.* **1994**, *59*, 3547–3552.

(25) Schreiner, P. R.; Wittkopp, A. H-Bonding Additives Act like Lewis Acid Catalysts. *Org. Lett.* **2002**, *4*, 217–220.

(26) Wittkopp, A.; Schreiner, P. R. Metal-Free, Noncovalent Catalysis of Diels–Alder Reactions by Neutral Hydrogen Bond Donors in Organic Solvents and in Water. *Chem. Eur. J.* **2003**, *9*, 407–414.

(27) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. A General Catalyst for the Asymmetric Strecker Reaction. *Angew. Chemie - Int. Ed.* **2000**, *39*, 1279–1281.

(28) Vachal, P.; Jacobsen, E. N. Structure-Based Analysis and Optimization of a Highly Enantioselective Catalyst for the Strecker Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.

(29) Wenzel, A. G.; Jacobsen, E. N. Asymmetric Catalytic Mannich Reactions Catalyzed by Urea Derivatives: Enantioselective Synthesis of-Aryl-Amino Acids. *J. Am.Chem.Soc* **2002**, *124*, 12964–12965.

(30) Miyabe, H.; Takemoto, Y. Discovery and Application of Asymmetric Reaction by Multi-Functional Thioureas. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785–795.

(31) Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *J. Chem. Soc., Chem. Commun* **2003**, 12672–12673.

(32) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y.; Chem, T. W. J. A. Enantio- and Diastereoselective Michael Reaction of 1 , 3-Dicarbonyl

Compounds to Nitroolefins Catalyzed by a Bifunctional Thiourea. *J. Am.Chem.Soc* **2005**, *127*, 119–125.

(33) Cao, C.; Ye, M.; Sun, X.; Tang, Y. Pyrrolidine − Thiourea as a Bifunctional Organocatalyst : Highly Enantioselective Michael Addition of Cyclohexanone to Nitroolefins. *Org. Lett.* **2006**, *8*, 2901–2904.

(34) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. Organocatalytic Asymmetric Michael Addition of 2,4-Pentandione to Nitroolefins. *Org. Lett.* **2005**, *7*, 4713–4716.

(35) McCooey, S. H.; Connon, S. J. Urea- and Thiourea-Substituted Cinchona Alkaloid Derivatives as Highly Efficient Bifunctional Organocatalysts for the Asymmetric Addition of Malonate to Nitroalkenes: Inversion of Configuration at C9 Dramatically Improves Catalyst Performance. *Angew. Chemie - Int. Ed.* **2005**, *44*, 6367–6370.

(36) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. Highly Enantioselective Conjugate Addition of Nitromethane to Chalcones Using Bifunctional Cinchona Organocatalysts. *Org. Lett.* **2005**, *7*, 1967–1969.

(37) Klausen, R. S.; Jacobsen, E. N. Weak Brønsted Acid-Thiourea Co-Catalysis: Enantioselective, Catalytic Protio-Pictet-Spengler Reactions. *Org. Lett.* **2009**, *11*, 887–890.

(38) Klausen, R. S.; Kennedy, C. R.; Hyde, A. M.; Jacobsen, E. N. Chiral Thioureas Promote Enantioselective Pictet-Spengler Cyclization by Stabilizing Every Intermediate and Transition State in the Carboxylic Acid-Catalyzed Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 12299–12309.

(39) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. Thiourea-Catalyzed Enantioselective Iso-Pictet-Spengler Reactions. *Org. Lett.* **2011**, *13*, 5564–5567.

(40) Liu, M.; Ji, N.; Wang, L.; Liu, P.; He, W. D-Mannitol-Derived Novel Chiral Thioureas: Synthesis and Application in Asymmetric Henry Reactions. *Tetrahedron Lett.* **2018**, *59*, 999–1004.

(41) Liu, K.; Cui, H. F.; Nie, J.; Dong, K. Y.; Li, X. J.; Ma, J. A. Highly Enantioselective Michael Addition of Aromatic Ketones to Nitroolefins Promoted by Chiral Bifunctional Primary Amine-Thiourea Catalysts Based on Saccharides. *Org. Lett.* **2007**, *9*, 923–925.

(42) Miyabe, H.; Tuchida, S.; Massashige, Y.; Takemoto, Y. Reaction of Nitroorganic Compounds Using Thiourea Catalysts Anchored to Polymer Support. *Synthesis.* **2006**, *19*, 3295–3300.

(43) Pedrosa, R.; Andrés, J. M.; Ávila, D. P.; Ceballos, M.; Pindado, R. Chiral Ureas and Thioureas Supported on Polystyrene for Enantioselective Aza-Henry Reactions under Solvent-Free Conditions. *Green Chem.* **2015**, *17*, 2217–2225.

(44) Andrés, J. M.; González, F.; Maestro, A.; Pedrosa, R.; Valle, M. Biodegradable Chitosan-Derived Thioureas as Recoverable Supported Organocatalysts - Application to the Stereoselective Aza-Henry Reaction. *European J. Org. Chem.* **2017**, 3658–3665.

(45) Andrés, J. M.; González, M.; Maestro, A.; Naharro, D.; Pedrosa, R. Recyclable Chiral Bifunctional Thioureas Derived from [60]Fullerene and Their Use as Highly Efficient Organocatalysts for the Asymmetric Nitro-Michael Reaction. *European J. Org. Chem.* **2017**, 2683–2691.

