Metal-Mediated Couplings of Primary Alcohols with Amines and Carbohydrates

Maggi, Agnese; Madsen, Robert

Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

Metal-Mediated Couplings of Primary Alcohols with Amines and Carbohydrates

Ph.D. Thesis

Agnese Maggi

December 2012

Department of Chemistry

Technical University of Denmark

Metal-Mediated Couplings of Primary Alcohols with Amines and Carbohydrates

Ph.D. Thesis by Agnese Maggi

Acknowledgements

First I would like to thank my supervisor Professor Robert Madsen for hosting me as a Ph.D. student in his group, for providing an excellent and inspiring working environment and for his support.

I would like to express my gratitude to my dear friends and colleagues Ilya Makarov, Camilla Arboe Jennum and Amanda Birgitte Sølvhøj for the great time we have had working together, for their support and for the numerous and inspiring conversations about chemistry and everything else. It was a great pleasure to share the office and my lunch breaks with you.

My friend Dr. Gyorgyi Osztrovszky is acknowledged for being a great lab mate and for the in-depth discussions about problems and challenges I have encountered during my doctorate. Especially I would like to thank Gyorgyi for creating an exceptional atmosphere in the lab and for her fine music selection.

I would like to express my thankfulness to Dr. Christoph Röhrig for proofreading this thesis.

Special thanks go to Anne Hector, Tina Gustafsson, Patrick Scholer, Janne Borg Rasmussen, Brian Ekman-Gregersen and Brian Brylle Dideriksen for providing an excellent technical support.

I also would like to thank current and former Ph.D. fellows from Building 201, particularly Kennedy Taveras, Alexandra Zakharova, Vitaly Komnatnyy and Helene Viart for making my stay at DTU a splendid experience.

The Technical University of Denmark (DTU) is acknowledged for financing my Ph.D. project.

Last, but not least, I would like to thank my parents, Luigi and Fiorella, for their patience, love and support.

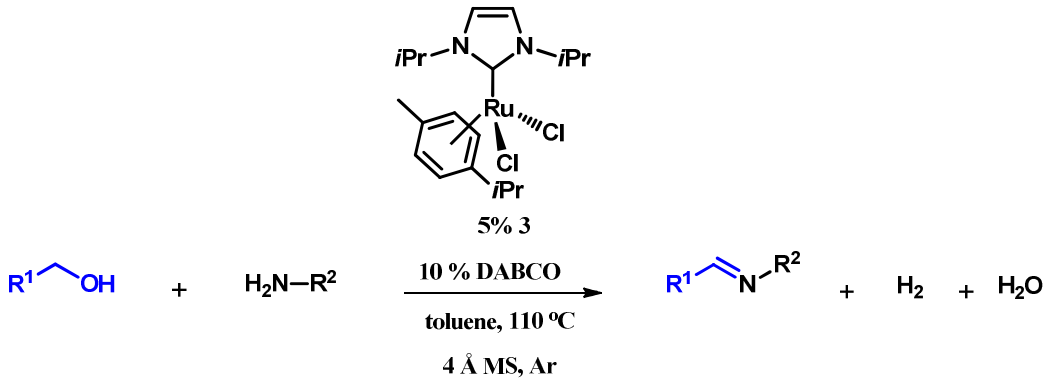
Agnese Maggi

Kgs. Lyngby, December 2012

Abstract

The work presented in this thesis was performed at the Department of Chemistry of the Technical University of Denmark during a three year Ph.D. program. The thesis involves two distinct projects related to organometallic and carbohydrate chemistry.

Project 1: Dehydrogenative synthesis of imines from alcohols and amines catalyzed by a ruthenium *N*-heterocyclic carbene complex

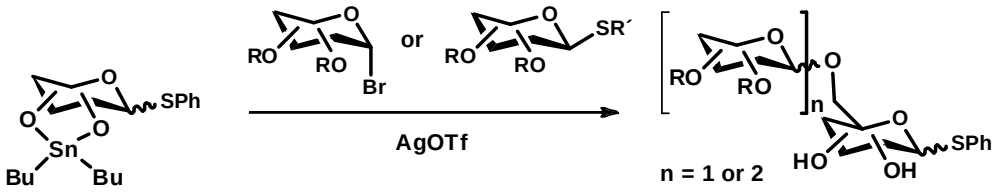


The successful method development and application of a convenient and direct (one step) synthesis of imines from alcohols and amines is described. The developed method provides quick and extended access to structurally diverse and synthetically important imines. The reaction is catalyzed by the ruthenium *N*-heterocyclic carbene complex [$RuCl_2$(I*i*Pr)(*p*-cymene)] (**3**) and proceeds in the presence of the ligand DABCO and molecular sieves with concomitant extrusion of water and hydrogen. A range of different primary alcohols and amines have been coupled in the presence of the catalyst to afford the corresponding imines in moderate to good yields. Optically pure amines gave the corresponding imines without any sign of racemization. Moreover, the one-pot diastereoselective addition of different organometallic reagents to the imine, obtained from the coupling between benzyl alcohol and (*R*)-1-phenylethylamine, was performed.

To address specifics of the reaction mechanism, different experiments with deuterium-labeled benzyl alcohol were carried out indicating that that the catalytically active species is a ruthenium

dihydride. The reaction is proposed to proceed by initial dehydrogenation of the alcohol to the aldehyde, which stays coordinated to the ruthenium centre. Then, nucleophilic attack of the amine affords the hemiaminal, which is released from ruthenium and converted into the imine.

Project 2: Tin-mediated regioselective 6-*O*-glycosylations of unprotected phenyl 1-thio-glycopyranosides

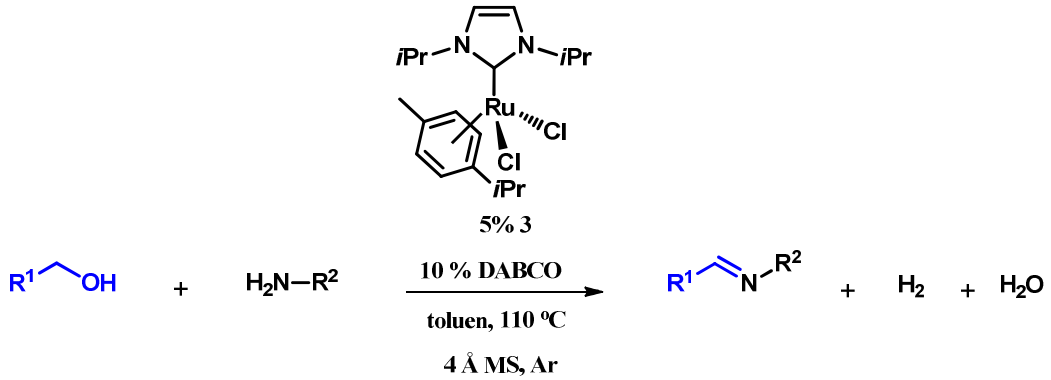


Chemical glycosylation is of outstanding importance to access biologically relevant carbohydrate structures, but classical methods suffer from the disadvantage of extensive protecting group manipulations. Thus, approaches to reduce the number of steps connected to chemical synthesis are highly important. In this thesis approaches to the regioselective glycosylation of fully unprotected phenyl 1-thio-glycopyranoside acceptors via tin activation are described. Tin-mediated Koenigs-Knorr glycosylation of phenyl 1-thio-β-D-glucopyranoside (**28**), phenyl 1-thio-β-D-galactopyranoside (**32**) and phenyl 1-thio-α-D-mannopyranoside (**33**) with different bromide donors afforded the corresponding (1→6) linked disaccharides in good to moderate yields. The disaccharides obtained from the first coupling can be activated as donors for subsequent tin-mediated glycosylation reactions. The activation has been performed following two different strategies. The first involved one-step activation with a thiophilic reagent, while the second employed a two-step activation which entailed first formation of a glycosyl halide, and then activation with a halophilic reagent. This last approach is of particular interest; in fact, thioglycosides can be used as acceptors enabling an iterative oligosaccharide synthesis. Following these strategies a number of different trisaccharides have been successfully synthesized.

Resumé

Arbejdet præsenteret i denne afhandling blev udført på Institutet for Kemi ved Danmarks Tekniske Universitet i løbet af et treårigt ph.d. program. Afhandlingen omfatter to forskellige projekter - et vedrørende metalorganisk kemi og et omhandlende kulhydrat kemi.

Projekt 1: Dehydrogenativ syntese af iminer fra alkoholer og aminer katalyseret af et ruthenium *N*-heterocyklisk carben kompleks

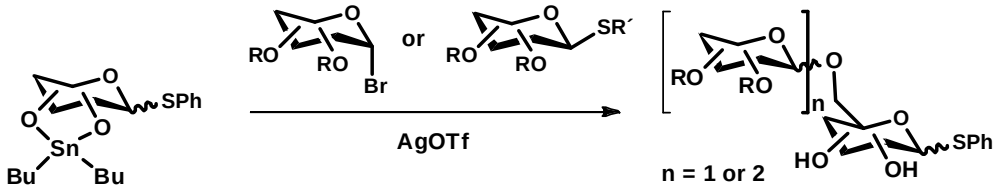


Udviklingen og anvendelse af en praktisk methode til direkte (et trins) syntese af iminer fra alkoholer og aminer er beskrevet. Den udviklede metode giver hurtig adgang til strukturelt forskellige og syntetisk vigtige iminer. Reaktionen er katalyseret af ruthenium N-heterocyclisk carben komplekset [$RuCl_2$(I*i*Pr)(*p*-cymen)](**3**) og forløber i nærvær af liganden DABCO samt molekylsi, der anvendes til at fjerne vand molekyler, som dannes sideløbende med hydrogen gas. En række forskellige primære alkoholer og aminer er blevet koblet i nærvær af katalysatoren til dannelse af de tilsvarende iminer i moderate til gode udbytter. Optisk rene aminer gav de tilsvarende iminer uden tegn på racemisering. Desuden blev der udført diastereoselektiv one-pot addition af forskellige metalorganiske reagenser til iminen, der blev fremstillet af koblingen mellem benzylalkohol og (*R*)-1-phenylethylamin.