(46) Andrés, J. M.; de La Cruz, N.; Valle, M.; Pedrosa, R. Bottom-Up Synthesis of Supported Thioureas and Their Use in Enantioselective Solvent-Free Aza-Henry and Michael Additions. *Chempluschem* **2016**, *81*, 86–92.

(47) Andrés, J. M.; Ceballos, M.; Maestro, A.; Sanz, I.; Pedrosa, R. Supported Bifunctional Thioureas as Recoverable and Reusable Catalysts for Enantioselective Nitro-Michael Reactions. *Beilstein J. Org. Chem.* **2016**, *12*, 628–635.

(48) Xuan, J.; Feng, Y. Enantiomeric Tartaric Acid Production Using Cis-Epoxysuccinate Hydrolase: History and Perspectives. *Molecules* **2019**, *24*.

(49) Derewenda, Z. S. On Wine, Chirality and Crystallography. *Acta Crystallogr.*

Sect. A Found. Crystallogr. **2008**, *64*, 246–258.

(50) Y. Ukaji; Soeta, T. Acetogenin (Polypriopionate) Derived Auxiliaries: Tartaric Acid. In *Comprehensive Chirality*; Carreira, E. M., Hisashi Yamamoto, Eds.; Elsevier, 2012; pp 176–201.

(51) Gratzer, K.; Gururaja, G. N.; Waser, M. Towards Tartaric-Acid-Derived Asymmetric Organocatalysts. *European J. Org. Chem.* **2013**, 4471–4482.

(52) Maycock, C. D.; Ventura, M. R. New Organocatalysts Derived from Tartaric and Glyceric Acids for Direct Aldol Reactions. *Tetrahedron: Asymmetry* **2012**, *23*, 1262–1271.

(53) Park, Y.; Harper, K. C.; Kuhl, N.; Kwan, E. E.; Liu, R. Y.; Jacobsen, E. N. Macrocyclic Bis-Thioureas Catalyze Stereospecific Glycosylation Reactions. *Science.* **2017**, *355*, 162–166.

(54) Gao, X.; Han, J.; Wang, L. Design of Highly Stable Iminophosphoranes as Recyclable Organocatalysts: Application to Asymmetric Chlorinations of Oxindoles. *Org. Lett.* **2015**, *17*, 4596–4599.

(55) Berens, U.; Leckel, D.; Oepen, S. C. Transacetalization of Diethyl Tartraee with Acetals of α-Dicarbonyl Compounds: A Simple Access to a New Class of C2-Symmetric Auxiliaries and Ligands. *J. Org. Chem.* **1995**, *60*, 8204–8208.

(56) Mathew, A. E.; Stella, V. J.; Mejillano, M. R.; Nath, J. P.; Himes, R. H. Synthesis and Evaluation of Some Water-Soluble Prodrugs and Derivatives of Taxol with Antitumor Activity. *J. Med. Chem.* **1992**, *35*, 145–151.

(57) Chauvette, R. R.; Pennington, P. A.; Ryan, C. W.; Cooper, R. D. G.; José, F. L.; Ian, G. W.; Van Heyningen, E. M.; Huffman, G. W. Chemistry of Cephalosporin Antibiotics. XXI. Conversion of Penicillins to Cephalexin. *J. Org. Chem.* **1971**, *9*, 1259–1267.

(58) Zinelaabidine, C.; Souad, O.; Zoubir, J.; Malika, B.; Nour-Eddine, A. A

Simple and Efficient Green Method for the Deprotection of N-Boc in Various Structurally Diverse Amines under Water-Mediated Catalyst-Free Conditions. *Int. J. Chem.* **2012**, *4*, 73–79.

(59) Bellamy, F. D.; Ou, K. Selective Reduction of Aromatic Nitro Compounds with Stannous Chloride in Non Acidic and Non Aqueous Medium. *Tetrahedron Lett.* **1984**, *25*, 839–842.

(60) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. Enantioselective α-Amination of 1,3-Dicarbonyl Compounds Using Squaramide Derivatives as Hydrogen Bonding Catalysts. *Org. Lett.* **2010**, *12*, 2028–2031.

(61) Yang, Z.-H.; Wang, L.-X.; Zhou, Z.-H.; Zhou, Q.-L.; Tang, C.-C. Synthesis of New Chiral Schiff Bases and Their Application in the Asymmetric Trimethylsilylcyanation of Aromatic Aldehydes. *Tetrahedron Asymmetry* **2001**, *12*, 1579–1582.

(62) Tyrode, M. V. Camphoric Acid, Its Action and Uses. *Bost. Med. Surg. J.* **1908**, *11*, 908.

(63) Murtinho, D.; Elisa Silva Serra, M.; Rocha Gonsalves, A. M. d. A. Enantioselective Ethylation of Aldehydes with 1,3-N-Donor Ligands Derived from (+)-Camphoric Acid. *Tetrahedron Asymmetry* **2010**, *21*, 62–68.

(64) Serra, M. E. S.; Murtinho, D.; Paz, V. Enantioselective Alkylation of Aromatic Aldehydes with (+)-Camphoric Acid Derived Chiral 1,3-Diamine Ligands. *Tetrahedron Asymmetry* **2017**, *28*, 381–386.

(65) Yang, T. F.; Shen, C. H.; Hsu, C. T.; Chen, L. H.; Chuang, C. H. Selective Reaction of Camphor-Derived Exo-Formyl [2.2.1]Bicyclic Carbinol with Alkyl Primary Amines: Application to the Preparation of New Chiral Catalysts for Asymmetric Reduction of Aryl Ketones. *Tetrahedron* **2010**, *66*, 8734–8738.

(66) Serra, M. E. S.; Murtinho, D.; Goth, A.; Rocha Gonsalves, A. M. d'A; Abreu, P. E.; Pais, A. A. C. C. Ultrasound-Mediated Synthesis of Camphoric Acid-

Based Chiral Salens for the Enantioselective Trimethylsilylcyanation of Aldehydes. *Chirality* **2010**, *22*, 425–431.

(67) Ričko, S.; Svete, J.; Štefane, B.; Perdih, A.; Golobič, A.; Meden, A.; Grošelj, U. 1,3-Diamine-Derived Bifunctional Organocatalyst Prepared from Camphor. *Adv. Synth. Catal.* **2016**, *358*, 3786–3796.

(68) Ričko, S.; Meden, A.; Ivančič, A.; Perdih, A.; Štefane, B.; Svete, J.; Grošelj, U. Organocatalyzed Deracemization of Δ2-Pyrrolin-4-Ones. *Adv. Synth. Catal.* **2017**, *359*, 2288–2296.

(69) Verkuijl, B. J. V.; Johannes G. de Vries; Feringa, B. L. 3,3′-Diaryl-BINOL Phosphoric Acids as Enantioselective Extractants of Benzylic Primary Amines. *Chirality* **2011**, *43*, 34–43.

(70) Ričko, S.; Pozgan, F.; Štefane, B.; Svete, J.; Golobic, A.; Grošelj, U. Stereodivergent Synthesis of Camphor-Derived Diamines and Their Application as Thiourea Organocatalysts. *Molecules* **2020**, *25*, 1–22.

(71) Andrés, J. M.; Manzano, R.; Pedrosa, R. Novel Bifunctional Chiral Urea and Thiourea Derivatives as Organocatalysts: Enantioselective Nitro-Michael Reaction of Malonates and Diketones. *Chem. Eur. J.* **2008**, *14*, 5116–5119.

(72) Amarasinghe, N. R.; Turner, P.; Todd, M. H. The First Catalytic, Enantioselective Aza-Henry Reaction of an Unactivated Cyclic Imine. *Adv. Synth. Catal.* **2012**, *354*, 2954–2958.

(73) Dündar, E.; Tanyeli, C. Enantioselective Friedel-Crafts Alkylation of Indole with Nitroalkenes in the Presence of Bifunctional Squaramide Organocatalysts. *Tetrahedron Lett.* **2021**, *73*, 16–19.

(74) Anif Pasha, M.; Peraka, S.; Ramachary, D. B. Catalytic Asymmetric Synthesis of Benzobicyclo[3.2.1]Octanes. *Chem. - A Eur. J.* **2021**, *27*, 10563–10568.

(75) Kuwano, S.; Ogino, E.; Arai, T. Enantio- and Diastereoselective Double

Mannich Reaction of Malononitrile with: N-Boc Imines Using Quinine-Derived Bifunctional Organoiodine Catalyst. *Org. Biomol. Chem.* **2021**, *19*, 6969–6973.

(76) Carceller-Ferrer, L.; González del Campo, A.; Vila, C.; Blay, G.; Muñoz, M. C.; Pedro, J. R. Organocatalytic Enantioselective Aminoalkylation of 5-Aminopyrazole Derivatives with Cyclic Imines. *European J. Org. Chem.* **2020**, *2020*, 7450–7454.

(77) Pasuparthy, S. D.; Mait, D. B. Enantioselective Organocatalytic Michael Addition Reactions Catalyzed by Proline/Prolinol/Supported Proline Based Organocatalysts: An Overview. *ChemistrySelect* **2022**, *7*, 2365–6549.

(78) Malkar, R. S.; Jadhav, A. L.; Yadav, G. D. Innovative Catalysis in Michael Addition Reactions for C-X Bond Formation. *Mol. Catal.* **2020**, *485*.

(79) Kozma, V.; Fülöp, F.; Szőllősi, G. 1,2-Diamine-Derived (Thio)Phosphoramide Organocatalysts in Asymmetric Michael Additions. *Adv. Synth. Catal.* **2020**, *362*, 2444–2458.

(80) Kuremoto, T.; Sadatsune, R.; Yasukawa, T.; Yamashita, Y.; Kobayashi, S. Machine-Assisted Preparation of a Chiral Diamine Ligand Library and In Silico Screening Using Ab Initio Structural Parameters for Heterogeneous Chiral Catalysts. *Adv. Synth. Catal.* **2021**, *363*, 4204–4208.

(81) Kucharski, D. J.; Kowalczyk, R.; Boratýnski, P. J. Chiral Vicinal Diamines Derived from Mefloquine. *J. Org. Chem.* **2021**, *86*, 10654–10664.

(82) Juaristi, E. Recent Developments in next Generation (S) -Proline-Derived Chiral Organocatalysts. *Tetrahedron* **2021**, *88*.

(83) Xue, Z.; Li, Y.; Luo, S. Chiral Primary Amine Catalyzed Divergent Coupling of α-Substituted Acrylaldehydes with α -Diazoesters. *ACS Catal.* **2020**, *10*, 10989–10998.

(84) Han, W.; Oriyama, T. Asymmetric Michael Addition of Isobutyraldehyde to Nitroolefins Using an α, α-Diphenyl- (S) -Prolinol-Derived Chiral Diamine Catalyst. *Bull. Chem. Soc. Jpn.* **2020**, *93*, 988–992.