For at belyse reaktionsmekanismen blev der udført forskellige eksperimenter med deuterium-mærket benzylalkohol. Disse eksperimenter viser, at det er en ruthenium-dihydrid forbindelse, som er den katalytisk aktive species. Reaktionen foreslås at forløbe ved først dehydrogenering af

alkoholen til aldehydet, som forbliver koordineret til rutheniumcenteret. Herefter sker der et nukleofilt angreb af aminen, som resulterer i hemiaminalen, der frigives fra ruthenium og herved dannes iminen.

Projekt 2: Tin medieret regioselektiv 6-O-glycosyleringer af ubeskyttede phenyl-1-thio-glycopyranosider



Kemisk glycosylering er en vigtig metode til at få adgang til biologisk relevante kulhydratstrukturer, men klassiske metoder har den ulempe, at disse er afhængige af omfattende beskyttelsesgruppe manipulationer. Derfor er det vigtigt at udvikle metoder, hvorved man kan reducere antallet af trin forbundet med kemisk syntese. I denne afhandling er regioselektiv glycosylering af fuldt ubeskyttede phenyl 1-thio-glycopyranosid acceptorer via tin aktivering beskrevet. Tin-medieret Koenigs-Knorr glycosylering af phenyl 1-thio-β-D-glucopyranosid (**28**), phenyl 1-thio-β-D-galactopyranosid (**32**) og phenyl 1-thio-α-D-mannopyranosid (**33**) med forskellige bromid donorer gav de tilsvarende (1 → 6) bundne disakkarider i gode til moderate udbytter. Disakkariderne dannet ved den første kobling kan aktiveres som donorer til efterfølgende tin-medierede glycosyleringsreaktioner. Der er anvendt to forskellige strategier til aktiveringen af sakkariddonorerne. Den første metode omhandler en ettrins-aktivering med et thiofilt reagens, mens den anden strategi involverer en totrins aktivering, hvor der først dannes et glycosylhalogenid, som derefter aktiveres med et halofilt reagens. Sidstnævnte fremgangsmåde er af særlig interesse, da man kan anvende thioglycosider som acceptorer, hvilket muliggør en iterativ oligosakkaridsyntese. Disse strategier er blevet anvendt til at syntetisere en række forskellige trisakkarider.

List of Abbreviations

$(Bu_3Sn)_2O$	bis(tributyltin)oxide
1,2-DCE	1,2-dichloroethylene
Ac	acetyl
acac	acetylacetonate
BBN	borabicyclononane
Bn	benzyl
BnOH	benzyl alcohol
Bu	butyl
Bu_2SnO	dibutyltinoxide
Bz	benzoyl
$CDCl_3$	deuterated chloroform
CH_2Cl_2	diclhoromethane
CH_3CN	acetonitrile
COD	1,5-cyclooctadiene
COSY	homonuclear correlation spectroscopy
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
DMBQ	2,6-dimethoxy-1,4-benzoquinone
DMTST	dimethyl(methylthio)sulfonium triflate
dppe	1,2-bis(diphenylphosphino)ethane
EI	electronic impact
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
Gal	galactoside
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
Glc	glucoside

HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
IDCP	iodonium dicollidine perchlorate
I*i*Pr	1,3-di-*iso*-propylimidazol-2-ylidene
I*i*Pr·HCl	1,3-di-iso-propylimidazolium chloride
IMe	1,3-dimethylimidazol-2-ylidene
IMe·HI	1,3-dimethylimidazolium iodide
I*t*Bu	1,3-di-*tert*-butylimidazol-2-ylidene
I*t*Bu·HCl	1,3-di-tert-butylimidazolium chloride
KIE	kinetic isotope effect
LC	liquid chromatography
LC-HRMS	liquid chromatography-high resolution mass spectrometry
LCT	liquid chromatography time of flight
Me	methyl
Me_2S_2	dimethyl disulfide
MeOH	methanol
MeOTf	methyl triflate
MS	molecular sieves
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
PCy_3	tricyclohexylphosphine
PDA	photodiode array
Ph	phenyl
Ph_2SO	diphenyl sulfoxide
$PhCD_2OH$	benzyl alcohol-α,α-d_2
PhCDHOH	benzyl alcohol-α-d_1
$PhCH_2OH$	benzyl alcohol
Phth	phthalimido
Piv	pivaloyl
PNN	2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine
PNP	2,6-bis(di-*iso*-propylphosphinomethyl)pyridine

PPh_3	triphenylphosphine
SQD	single quadrupole detection
TBDMSCl	tert-butyldimethylsilyl chloride
TBS	tert-butyldimethylsilyl
TCA	trichloroacetyl
TESOTf	triethylsilyl trifluoromethanesulfonate
TfO-	trifluoromethanesulfonate
TfO_2	triflic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TMU	tetramethylurea
UPLC	ultra performance liquid chromatography
UV	ultraviolet
xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Publications

- Publication Included in the Appendix

"Dehydrogenative Synthesis of Imines from Alcohols and Amines Catalyzed by a Ruthenium N-Heterocyclic Carbene Complex" A. Maggi, R. Madsen, *Organometallics* **2012**, *31*, 451-455.

- Publication in Preparation

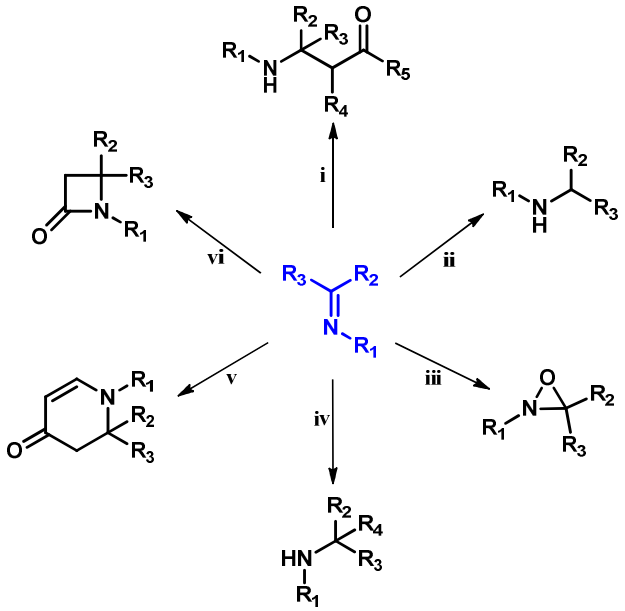
"Stannylene-Mediated Regioselective 6-O-Glycosylation of Unprotected Phenyl 1-Thioglycopyranosides" A. Maggi, R. Madsen, *in preparation*.

Table of Contents

1. Dehydrogenative synthesis of imines from alcohols and amines catalyzed by a ruthenium *N*-heterocyclic carbene complex

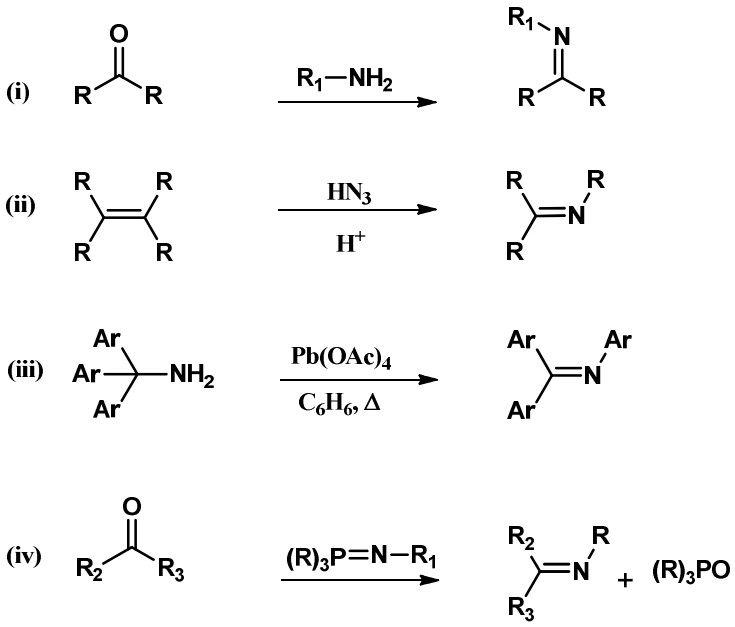
1.1. Introduction

Imines or Schiff bases are an important class of compounds in organic chemistry. These electrophiles can be involved in many different reactions constituting versatile building blocks in organic synthesis. For example imines can undergo condensations, hydrogenations, peracid oxidations, nucleophilic additions, aza-Diels-Alder reactions and [2+2] cycloadditions (Scheme 1). Many of these reactions can be performed with high enantioselectivity. Imines can also be used as ligands or additives in catalytic transformations.[1–3]



Scheme 1. (i) Mannich reaction;[4] (ii) hydrogenation;[5] (iii) peracid oxidation;[6] (iv) nucleophilic addition;[7] (v) aza-Diels-Alder;[8] (vi) [2+2] cycloaddition.[9]

Imines are typically synthesized by condensation of aldehydes or ketones with primary amines, but several other methods have been developed. For instance, they can be formed by addition of hydrazoic acid (HN_3) to alkenes in the so-called Schmidt[10] reaction or through the Stieglitz[11] rearrangement (Scheme 2).