(85) Guo, F.; Chen, J.; Huang, Y. A Bifunctional N - Heterocyclic Carbene as a Noncovalent Organocatalyst for Enantioselective Aza-Michael Addition Reactions. *ACS Catal.* **2021**, *11*, 6316–6324.

(86) Shim, J. H.; Ahn, B. K.; Lee, J. Y.; Kim, H. S.; Ha, D. C. Organocatalysis for the Asymmetric Michael Addition of Cycloketones and α, β-Unsaturated Nitroalkenes. *Catalysts* **2021**, *11*.

(87) Rufino, V. C.; Pliego, J. R. Bifunctional Primary Amino-Thiourea Asymmetric Catalysis : The Imine-Iminium Ion Mechanism in the Michael Addition of Nitromethane to Enone. *Asian J. Org. Chem.* **2021**, *10*, 1472–1485.

(88) Gandhi, S.; Sivadas, V.; Baire, B. Thiourea – Tertiary Amine Promoted Cascade Catalysis : A Tool for Complexity Generation. *European J. Org. Chem.* **2020**, 220–234.

(89) Han, Z.; Lin, X. Synthesis of Chiral Tertiary Amine-Thioureas Based on Spirobi Indane and Application in Catalytic Asymmetric Michael Addition Reaction. *Synthesis.* **2020**, *52*, 1131–1139.

(90) Huang, X.; Zhang, W. Recyclable Fluorous Cinchona Organocatalysts for Asymmetric Synthesis of Biologically Interesting Compounds. *Chem Commun* **2021**, *57*, 10116–10124.

(91) Chhanda, S. A.; Itsuno, S. Design and Synthesis of Cinchona-Based Chiral Hyperbranched Polymers and Their Application in Asymmetric Reactions. *Tetrahedron* **2020**, *76*.

(92) Tözendemir, D.; Tanyeli, C. The Synthesis of Chiral β -Naphthyl- β -Sulfanyl Ketones via Enantioselective Sulfa-Michael Reaction in the Presence of a Bifunctional Cinchona / Sulfonamide Organocatalyst. *Beilstein J. Org. Chem.* **2021**, *17*, 494–503.

(93) Yoshida, K.; Inoue, H.; Oji, Y.; Suzuki, H.; Takao, K. Enantioselective Organocatalytic Construction of Spirochroman Derivatives. *J. Org. Chem.* **2020**, *85*, 10189–10197.

(94) Curran, S. P.; Fallon, B. J.; Connon, S. J. C2 -Symmetric Cinchona Alkaloid Derivatives: Versatile Catalysts for the Enantioselective C-C Bond Forming Conjugate Addition of Nucleophiles to Simple α,β-Unsaturated Acyl Pyrazoles. *ChemistrySelect* **2020**, *5*, 15190–15194.

(95) Arai, R.; Hirashima, S.; Nakano, T.; Kawada, M.; Akutsu, H.; Nakashima, K.; Miura, T. Asymmetric Conjugate Addition of Phosphonates to Enones Using Cinchona − Diaminomethylenemalononitrile Organocatalysts. *J. Org. Chem.* **2020**, *85*, 3872–3878.

(96) Afrin, S.; Itsuno, S. Synthesis of Cinchona Squaramide Polymers by Yamamoto Coupling Polymerization and Their Application in Asymmetric Michael Reaction. *React. Funct. Polym.* **2021**, *164*.

(97) Roncak, R.; Tvrdonova, M.; Gonda, J.; Elecko, J. Novel Carbohydrate-Based Thioureas as Organocatalysts for Asymmetric Michael Addition of 1,3-Dicarbonyl Compounds to Nitroolefins. *Tetrahedron* **2020**, *76*.

(98) Yan, J.; Li, X.; Chen, Y.; Li, Y.; Chen, W.; Zhan, R.; Huang, H. Organocatalytic 1,4-Addition of Azadienes with 3 - Homoacyl Coumarins toward Highly Enantioenriched Benzofuran Coumarin Skeletons. *J. Org. Chem.* **2020**, *85*, 12175–12186.

(99) Takemoto, Y. Development of Chiral Thiourea Catalysts and Its Application to Asymmetric Catalytic Reactions. *Chem. Pharm. Bull.* **2010**, *58*, 593–601.

(100) Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

(101) Zhang, X. jing; Liu, S. ping; Lao, J. hua; Du, G. jian; Yan, M.; Chan, A. S. C. Asymmetric Conjugate Addition of Carbonyl Compounds to Nitroalkenes Catalyzed by Chiral Bifunctional Thioureas. *Tetrahedron Asymmetry* **2009**, *20*, 1451–1458.

(102) Yan, L. J.; Liu, Q. Z.; Wang, X. L. Novel Chiral Thioureas for Highly

Enantioselective Michael Reactions of Malonates to Nitroalkenes. *Chinese Chem. Lett.* **2009**, *20*, 310–313.

(103) Konda, S.; Zhao, J. C. G. High Enantioselective Michael Addition of Malonates to β,γ-Unsaturated α-Ketoesters Catalyzed by Bifunctional Thioureas. *Tetrahedron Lett.* **2014**, *55*, 5216–5218.

(104) Wang, W. H.; Abe, T.; Wang, X. B.; Kodama, K.; Hirose, T.; Zhang, G. Y. Self-Assembled Proline-Amino Thioureas as Efficient Organocatalysts for the Asymmetric Michael Addition of Aldehydes to Nitroolefins. *Tetrahedron Asymmetry* **2010**, *21*, 2925–2933.

(105) Mayans, E.; Gargallo, A.; Álvarez-Larena, Á.; Illa, O.; Ortuño, R. M. Diastereodivergent Synthesis of Chiral Vic-Disubstituted-Cyclobutane Scaffolds: 1,3-Amino Alcohol and 1,3-Diamine Derivatives - Preliminary Use in Organocatalysis. *European J. Org. Chem.* **2013**, 1425–1433.

(106) Yao, W.; Chen, M.; Liu, X.; Jiang, R.; Zhang, S.; Chen, W. Ferrocene as a Scaffold for Effective Bifunctional Amine-Thiourea Organocatalysts. *Catal. Sci. Technol.* **2014**, *4*, 1726–1729.

(107) Ren, X.; He, C.; Feng, Y.; Chai, Y.; Yao, W.; Chen, W.; Zhang, S. Novel Ferrocene-Based Bifunctional Amine-Thioureas for Asymmetric Michael Addition of Acetylacetone to Nitroolefins. *Org. Biomol. Chem.* **2015**, *13*, 5054–5060.

(108) Horitsugi, N.; Kojima, K.; Yasui, K.; Sohtome, Y.; Nagasawa, K. Asymmetric Michael Reaction of Nitroolefins with β-Dicarbonyl Compounds Catalysed by 1,3-Diamine-Tethered Guanidine-Thiourea Bifunctional Organocatalysts. *Asian J. Org. Chem.* **2014**, *3*, 445–448.

(109) Sohtome, Y.; Horitsugi, N.; Takagi, R.; Nagasawa, K. Enantioselective Phospha-Michael Reaction of Diphenyl Phosphonate with Nitroolefins Utilizing Conformationally Flexible Guanidinium/Bisthiourea Organocatalyst: Assembly-State Tunability in Asymmetric Organocatalysis. *Adv. Synth. Catal.* **2011**, *353*, 2631–2636.

(110) Yu, L.; Li, P. New Simple Primary Amine-Thiourea Organocatalysts and Their Application in Asymmetric Conjugate Addition. *Tetrahedron Lett.* **2014**, *55*, 3697–3700.

(111) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. Catalytic Enantioselective Friedel-Crafts Alkylation of Indoles with Nitroalkenes by Using a Simple Thiourea Organocatalyst. *Angew. Chemie - Int. Ed.* **2005**, *44*, 6576–6579.

(112) Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. Hydrogen-Bonding Thiourea Organocatalysts: The Privileged 3,5-Bis(Trifluoromethyl)Phenyl Group. *European J. Org. Chem.* **2012**, 5919–5927.

(113) Chauhan, P.; Chimni, S. S. Grinding-Assisted Asymmetric Organocatalysis: A Solvent-Free Approach to the Formation of Vicinal Quaternary and Tertiary Stereocenters. *Asian J. Org. Chem.* **2012**, *1*, 138–141.

(114) Nemoto, T.; Obuchi, K.; Tamura, S.; Fukuyama, T.; Hamada, Y. Novel Chiral Hydrogen Bond Donor Catalysts Based on a 4,5-Diaminoxanthene Scaffold: Application to Enantioselective Conjugate Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes. *Tetrahedron Lett.* **2011**, *52*, 987–991.

(115) Teresa Barros, M.; Phillips, A. M. F. Synthesis of New Chiral Amines with a Cyclic 1,2-Diacetal Skeleton Derived from (2R,3R)-(+)-Tartaric Acid. *Molecules* **2006**, *11*, 177–196.

(116) Choudary, B. M.; Chowdari, N. S.; Kantam, M. L. Enantioselective Michael Addition Reactions Catalyzed by a New Heterobimetallic Asymmetric Complex. *J. Mol. Catal. A Chem.* **1999**, *142*, 389–392.

(117) Mahajan, D. P.; Godbole, H. M.; Singh, G. P.; Shenoy, G. G. Enantioselective Michael Addition of Malonic Esters to Benzalacetophenone by Using Chiral Phase Transfer Catalysts Derived

from Proline-Mandelic Acid/Tartaric Acid. *J. Chem. Sci.* **2019**, *131*.

(118) Kimura, T.; Eto, T.; Takahashi, D.; Toshima, K. Stereocontrolled Photoinduced Glycosylation Using an Aryl Thiourea as an Organo Photoacid. *Org. Lett.* **2016**, *18*, 3190–3193.

(119) Ajit Varki and Nathan Sharon. *Essentials of Glycobiology*, 2nd ed.; Varki, A., Cummings, R. D., Esko, J. D., Stanley, P., Hart, G. W., Aebi, M., Mohnen, D., Kinoshita, T., Packer, N. H., Prestegard, J. H., Schnaar, R. L., Seeberger, P. H., Eds.; Cold Spring Harbor (NY), 2009.

(120) Williams, R.; Galan, M. C. Recent Advances in Organocatalytic Glycosylations. *European J. Org. Chem.* **2017**, *42*, 6247–6264.

(121) Xu, C.; Loh, C. C. J. An Ultra-Low Thiourea Catalyzed Strain-Release Glycosylation and a Multicatalytic Diversification Strategy. *Nat. Commun.* **2018**, *9*, 1–12.

(122) K. Toshima, K. S. *Comprehensive Glycoscience*, 2nd ed.; Barchi, J., Ed.; Elsevier, 2021.