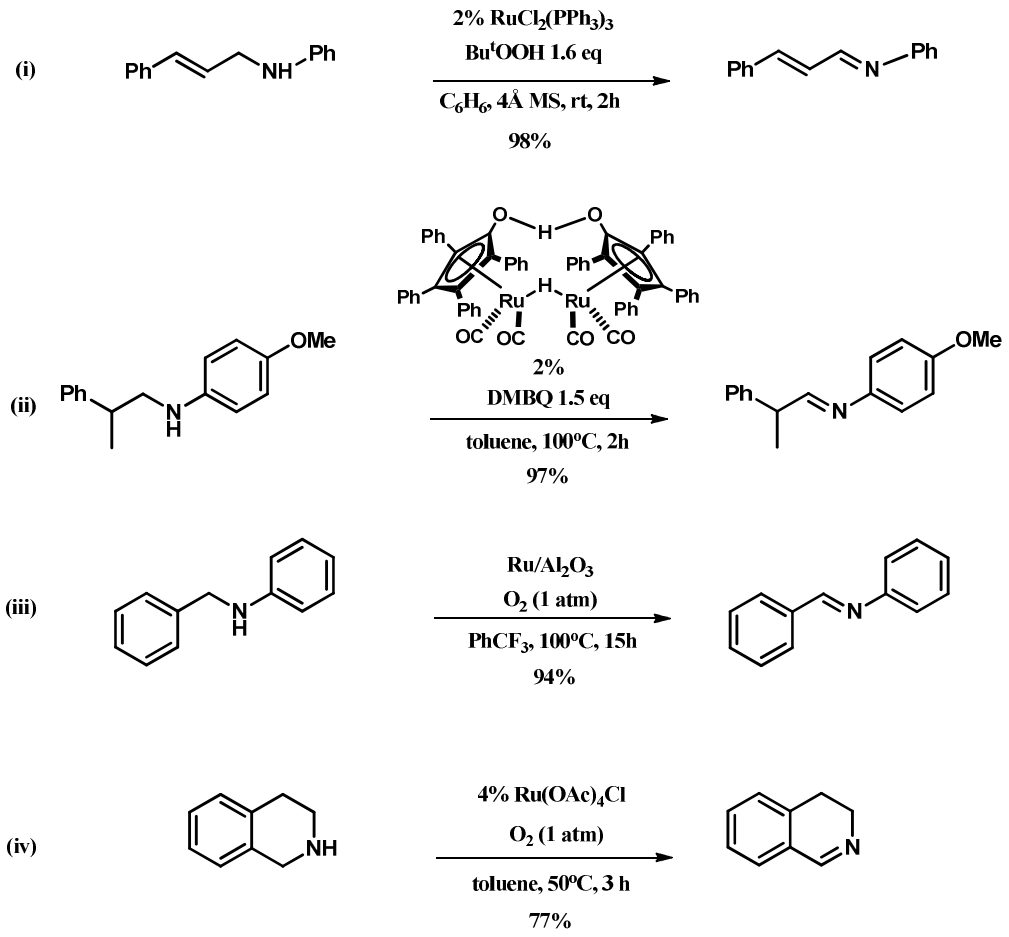
Scheme 2. (i) condensation of aldehydes or ketones with primary amines; (ii) Schmidt reaction; (iii) Stieglitz rearrangement[11]; (iv) aza-Wittig reaction[12].

Drawbacks of these methods are either the use of toxic and/or explosive reagents in the case of the Schmidt reaction, or a narrow substrate scope for the Stieglitz rearrangement.

Carbon-nitrogen double bonds can also be formed *via* the aza-Wittig reaction (Scheme 2, equation iv). In fact, several different functionalized imines have been synthesized by reacting phosphazenes with aldehydes or ketones.[12]

1.1.1. Imine synthesis from catalytic oxidation of secondary amines

Another possible way to obtain imines is through catalytic oxidation of secondary amines. This method has been extensively investigated leading to the optimization of many different catalytic systems[13–20], among which ruthenium based catalysts have played an important role. In fact, it was demonstrated that diverse catalysts such as $RuCl_2(PPh_3)_3$ in presence of *t*-butyl-hydroperoxide (Bu^tOOH),[17] the Shvo catalyst in presence of 2,6-dimethoxy-1,4-benzoquinone (DMBQ),[18] Ru/Al_2O_3,[19] and $Ru_2(OAc)_4Cl$[20] can oxidize a large range of secondary amines to afford imines. Some examples are shown in Scheme 3.

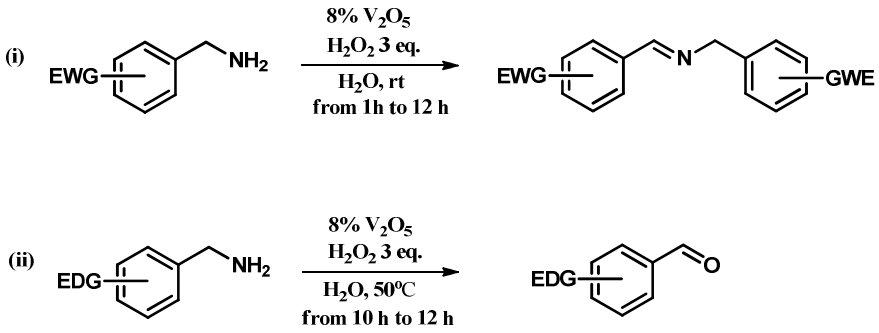


Scheme 3. Secondary amine oxidation: (i) *N*-cinnamyl aniline oxidation catalyzed by $RuCl_2(PPh_3)_3$;[17] (ii) 4-methoxy-*N*-(2-phenylpropyl) aniline oxidation catalyzed by the Shvo catalyst;[18] (iii) *N*-benzyl aniline oxidation catalyzed by Ru/Al_2O_3,[19] (iv) tetrahydoisoquinoline oxidation catalyzed by $Ru_2(OAc)_4Cl$.[20]

Generally, ruthenium mediated oxidation of secondary amines can be rationalized by the following mechanism: the first step involves the formation of a ruthenium amine complex which undergoes β-elimination to afford the imine and a hydrido-ruthenium complex. At this point, oxidation of the ruthenium hydride species completes the catalytic cycle. The oxidation step differs depending on the catalytic system considered. For instance, in the case of Ru/Al_2O_3 and $Ru_2(OAc)_4Cl$ the formation of a ruthenium hydroperoxide species, deriving from insertion of molecular oxygen, has been proposed.[19,20] While, in the case of the Shvo catalyst the oxidation is promoted by DMBQ that is reduced to the corresponding hydroquinone.[18]

1.1.2. Imine synthesis from self- and cross-condensation of primary amines

Imines can also be obtained by self-[21] or cross-condensation[22] of primary amines. As reported by Chu *et al*[21] oxidative self-condensation of primary amines can be achieved using hydrogen peroxide (H_2O_2) and vanadium pentoxide (V_2O_5) in water. With this system the self-coupling of benzylamines bearing electron-withdrawing groups was successfully performed to afford imines in good to excellent yields at room temperature. In contrast, the reaction of benzylamines bearing electron-donating groups required higher temperatures (50˚C) and gave the corresponding aldehydes (Scheme 4).

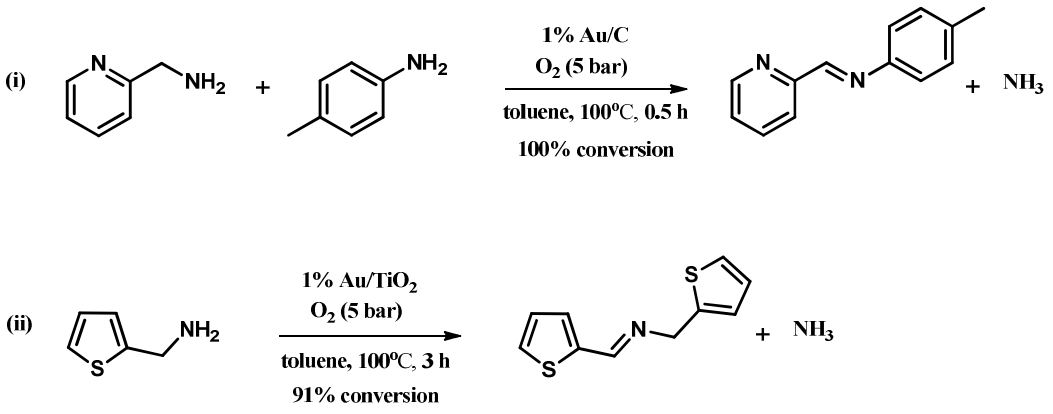


Scheme 4. Self-condensation of primary amines: (i) Oxidation of benzyl amines to imines; (ii) Oxidation of benzylamines to aldehydes.[21]

These results were explained by the authors considering that the system V_2O_5/ H_2O_2 catalyzes the oxidation of the amine to the corresponding aldehyde, both for benzyl amines bearing electron-donating and electron-withdrawing groups. Once formed, the aldehyde reacts with the amine still present in the reaction medium to afford the imine. When the reaction is performed at room temperature, like in the case of amines bearing electron-withdrawing groups, the newly formed imine is stable and can be isolated. Whereas, when the reaction is performed at 50˚C the imines hydrolyze and the liberated amines are then oxidized to the aromatic aldehydes.

The most attractive feature of this procedure is its environmental friendliness, in fact H_2O_2 is regarded to be a green oxidant and water is the cheapest and most safe reaction medium available.