(123) Zhu, X.; Schmidt, R. R. New Principles for Glycoside-Bond Formation. *Angew. Chemie - Int. Ed.* **2009**, *48*, 1900–1934.

(124) Van der Vorm, S.; Hansen, T.; Overkleeft, H. S.; Van der Marel, G. A.; Codée, J. D. C. The Influence of Acceptor Nucleophilicity on the Glycosylation Reaction Mechanism. *Chem. Sci.* **2017**, *8*, 1867–1875.

(125) Mydock, L. K.; Demchenko, A. V. Mechanism of Chemical O-Glycosylation: From Early Studies to Recent Discoveries. *Org. Biomol. Chem.* **2010**, *8*, 497–510.

(126) Bohé, L.; Crich, D. A Propos of Glycosyl Cations and the Mechanism of Chemical Glycosylation; The Current State of the Art. *Carbohydr. Res.* **2015**, *403*, 48–59.

(127) Ranade, S. C.; Demchenko, A. V. Mechanism of Chemical Glycosylation: Focus on the Mode of Activation and Departure of Anomeric Leaving

Groups. *J. Carbohydr. Chem.* **2013**, *32*, 1–43.

(128) Bohé, L.; Crich, D. A Propos of Glycosyl Cations and the Mechanism of Chemical Glycosylation. *Comptes Rendus Chim.* **2011**, *14*, 3–16.

(129) Geng, Y.; Kumar, A.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. Cooperative Catalysis in Glycosidation Reactions with O-Glycosyl Trichloroacetimidates as Glycosyl Donors. *Angew. Chemie - Int. Ed.* **2013**, *52*, 10089–10092.

(130) Weil, T.; Kotke, M.; Kleiner, C. M.; Schreiner, P. R. Cooperative Brønsted Acid-Type Organocatalysis : Alcoholysis of Styrene Oxides. *Org. Lett.* **2008**, *10*, 1513–1516.

(131) Zhang, Z.; Lippert, K. M.; Hausmann, H.; Kotke, M.; Schreiner, P. R. Cooperative Thiourea−Brønsted Acid Organocatalysis: Enantioselective Cyanosilylation of Aldehydes with TMSCN. *J. Org. Chem.* **2011**, *76*, 9764–9776.

(132) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. (Thio)Urea Organocatalyst Equilibrium Acidities in DMSO. *Org. Lett.* **2012**, *14*, 1724–1727.

(133) Levi, S. M.; Li, Q.; Rötheli, A. R.; Jacobsen, E. N. Catalytic Activation of Glycosyl Phosphates for Stereoselective Coupling Reactions. *Proc. Natl. Acad. Sci. U. S. A.* **2019**, *116*, 35–39.

(134) Westheimer, F. H. Nature Chose Phosphates The Role of Phosphates The Importance of Being Ionized. *Science* **1987**, *235*, 1173–1178.

(135) Kennedy, C. R.; Lehnherr, D.; Rajapaksa, N. S.; Ford, D. D.; Park, Y.; Jacobsen, E. N. Mechanism-Guided Development of a Highly Active Bis-Thiourea Catalyst for Anion-Abstraction Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 13525–13528.

(136) Benjamim G. Davis; Antony J. Fairbanks. *Carbohydrate Chemistry*, 1st ed.; Oxford Chemistry Primers, 2002.

(137) Crich, D.; Sun, S. Formation of β-Mannopyranosides of Primary Alcohols

Using the Sulfoxide Method. *J. Org. Chem.* **1996**, *61*, 4506–4507.

(138) De Meo, C.; Kamat, M. N.; Demchenko, A. V. Remote Participation-Assisted Synthesis of β-Mannosides. *European J. Org. Chem.* **2005**, 706–711.

(139) Li, Q.; Levi, S. M.; Jacobsen, E. N. Highly Selective β-Mannosylations and β-Rhamnosylations Catalyzed by Bis-Thiourea. *J. Am. Chem. Soc.* **2020**, *142*, 11865–11872.

(140) Manjunathan, P.; Prasanna, V.; Shanbhag, G. V. Exploring Tailor-Made Brønsted Acid Sites in Mesopores of Tin Oxide Catalyst for β-Alkoxy Alcohol and Amino Alcohol Syntheses. *Sci. Rep.* **2021**, *11*.

(141) Biggs, B. J.; Chapman, N. B.; Finch, A. F.; Wray, V. Mechanism of Acid-Catalysed Alcoholysis of Epoxides. Part 1. Reactions of Substituted (1.2-Epoxyethy1)Benzenes. *J. Chem. Soc. B* **1971**, 55–63.

(142) Prestat, G.; Baylon, C.; Heck, M. P.; Mioskowski, C. Lewis Acid-Catalyzed Regiospecific Opening of Vinyl Epoxides by Alcohols. *Tetrahedron Lett.* **2000**, *41*, 3829–3831.

(143) Solodenko, W.; Jas, G.; Kunz, U.; Kirschning, A. Continuous Enantioselective Kinetic Resolution of Terminal Epoxides Using Immobilized Chiral Cobalt-Salen Complexes. *Synthesis (Stuttg).* **2007**, *4*, 583–589.

(144) Li, C. J. Cross-Dehydrogenative Coupling (CDC): Exploring C-C Bond Formations beyond Functional Group Transformations. *Acc. Chem. Res.* **2009**, *42*, 335–344.