Grirrane *et al*, in turn, have shown that heterogeneous gold catalysts can promote both self- and cross-condensation of primary amines to afford imines.[22] In fact, it has been shown that gold supported on titanium oxide (Au/TiO_2) can catalyze the self-coupling of different benzylamines as well as heterocyclic amines. While, using gold supported on carbon (Au/C) amines cross-condensation is obtained (Scheme 5).

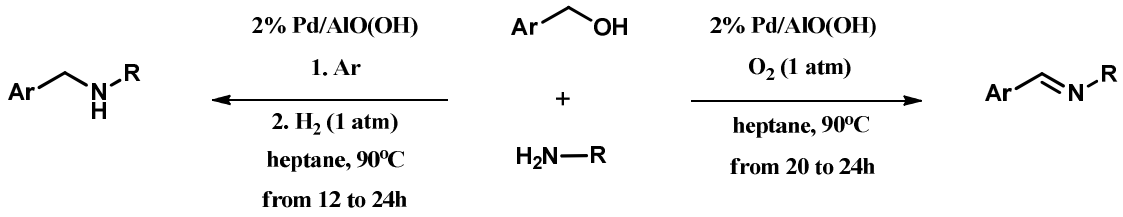


Scheme 5. Self- and cross-condensation of primary amines: (i) Au/C catalyzed cross condensation of 2-pyridinemethaneamine and *p*-toluidine; (ii) Au/TiO_2 catalyzed self-condensation of 2-thiophene methylamine.[22]

1.1.3. Imine synthesis from direct coupling of alcohols and amines

In the last decade the possibility to synthesize imines from the direct coupling of alcohols and amines has become of great interest mainly for its potential broad applicability and versatility.

The coupling between alcohols and amines can be performed either in an oxidative or dehydrogenative fashion. Oxidative coupling can be carried out either using manganese dioxide (MnO_2) as *in situ* oxidant,[23] or using heterogeneous catalysts such as manganese octahedral molecular sieves (OMS-2)[24], gold supported on hydroxyapatite (Au/HAP)[25] and Pd/AlO(OH).[26] The last case is quite interesting; in fact, this catalyst is able to perform two different transformations depending on the reaction conditions. If the reaction is performed in the presence of oxygen, imine formation is observed, while if the reaction is carried out under argon atmosphere and in the presence of hydrogen a secondary amine is formed (Scheme 6).



Scheme 6. Synthesis of imines and secondary amines by direct coupling of benzyl alcohols and amines catalyzed by Pd/AlO(OH).[26]

Thus, Pd/AlO(OH) can catalyze secondary amine formation from alcohols and primary amines through alcohol oxidation, imine formation and imine hydrogenation.[26]

As mentioned above, synthesis of imines by direct coupling of alcohols and amines can also be achieved following a dehydrogenative process. The first dehydrogenative coupling procedure has been reported in 2010 by Milstein and co-workers[27] followed in short time by three additional contributions (Scheme 7).[28–30] The growing interest for this new method is mainly related to its environmentally friendliness; in fact the imine formation is accompanied only by liberation of molecular hydrogen and water.

Milstein *et al* had shown that reacting alcohols and amines in presence of the PNP ruthenium pincer complex $\mathbf{1_a}$ (Figure 1) led to the formation of the corresponding imines in high yield with a reaction time between 32 and 56 hours (Scheme 7, equation i). This reaction occurs under neutral conditions in refluxing toluene and it has a good selectivity toward imine formation. In fact, the only observed by-products were small amounts of amide (between 0 and 18%) and traces of ester. Generally the coupling was performed under an argon atmosphere, but it was shown that the same reaction can be carried out also in air.

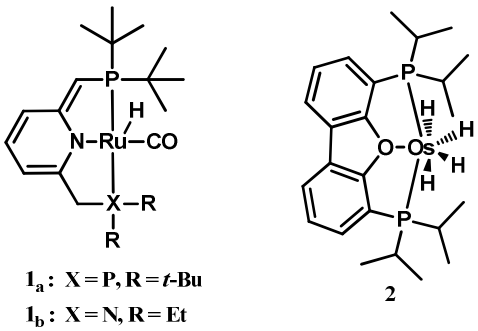
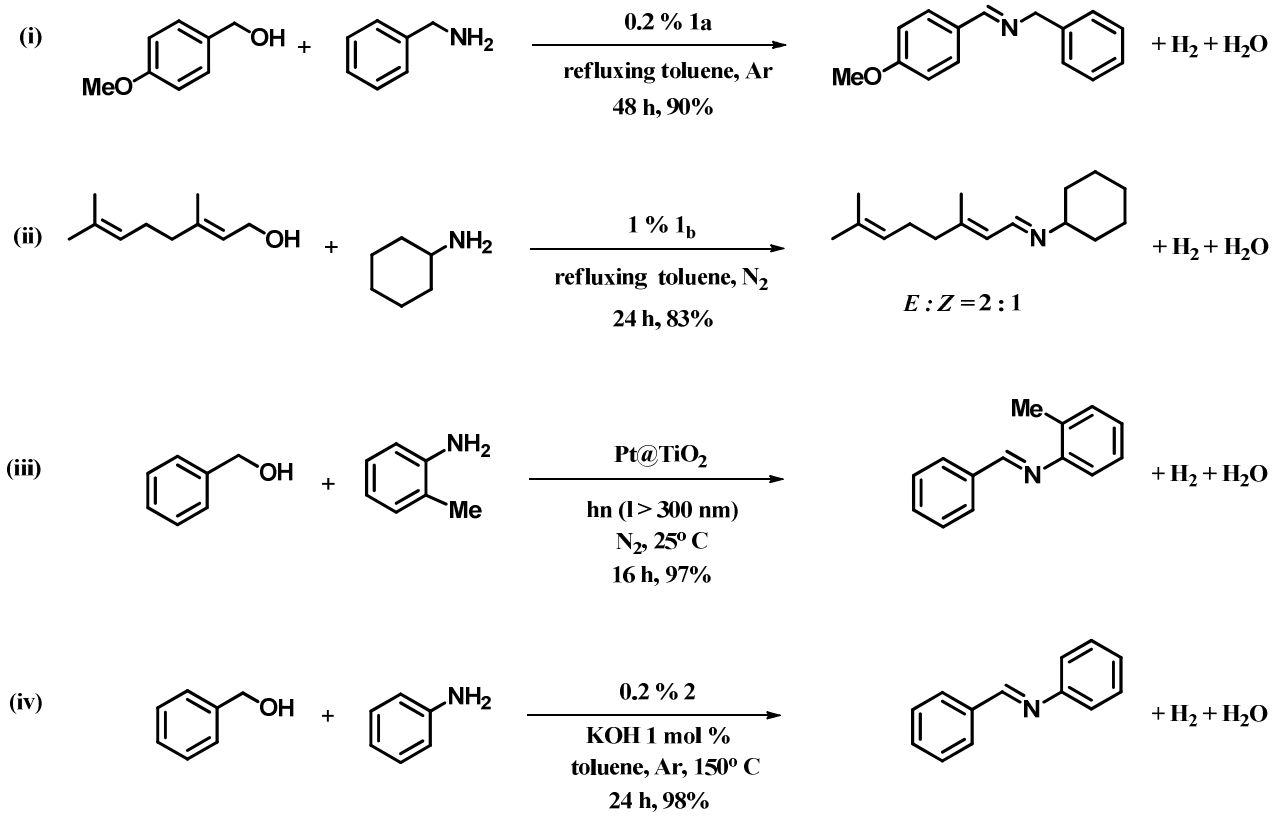
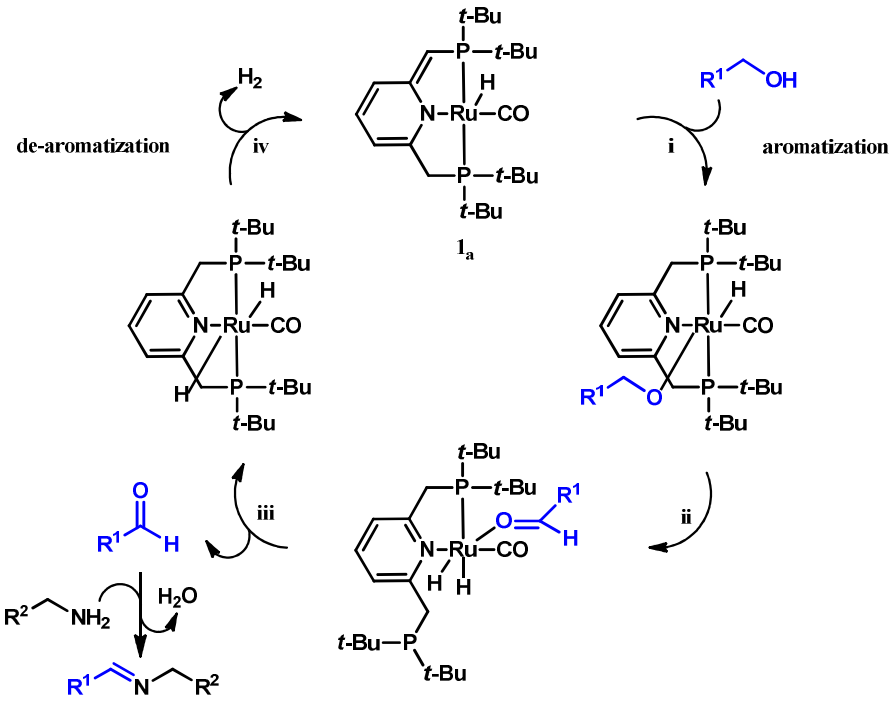


Figure 1. PNP and PNN ruthenium pincer complex $\mathbf{1_a}$ and $\mathbf{1_b}$;[27,31] $OsH_4\{dbf(P^iPr_2)_2\}$ pincer complex **2**.[29]



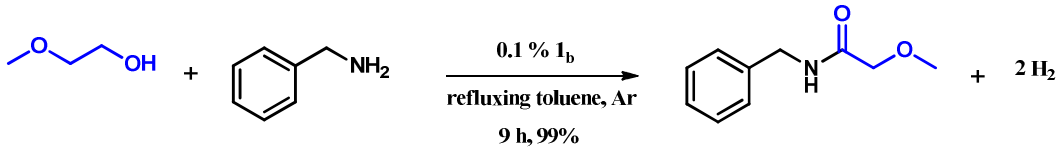
Scheme 7. Examples of imine synthesis *via* dehydrogenative coupling: (i) Milstein´s imine synthesis catalyzed by complex $\mathbf{1_a}$;[27] (ii) Schomaker´s α,β-unsaturated imines synthesis catalyzed by complex $\mathbf{1_b}$;[30] (iii) Hirai´s imine synthesis catalyzed by $Pt@TiO_2$;[28] (iv) Esteruelas´s imine synthesis catalyzed by the osmium pincer complex **2**.[29]

The proposed mechanism for this transformation (Scheme 8) involves, in the first step, the activation of the O-H bond of the alcohol by complex **1**$_a$ and aromatization of the pincer ligand. The resulting intermediate undergoes β-hydrogen elimination giving a coordinated aldehyde and causing the opening of the phosphine arm. At this point rapid closure of the phosphine arm results in the dissociation of the aldehyde and leads to the formation of a dihydride ruthenium species which liberates H_2 to regenerate complex **1**$_a$. The formed aldehyde is then attacked by the amine in solution. Thus, it is clear that complex **1**$_a$ participates only in the alcohol dehydrogenation, while imine formation is not mediated by the catalyst.[27]



Scheme 8. Proposed mechanism for imination reaction with complex **1**$_a$[27] (i) O-H bond activation and ligand aromatization; (ii) β-hydrogen elimination-aldehyde formation; (iii) aldehyde release and imine formation; (iv) H_2 liberation.

Milstein *et al* had also shown that when primary alcohols and amines are reacted in presence of the PNN ruthenium pincer complex **1**$_b$ the dehydrogenative coupling to form amides, rather than imines, takes place (Scheme 9).[31]



Scheme 9. Milstein´s amide synthesis catalyzed by pincer complex $\mathbf{1_b}$.[31]

The different outcome observed in the case of the PNN complex $\mathbf{1_b}$ has been explained considering that, after dehydrogenation of the alcohol, the newly formed aldehyde is attacked by the amine while being coordinated to the metal center. This is followed by rapid dehydrogenation of the coordinated hemiaminal with formation of the amide. It has been hypothesized that hemiaminal formation within the coordination sphere of the metal is possible with complex $\mathbf{1_b}$, due to the presence of the hemi-labile NEt_2 ligand that is lost after coordination of the alcohol and remains open during the catalytic cycle.[31]

Interestingly Schomaker and coworkers had shown that the PNN complex $\mathbf{1_b}$ can catalyze the coupling between allylic alcohols and primary amines to yield α,β-unsaturated imines (Scheme 7, equation ii) rather than amides. Whereas, when the same reaction was performed in presence of the PNP complex $\mathbf{1_a}$ imine formation was accompanied by reduction of the olefinic double bond.[30]

Another contribution to this field was provided by Hirai and co-workers, who demonstrated that imine synthesis can be promoted by titanium oxide loading platinum particles ($Pt@TiO_2$) under UV irradiation ($\lambda > 300$ nm) (Scheme 7, equation iii).[28] In this case the imine is produced by tandem photo-catalytic and catalytic reaction. The reaction is initiated by photo-excitation of TiO_2 with formation of pairs of electrons (e^-) and positive holes (h^+). The alcohol is then oxidized by the h^+ to the aldehyde with liberation of two protons. At this point TiO_2 acts as a Lewis acid promoting the condensation between the formed aldehyde and the amine. The protons, deriving from the alcohol oxidation, are then reduced to H_2 with the electrons trapped by the Pt particles. With this procedure primary alcohols and different anilines were successfully coupled to afford the corresponding imines with a reaction time between 2 and 16 hours.

More recently Esteruelas and co-workers have reported that also the $OsH_4\{dbf(P^iPr_2)_2\}$ pincer complex **2** (Figure 1) is able to accomplish the dehydrogenative coupling of alcohols and amines to give imines in good to excellent yield with a reaction time of 24 hours (Scheme 7, equation iv).[29]

Like for the PNP ruthenium pincer complex $\mathbf{1_a}$ the proposed reaction mechanism involves alcohol O-H bond activation, β-hydrogen elimination with aldehyde formation, aldehyde release and imine

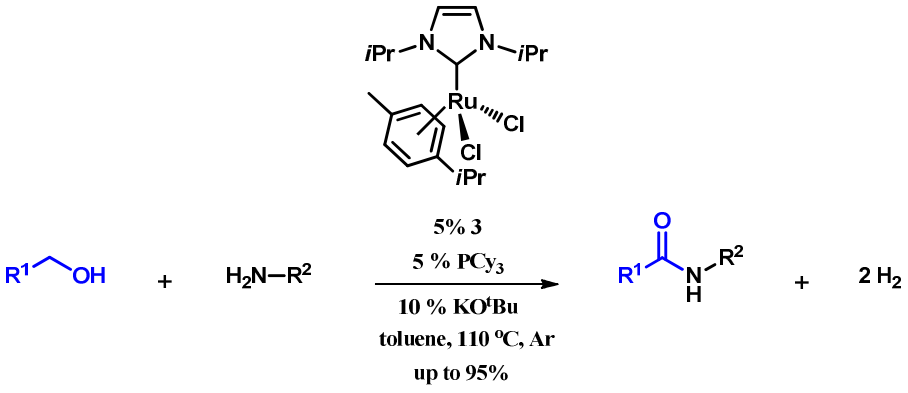
formation. However, in contrast to the Milstein system the reaction is carried out in presence of a base. In fact, since osmium has a higher tendency than ruthenium to be saturated by coordination and to activate C-H bonds, a large excess of potassium hydroxide (KOH) is needed to increase the nucleophilicity of the medium. This should facilitate the amine attack and prevent the decarbonilation of the newly formed aldehyde, which would deactivate the catalytic system. In fact reacting benzyl alcohol with complex **2** in absence of KOH led to alcohol decarbonylation and isolation of Os(CO)H{dbf(P^iPr_2)$_2$}.[29]

1.2. Aim of the project

The possibility to synthesize imines *via* dehydrogenative coupling of alcohols and amines has become of great interest mainly for its potential broad applicability and environmentally friendliness. The result of this growing interest was the development of four different catalyst systems within a very short time.[27–30]

The goal of this project was to develop a new and competitive method for the dehydrogenative imination reaction using a ruthenium *N*-heterocyclic carbene complex (Ru-NHC). In the last years the use of Ru-NHC complexes has been expanded beyond the scope of metathesis, resulting in diverse applications in organic synthesis.[32,33] For instance, it has been shown that this type of complexes can be exploited to perform amine *N*-alkylation and transfer hydrogenation reactions,[34] dehydrogenative homocoupling of alcohols to form esters[35] or the synthesis of amides by direct coupling of alcohols and amines. In this regard a different variety of catalytic systems based on Ru-NHC complexes have been proposed.[36–40]

The first contribution was given by Madsen and co-workers, who in 2008 performed the amide synthesis with an *in situ* generated Ru-NHC catalyst.[39] Two years later Madsen[40] and Hong[36] developed two different catalytic systems for the direct amide synthesis from alcohols and amines, both based on a well-defined Ru-NHC catalyst. Particularly Madsen and co-workers demonstrated that the complex [$RuCl_2$(I*i*Pr)(*p*-cymene)] (**3**) together with tricyclohexylphosphine (PCy_3) and a base afforded amides in good to excellent yields (Scheme 10).[40]

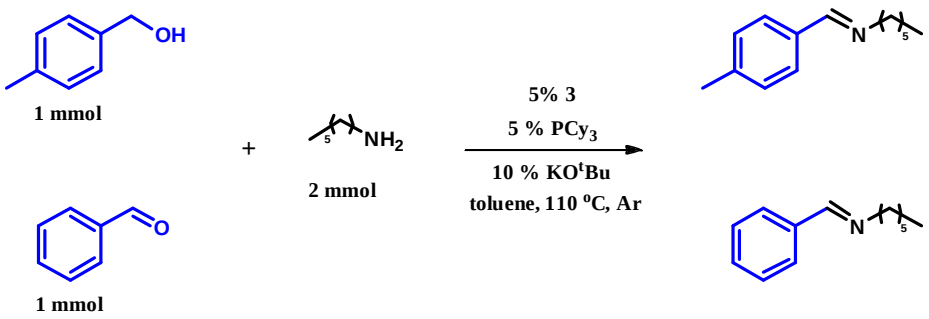


Scheme 10. Amidation reaction with complex **3**[40]

The amidation reaction with complex **3** is believed to proceed through alcohol oxidation to the aldehyde which is then attacked by the amine to form a hemiaminal. Interestingly, during a preliminary study of the reaction mechanism imine formation was observed to a significant extent.

In order to establish whether the aldehyde is attacked by the amine in solution or while still coordinated to the catalyst, the amidation reaction was performed in presence of an aldehyde. In fact, if hemiaminal formation takes place within the coordination sphere of the metal an externally added aldehyde should not be able to enter the catalytic cycle and form the amide.