(145) Li, C. J.; Li, Z. Green Chemistry: The Development of Cross-Dehydrogenative Coupling (CDC) for Chemical Synthesis. *Pure Appl. Chem.* **2006**, *78*, 935–945.

(146) Murahashi, S. I.; Komiya, N.; Terai, H.; Nakae, T. Aerobic Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Sodium Cyanide.

J. Am. Chem. Soc. **2003**, *125*, 15312–15313.

(147) Li, Z.; Li, C. J. CuBr-Catalyzed Direct Indolation of Tetrahydroisoquinolines via Cross-Dehydrogenative Coupling between Sp3 C-H and Sp2 C-H Bonds. *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969.

(148) Li, Z.; Bohle, D. S.; Li, C. J. CU-Catalyzed Cross-Dehydrogenative Coupling: A Versatile Strategy for C-C Bond Formations via the Oxidative Activation of Sp3 C-H Bonds. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 8928–8933.

(149) Kafarski, P.; Lejczak, B. Biological Activity of Aminophosphonic Acids. *Phosphorus. Sulfur. Silicon Relat. Elem.* **1991**, *63*, 193–215.

(150) Hiratake, L.; Oda, J. Aminophosphonic and Aminoboronic Acids as Key Elements of a Transition State Analogue Inhibitor of Enzymes. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 211–218.

(151) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. Synthesis and Structure-Activity Relationships of Antibacterial Phosphonopeptides Incorporating (1-Aminoethyl)Phosphonic Acid and (Aminomethyl)Phosphonic Acid. *J. Med. Chem.* **1986**, *29*, 29–40.

(152) Shu, X. Z.; Yang, Y. F.; Xia, X. F.; Ji, K. G.; Liu, X. Y.; Liang, Y. M. Platinum-Catalyzed Cross-Dehydrogenative Coupling Reaction in the Absence of Oxidant. *Org. Biomol. Chem.* **2010**, *8*, 4077–4079.

(153) Wang, B.; Shelar, D. P.; Han, X. Z.; Li, T. T.; Guan, X.; Lu, W.; Liu, K.; Chen, Y.; Fu, W. F.; Che, C. M. Long-Lived Excited States of Zwitterionic Copper(I) Complexes for Photoinduced Cross-Dehydrogenative Coupling Reactions. *Chem. - A Eur. J.* **2015**, *21*, 1184–1190.

(154) Ratnikov, M. O.; Xu, X.; Doyle, M. P. Simple and Sustainable Iron-Catalyzed Aerobic C-H Functionalization of N, N-Dialkylanilines. *J. Am. Chem. Soc.* **2013**, *135*, 9475–9479.

(155) Gröll, B.; Schaaf, P.; Schnürch, M. Improved Simplicity and Practicability in Copper-Catalyzed Alkynylation of Tetrahydroisoquinoline. *Monatshefte*

fur Chemie - Chem. Montly **2017**, *148*, 91–104.

(156) Pan, Y.; Kee, C. W.; Chen, L.; Tan, C. H. Dehydrogenative Coupling Reactions Catalysed by Rose Bengal Using Visible Light Irradiation. *Green Chem.* **2011**, *13*, 2682–2685.

(157) Zhang, Z.; Bao, Z.; Xing, H. N,N'-Bis[3,5-Bis(Trifluoromethyl)Phenyl]Thiourea: A Privileged Motif for Catalyst Development. *Org. Biomol. Chem.* **2014**, *12*, 3151–3162.

(158) Rueping, M.; Vila, C.; Bootwicha, T. Continuous Flow Organocatalytic C−H Functionalization and Cross- Dehydrogenative Coupling Reactions: Visible Light Organophoto. *ACS Catal.* **2013**, *3*, 1676–1680.

(159) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. Visible-Light Photoredox Catalysis: Aza-Henry Reactions via C-H Functionalization. *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465.

(160) Tanoue, A.; Yoo, W. J.; Kobayashi, S. Sulfuryl Chloride as an Efficient Initiator for the Metal-Free Aerobic Cross-Dehydrogenative Coupling Reaction of Tertiary Amines. *Org. Lett.* **2014**, *16*, 2346–2349.

(161) Ueda, H.; Yoshida, K.; Tokuyama, H. Acetic Acid Promoted Metal-Free Aerobic Carbon-Carbon Bond Forming Reactions at α-Position of Tertiary Amines. *Org. Lett.* **2014**, *16*, 4194–4197.

(162) Yamaguchi, T.; Nobuta, T.; Tada, N.; Miura, T.; Nakayama, T.; Uno, B.; Itoh, A. Aerobic Photooxidative Carbon-Carbon Bond Formation between Tertiary Amines and Carbon Nucleophiles Using 2-Chloroanthra-9,10-Quinone. *Synlett* **2014**, *25*, 1453–1557.

(163) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. A Versatile C-H Functionalization of Tetrahydroisoquinolines Catalyzed by Iodine at Aerobic Conditions. *Org. Lett.* **2013**, *15*, 1092–1095.

(164) Liu, Q.; Li, Y. N.; Zhang, H. H.; Chen, B.; Tung, C. H.; Wu, L. Z. Reactivity and Mechanistic Insight into Visible-Light-Induced Aerobic Cross-

Dehydrogenative Coupling Reaction by Organophotocatalysts. *Chem. - A Eur. J.* **2012**, *18*, 620–627.