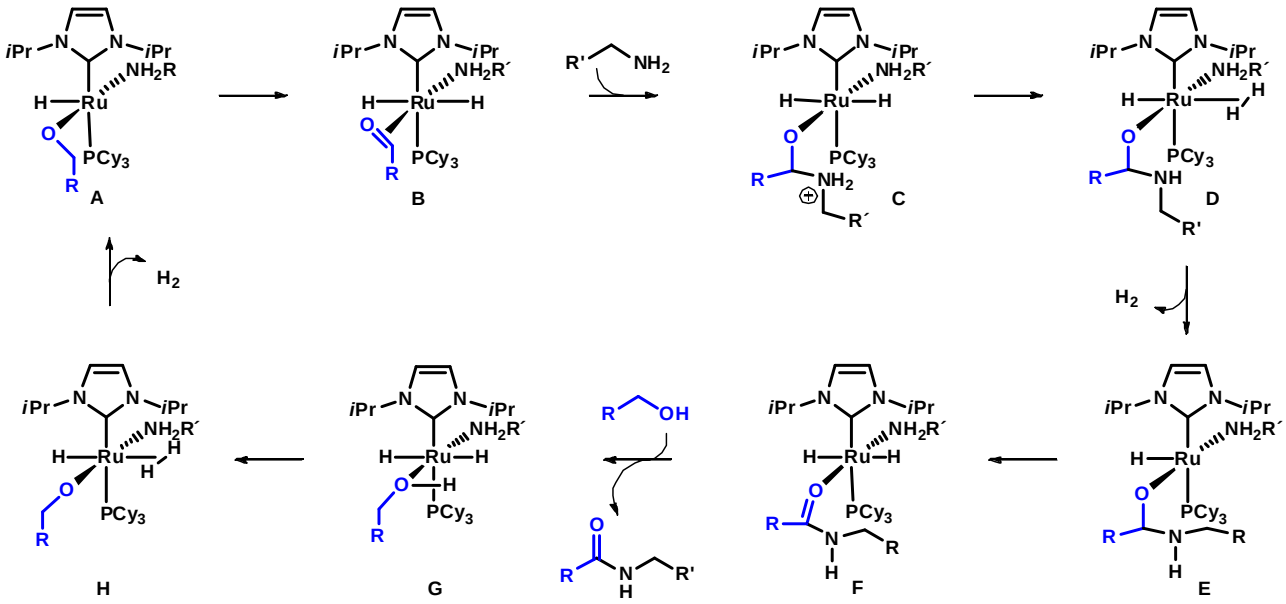
Thus *p*-methyl benzyl alcohol and benzaldehyde were reacted with two equivalents of *n*-hexylamine in presence of complex **3** under standard amidation conditions (Scheme 11).[40]



Scheme 11. Coupling between *p*-methyl benzyl alcohol and *n*-hexylamine in presence of benzaldehyde.

During the experiment the aldehyde was immediately converted to the imine, whereas the alcohol reacted slowly to form the corresponding imine, and not the amide, with about 50% conversion after 24h (Scheme 12). Thus it appears that the imine formation form the aldehyde inhibits formation of the amide from the alcohol. Imine formation from the alcohol was observed also when the aldehyde was slowly added to a reaction mixture containing *p*-methyl benzyl alcohol (1 equiv.), *n*-hexylamine (2 equiv.) and complex **3**. However, in this case the alcohol was also converted to the corresponding amide. In both experiments amide formation from the aldehyde was not observed thus it was concluded that the intermediate aldehyde in the amidation reaction stays coordinated to the ruthenium catalyst.

Very recently Madsen and co-workers reported a thorough mechanistic investigation of the amidation reaction. On the basis of experimental and computational studies the mechanism depicted in Scheme 12 has been proposed.[41]



Scheme 12. Mechanism for the amidation reaction catalyzed by the Ru-NHC **3**.[41]

The catalytic cycle is initiated by loss of the *p*-cymene ligand and replacement of the two chlorides with a hydride and an alkoxide leading to the formation of the 16-electron complex **A**, where an amine is also bound to the metal centre and the two bulky ligands (I*i*Pr and PCy_3) are in the apical position. At this point β-hydride elimination takes place leading to the formation of the ruthenium dihydride species **B** where the aldehyde acts as a η^2 ligand. The coordinated aldehyde is then attacked by the amine to generate a hemiaminal protonated at the nitrogen. This is followed by proton transfer to the hydride and hydrogen release with formation of hemiaminal complex **E**. In the next step the hemiaminal intermediate undergoes β-hydride elimination with formation of the amide that is released from the catalyst. The catalytic cycle is then completed by coordination of an alcohol molecule and release of a second equivalent of hydrogen.[41]

Eisenstein and co-workers performed a computational study on a hemiaminal ruthenium complex similar to complex **C** in order to determine whether an amide or an imine would be formed.[42] The computational investigation suggested that after formation of the hemiaminal complex a proton transfer takes place either between the nitrogen and the hydride or between the nitrogen and the oxygen. Amide is formed when the proton is transferred to the hydride, while the imine is generated when the proton migrates to the oxygen.

Hence, from these findings, we speculated whether the reaction conditions could be altered in order to achieve preferentially imine formation.

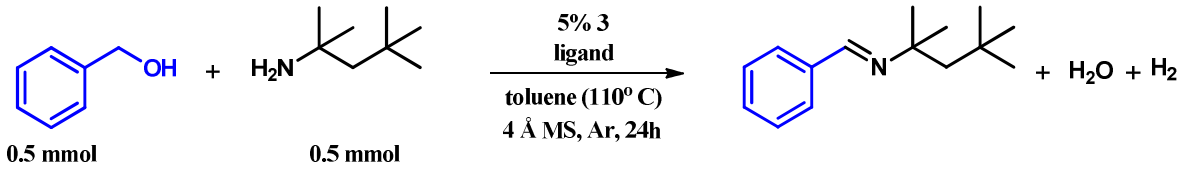
In fact, the advantage of complex **3**, compared to the Milstein and Esteruelas pincer complexes $\mathbf{1_a}$ and **2**, is that it can be easily synthesized *via* one-pot reaction from cheap and commercially available starting materials. Moreover, if necessary, its reactivity can be fine-tuned changing the nature of the carbene ligand.

1.3. Results and discussion

1.3.1. Optimisation studies

To optimize the reaction conditions benzyl alcohol (BnOH) and *tert*-octylamine were selected as the test substrates, and employed in equimolar amounts for the initial studies. They were reacted in presence of 5 mol% of the complex [$RuCl_2$(I*i*Pr)(*p*-cymene)] (**3**) in refluxing toluene under neutral conditions with an argon (Ar) flow. Molecular sieves (MS) were added to secure continuous removal of water during the reaction.

Table 1. Imination reaction with complexes **3** in presence of different ligands.



Entry	Ligand	Ligand loading [mol%]	BnOH Conv.[%]	GC yield [%]
1	none	-	55	40
2	PCy_3	5	67	60
3[a]	DABCO	5	80	65
4	dppe	5	42	41
5	xantphos	5	36	32
6	phenantroline	5	52	44
7	PCy_3	10	84	71
8	PPh_3	10	17	17
9	pyridine	10	48	44
10[a]	DABCO	10	83	81
11[b]	DABCO	10	83	74[c]
12[d]	DABCO	10	89	82[e]

All reactions were performed in 0.5 mmol scale using equimolar amounts of alcohol and amine in dry and degassed toluene (1 mL); benzyl alcohol conversion and GC yields were determined by GC-MS analysis using nonane (0.2 mmol) as internal standard; [a]1 mmol scale reactions; [b]without MS; [c]9% of secondary amine was also formed; [d]with [$RuCl_2$(IMe)(*p*-cymene)] (**4**); [e]6% of secondary amine was also formed.

As shown in table 1, entry 1 after 24 hours *N*-benzylidene tert-octylamine was obtained in 40% GC yield with 55% conversion of the alcohol. Only about 3% of the ester from self condensation of the alcohol was observed as the by-product and no secondary amine or amide could be detected.

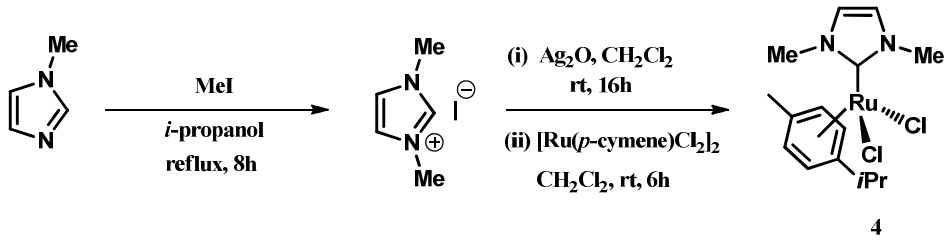
With this encouraging result in hand we decided to investigate the influence of different ligands in order to improve the yield of the reaction. Monodentate and bidentate phosphines, as well as amine ligands, were tested in different loadings (table 1, entries 2-10).We started by carrying out the reaction in the presence of 5 mol% of different ligands (entry 2-6). With 5% of PCy_3 or 1,4-diazabicyclo[2.2.2]octane (DABCO) the alcohol conversion increased (entries 2 and 3), while use of bidentate phosphines and phenanthroline gave lower conversion (entries 4-6). To further improve the alcohol conversion the reaction was performed in the presence of 10% of PCy_3 and DABCO (entries 7 and 10). Additionally, the screening was extended to other ligands such as triphenylphosphine (PPh_3) and pyridine (entries 8 and 9).

As shown in entry 10 DABCO gave the best result and this ligand was therefore selected for general use. In all experiments performed (entry 2-10) the selectivity of the reaction towards imine formation was good. For the reactions with phosphines and phenanthroline traces of the ester, deriving from self-coupling of benzyl alcohol, were detected by GC-MS analysis. In the case of PCy_3 the presence of trace amounts of the secondary amine, deriving from the imine reduction, were also observed. In the case of DABCO, in turn, only 2% of the secondary amine was detected.

At this point we decided to investigate the influence of molecular sieves on the outcome of the reaction. To this end, the experiment in entry 10 was repeated in the absence of molecular sieves (entry 11). The reaction gave the same benzyl alcohol conversion, but the amount of secondary amine had increased to 9%. Thus it is clear that molecular sieves do not influence the rate of the reaction, but the selectivity is affected by the continuous removal of water.

The catalyst loading was investigated next, and we found that lower loadings (2.5 mol%) resulted in lower conversions after 24 hours.

The influence of the carbene ligand was also examined. In particular, it would be of interest to clarify if the steric hindrance around the metal centre does affect the outcome of the reaction. With this purpose the carbene ligands 1,3-dimethylimidazol-2-ylidene (IMe) and 1,3-di-*tert*-butylimidazol-2-ylidene (I*t*Bu) were selected. The screening of the carbene ligand IMe was performed by using the corresponding [$RuCl_2$(IMe)(*p*-cymene)] complex (**4**) which was synthesized *via* silver carbene transfer methodology from 1,3-dimethylimidazolium iodide[43] and [Ru(*p*-cymene)Cl_2]$_2$ (Scheme 13).[36,44,45]

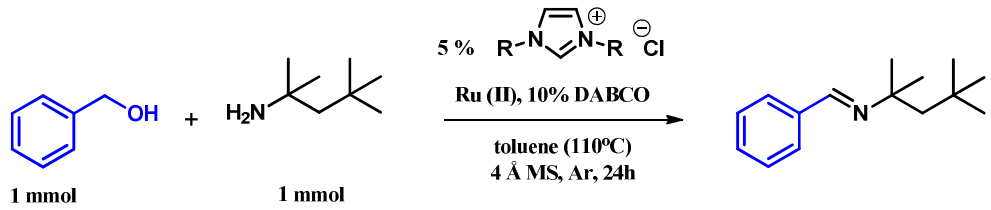


Scheme 13. Synthesis of [$RuCl_2$(IMe)(*p*-cymene)] complex (**4**)

As shown in table 1 entry 12 reacting benzyl alcohol and *tert*-octylamine in presence of 5 mol % of complex **4**, under standard reaction conditions, gave a slightly higher alcohol conversion then with complex **3**, but the product imine was obtained together with 6% of the corresponding secondary amine. Due to lower selectivity complex **4** does not constitute a better precatalyst than complex **3**. Madsen and co-workers demonstrated that *N*-heterocyclic carbene complexes can be generated *in situ* from Ru(COD)Cl_2, imidazolium salts and potassium *tert*-butoxide (KO*t*Bu).[39,40] Thus, since any attempts to synthesize the complex [$RuCl_2$(I*t*Bu)(*p*-cymene)] by silver carbene transfer methodology failed, the screening of the carbene ligand I*t*Bu was performed by generating the corresponding ruthenium complex *in situ* (Table 2, entry 3). To this end, [$RuCl_2$(*p*-cymene)]$_2$ was selected as the source of ruthenium (II), while the imidazolium salt 1,3-di-*tert*-butylimidazolium chloride[46] (I*t*Bu·HCl) was used as the carbene source[47].

Interestingly, when the imination reaction was performed in absence of the carbene ligand the desired imine was formed in 35% GC yield together with a considerable amount (15%) of the corresponding secondary amine (entry 1). While, performing the same reaction in the presence of 1,3-diisopropylimidazolium chloride (I*i*Pr·HCl) and KO*t*Bu afforded the imine as the sole product in 34% GC yield (entry 2). This demonstrates that the presence of the carbene ligand is important for the selectivity of the reaction. Good selectivity was obtained also in the case of I*t*Bu, but the higher steric hindrance lowered the alcohol conversion (entry 3). Ru(COD)Cl_2 was also investigated as a source of Ru (II), but it gave essentially the same result as [$RuCl_2$(*p*-cymene)]$_2$ (entries 4 and 5).

Table 2. Imination reaction with catalyst generated *in situ*.



Entry	Ru(II)	Ru(II) [mol%]	NHC·HCl	K*t*OBu [mol%]	BnOH Conv.[%]	GC yield [%]
1	$[RuCl_2(p\text{-cymene})]_2$	2.5	-	-	56	35[a]
2	$[RuCl_2(p\text{-cymene})]_2$	2.5	I*i*Pr·HCl	5	48	34
3	$[RuCl_2(p\text{-cymene})]_2$	2.5	I*t*Bu·HCl	5	40	31
4	$Ru(COD)Cl_2$	5	I*i*Pr·HCl	5	48	30
5	$Ru(COD)Cl_2$	5	I*t*Bu·HCl	5	44	36[b]

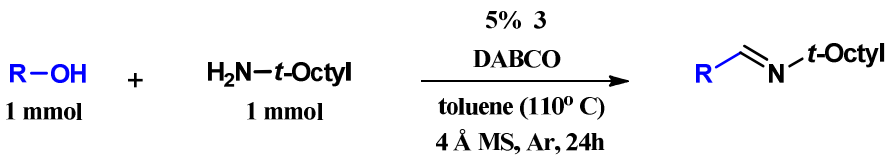
All reactions were performed in 1 mmol scale using equimolar amounts of alcohol and amine in dry and degassed toluene (1 mL); benzyl alcohol conversion and GC yields were determined by GC-MS analysis using nonane (0.2 mmol) as internal standard; [a]15% of the secondary amine was also formed; [b]8% of the secondary amine was also formed.

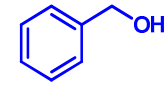
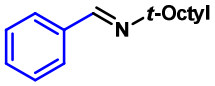
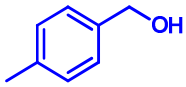
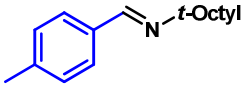
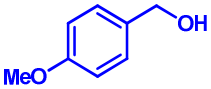
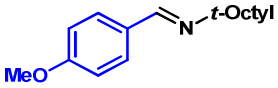
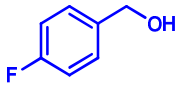
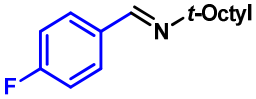
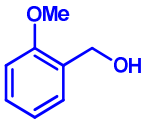
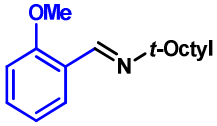
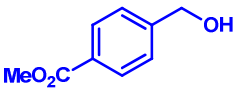
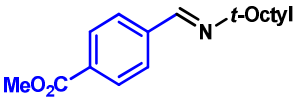
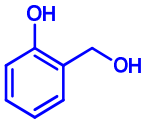
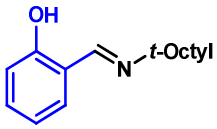
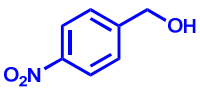
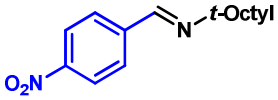
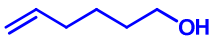
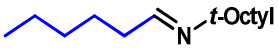
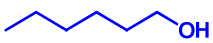
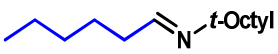
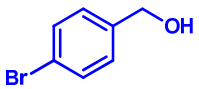
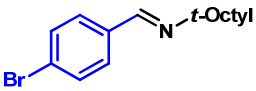
In conclusion, the latter results show that 1,3-diisopropylimidazol-2-ylidene (I*i*Pr) is the best carbene ligand for the imination reaction. Furthermore, preformed complex **3** together with DABCO resulted to be a more effective system than by generating the catalyst *in situ*.
Thus, for general use complex **3** in the presence of DABCO and molecular sieves presents the optimum catalyst for the imination reaction.

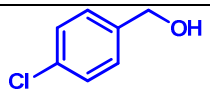
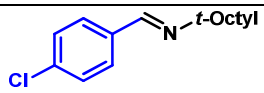
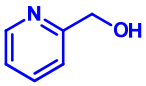
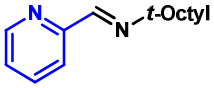
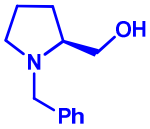
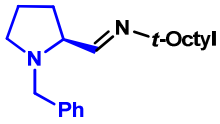
1.3.2. Substrate scope

With optimised reaction conditions in hand, our attention turned to other alcohols and amines in order to investigate the scope of the reaction (Table 3). The influence of substituents on the benzyl alcohol aromatic ring was investigated first. Para-substituted benzyl alcohols with methyl, methoxy, and fluoro substituents were good substrates for the imination reaction. In fact, for all the reactions imine formation was accompanied only by trace amounts of the corresponding secondary amine (entries 2-4).