(165) Tsang, A. S. K.; Todd, M. H. Facile Synthesis of Vicinal Diamines via Oxidation of N-Phenyltetrahydroisoquinolines with DDQ. *Tetrahedron Lett.* **2009**, *50*, 1199–1202.

(166) Su, W.; Yu, J.; Li, Z.; Jiang, Z. Solvent-Free Cross-Dehydrogenative Coupling Reactions under High Speed Ball-Milling Conditions Applied to the Synthesis of Functionalized Tetrahydroisoquinolines. *J. Org. Chem.* **2011**, *76*, 9144–9150.

(167) Narayan, R.; Matcha, K.; Antonchick, A. P. Metal-Free Oxidative C-C Bond Formation through C-H Bond Functionalization. *Chem. - A Eur. J.* **2015**, *21*, 14678–14693.

(168) Gu, K.; Zhang, Z.; Bao, Z.; Xing, H.; Yang, Q.; Ren, Q. Thiourea-Catalyzed Cross-Dehydrogenative Coupling of C(Sp3)–H with Diethyl Phosphite. *European J. Org. Chem.* **2016**, 3939–3942.

(169) Lin, B.; Lu, G.; Lin, R.; Cui, Y.; Liu, Y.; Tang, G.; Zhao, Y. Metal-Free Synthesis of α-Aminophosphonates from Tertiary Amines and P(O)H Compounds via a Cross-Dehydrogenative Coupling Reaction. *Synlett* **2018**, *29*, 2697–2700.

(170) W.L.F. Armarego. *Purification of Laboratory Chemicals, 5th Edition*, 5th ed.; Butterworth-Heinemann, 2003.

(171) Bellec, N.; Montalban, A. G.; Williams, D. B. G.; Cook, A. S.; Anderson, M. E.; Feng, X.; Barrett, A. G. M.; Hoffman, B. M. Porphyrazinediols: Synthesis, Characterization, and Complexation to Group IVB Metallocenes. *J. Org. Chem.* **2000**, *65*, 1774–1779.

(172) Marino, C.; Lima, C.; Mariño, K.; De Lederkremer, R. M. Synthesis of a Derivative of A-D-Glcp(1→2)-D-Galf Suitable for Further Glycosylation and of a-D-Glcp(1→2)-D-Gal, a Disaccharide Fragment Obtained from Varianose. *Beilstein J. Org. Chem.* **2012**, *8*, 2142–2148.

(173) Iwata, R.; Uda, K.; Takahashi, D.; Toshima, K. Photo-Induced Glycosylation Using Reusable Organophotoacids. *Chem. Commun.* **2014**, *50*, 10695–10698.

(174) Matwiejuk, M.; Thiem, J. New Method for Regioselective Glycosylation Employing Saccharide Oxyanions. *European J. Org. Chem.* **2011**, 5860–5878.

(175) Sabesan, S.; Neira, S. Synthesis of Glycosyl Phosphates and Azides. *Carbohydr. Res.* **1992**, *223*, 169–185.

(176) Liao, W.; Lu, D. Synthesis of a Hexasaccharide Acceptor Corresponding to the Reducing Terminus of Mycobacterial 3-O-Methylmannose Polysaccharide (MMP). *Carbohydr. Res.* **1996**, *296*, 171–182.

(177) Tennant-Eyles, R. J.; Davis, B. G.; Fairbanks, A. J. Peptide Templated Glycosylation Reactions. *Tetrahedron Asymmetry* **2000**, *11*, 231–243.

(178) Pekari, K.; Tailler, D.; Weingart, R.; Schmidt, R. R. Synthesis of the Fully Phosphorylated GPI Anchor Pseudohexasaccharide of Toxoplasma Gondii. *J. Org. Chem.* **2001**, *66*, 7432–7442.

(179) Geringer, S. A.; Demchenko, A. V. Iron(Iii) Chloride-Catalyzed Activation of Glycosyl Chlorides. *Org. Biomol. Chem.* **2018**, *16*, 9133–9137.

(180) Palanivel, A.; Chennaiah, A.; Dubbu, S.; Mallick, A.; Vankar, Y. D. AuCl3-AgOTf Promoted O-Glycosylation Using Anomeric Sulfoxides as Glycosyl Donors at Room Temperature. *Carbohydr. Res.* **2017**, *437*, 43–49.

(181) Cardona, A.; Boutureira, O.; Castillón, S.; Díaz, Y.; Matheu, M. I. Metal-Free and VOC-Free: O -Glycosylation in Supercritical CO2. *Green Chem.* **2017**, *19*, 2687–2694.

(182) Yang, L.; Hammelev, C. H.; Pedersen, C. M. Catalytic and Atom-Economic Glycosylation Using Glycosyl Formates and Cheap Metal Salts. *ChemSusChem* **2020**, *13*, 3166–3171.

(183) Lam, S. N.; Gervay-Hague, J. Solution- and Solid-Phase Oligosaccharide

Synthesis Using Glucosyl Iodides: A Comparative Study. *Carbohydr. Res.* **2002**, *337*, 1953–1965.

(184) Lee, J. C.; Francis, S.; Dutta, D.; Gupta, V.; Yang, Y.; Zhu, J. Y.; Tash, J. S.; Schönbrunn, E.; Georg, G. I. Synthesis and Evaluation of Eight- and Four-Membered Iminosugar Analogues as Inhibitors of Testicular Ceramide-Specific Glucosyltransferase, Testicular β-Glucosidase 2, and Other Glycosidases. *J. Org. Chem.* **2012**, *77*, 3082–3098.