Table 3. Imination of Alcohols with *tert*-Octylamine



Entry	Alcohol	Imine	Amine Conv. [%][a]	Yield [%][b]
1			82	80
2			90	77
3			70	63[c]
4			80	72
5			75	69[c]
6[d]			93	59[e]
7			-	33[f]
8			77	48[g]
9			84	40
10			75	55[h, i]
11			91	46[h, j]

Entry	Alcohol	Imine	Amine Conv. [%][a]	Yield [%][b]
12			90	71[h, k]
13			low	traces
14[l]			55	20[h, m]

[a]Determined by GC using nonane as internal standard; [b]Isolated yield; [c]3% of anisole was also formed; [d]performed in mesitylene at 165˚C using PCy_3 instead of DABCO; [e]14% of secondary amine, 17% of amide and 3% of methyl benzoate were also formed; [f]37% of secondary amine was also formed; [g]15% of *N*-(*p*-aminobenzylidene)-*tert*-octylamine was also formed; [h]GC yield, products were not isolated; [i]25% of secondary amine was also formed; [j]19% of the secondary amine, 16% of *N*-benzylidene-*tert*-octylamine and 7% of *N*-benzyl-*tert*-octylamine were also formed; [k]15% of the secondary amine and 5% of *N*-benzylidene-*tert*-octylamine were also formed; [l]48h reaction; [m]10% of *N*-benzylidene-*tert*-octylamine was also formed.

As shown in entry 5 the methoxy group could also be tolerated in the ortho position without affecting the yield of the reaction. Noteworthy, the formation of a small amount of anisole was observed in the case of entry 3 and 5, which could derive from decarbonylation of the intermediate aldehyde.[48] The coupling between *tert*-octylamine and methyl 4-(hydroxymethyl) benzoate afforded the desired product in lower yield and with lower selectivity (entry 6). In fact, the imine formed together with significant amounts of the secondary amine and amide. Furthermore the reaction temperature had to be increased from 110˚C to 165˚C.

o-Hydroxybenzyl alcohol resulted to be a poor substrate since the product was obtained as a 1:1 mixture of the desired imine and the corresponding secondary amine (entry 7).

When nitrobenzyl alcohol was subjected to the imination reaction the imine was obtained in moderate yield due to competing reduction of the nitro group (entry 8).

Interestingly, hex-5-enyl alcohol gave an imine in which the olefin had been completely reduced with the liberated hydrogen (entry 9). In this reaction the imine was the only product detected and the moderate yield is due to poor stability of alkylimines toward purification by flash column chromatography. In contrast, *n*-hexanol afforded a 2:1 mixture of the imine and the corresponding secondary amine (entry 10).

p-Chloro- and *p*-bromobenzyl alcohol were inferior substrates due to the formation of mixtures containing the desired imines, the corresponding secondary amines and dehalogenation by-products (entries 11 and 12).

2-Hydroxymethyl-pyridine reacted sluggishly with *tert*-octylamine leading to the formation of only trace amount of the desired product after 24 hours.

When *N*-benzyl-L-prolinol was coupled with *tert*-octylamine the corresponding imine was generated in only 20% GC yield after 48 hours together with 10% of *N*-benzylidene-*tert*-octylamine.

Other primary amines were also investigated as substrates for the imination reaction and benzyl alcohol was selected in this case as the alcohol component (Table 4).

Cyclohexylamine and 1-adamantylamine afforded the desired products in good yield with only trace amounts of the secondary amines (entries 1 and 2).

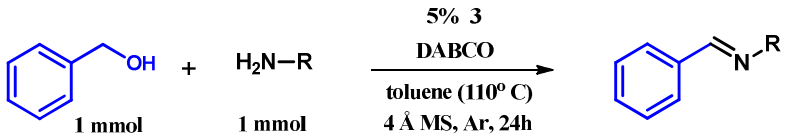
Notably, optically pure 1-phenylethylamine and 1-(1-naphthyl) ethylamine underwent the coupling with benzyl alcohol to give the corresponding imines without any sign of racemization and in good yields (entry 3 and 4).

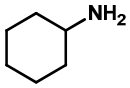
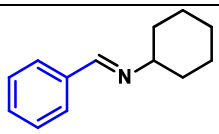
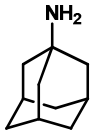
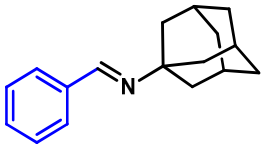
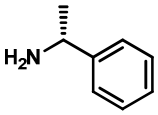
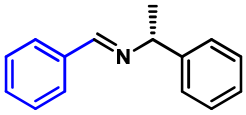
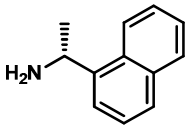
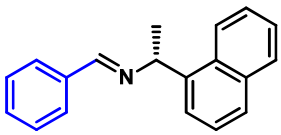
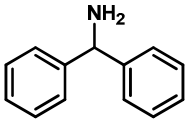
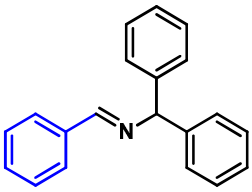
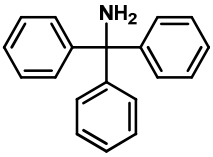
The more hindered benzhydrylamine (entry 5) participated very slowly to the imination reaction giving the corresponding imine in 40% yield after 48 hours. A further increase of the steric hindrance inhibited the reaction almost completely, as seen with tritylamine, where only a trace amount of the imine was observed together with benzyl benzoate from self-condensation of the alcohol. This result indicates that the amine has to attack the ruthenium complex in order for the imination to occur. In fact, it is known that tritylamine reacts readily with aldehydes to form the corresponding imines.[49]

Moreover, when benzyl alcohol was reacted with complex **3** in absence of the amine the formation of 10% of benzaldehyde was observed by GC-MS after 2h. Prolonged treatment did not raise the amount of aldehyde but small amounts of benzyl benzoate were obtained.

Aniline, benzylamine and hexylamine were also examined for the imination reaction, but turned out to be inferior substrates (results not shown). Aniline reacted very sluggishly with benzyl alcohol to give the imine in low yield together with several unidentified by-products. The coupling between hexylamine and benzyl alcohol led to the formation of a complex mixture of imines deriving from self- and cross-coupling. Self-coupling was observed also in the reaction between benzylamine and *p*-methyl-benzyl alcohol, which gave a 1:1 mixture of *N*-benzylidene-1-phenylmethanamine and *N*-4-methylbenzylidene-1-phenylmethanamine.

Table 4. Imination of Amines with Benzyl Alcohol



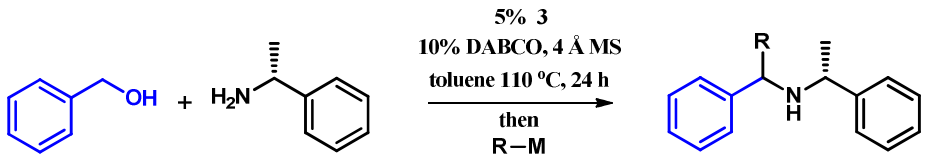
Entry	Amine	Imine	BnOH Conv. [%][a]	Yield [%][b]
1			75	60
2			82	70[c]
3			77	63[c]
4			70	52[d]
5[e]			73	40[f]
6[g]		-	75	-

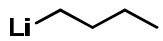
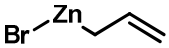
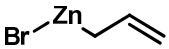
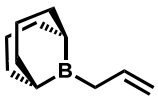
[a]Determined by GC using nonane as internal standard; [b]Isolated yeld; [c]10% of secondary amine was also formed; [d]7% of secondary amine was also formed; [e]reacted for 48h; [f]5% of secondary amine was also formed; [g] reacted for 52 h.

1.3.3. Diastereoselective addition of allyl- and butylmetal reagents to (*R*)-*N*-benzylidene-1-phenylethylamine

The possibility to synthesize optically pure imines by direct coupling of alcohols and chiral amines (Table 4, entries 3 and 4) has interesting applications. In fact, the formed imines can be used to synthesize enantiomerically pure secondary amines by addition of organometallic reagents.[7] For instance, the diasteroselective addition of several carbon nucleophiles to imines deriving from (*S*)- or (*R*)-1-phenylethylamine have been previously reported.[50–52] Thus, after the coupling between benzyl alcohol and (*R*)-1-phenylethylamine, the formed imine was directly reacted with different allylating and alkylating agents (Table 5).

Table 5. Addition of allyl- and butylmetal reagents to (*R*)-*N*-benzylidene-1-phenylethylamine



Entry	R−M	Solvent	Additive	Time	d.r. *S,R* : *R,R*[b]	d.e. [%]	Yield[a]
1		Toluene	$BF_3{\cdot}OEt_2$	6 h	1 : 1.7	26	45
2		THF	-	16 h	1.2 : 1	9	61
3		THF	$TiCl_4$	16 h	2.2 : 1	37	n.d.
4		Et_2O	-	16 h	9 : 1	80	53

[a]Isolated yields over two steps; [b]determined by GC-MS.

When crude (*R*)-*N*-benzylidene-1-phenylethylamine was reacted with *n*-butyllithium (*n*-BuLi) in the presence of boron trifluoride diethyl etherate (BF_3 OEt_2) the corresponding secondary amine was obtained in 45% overall yield and 26% diasteromeric excess (d.e.) of the *R,R* diastereomer (entry 1). Addition of allylzinc bromide (allyl-ZnBr) generated the homoallylic amine in good yield but with almost no diastereoselectivity (entry 2). When the same reaction was performed in

presence of titanium tetrachloride ($TiCl_4$) higher diastereoselection was achieved. In fact, the *S,R* amine formed with 37% d.e. (entry 3).

Excellent asymmetric induction was finally obtained with the more bulky *B*-allyl-9-borabicyclononane (allyl-BBN), which gave the corresponding amine in 53% overall yield and 80% d.e. of the *S,R* diastereomer (entry 4).

The amines absolute configuration was assigned by ^{1}H-NMR spectroscopy considering the chemical shift of the methine protons bound at the stereogenic centers, that in the (*R,R*)-diastereomers resonate at higher magnetic field than the corresponding protons in the (*S,R*)-diastereomers (Figure 2).[51,52]

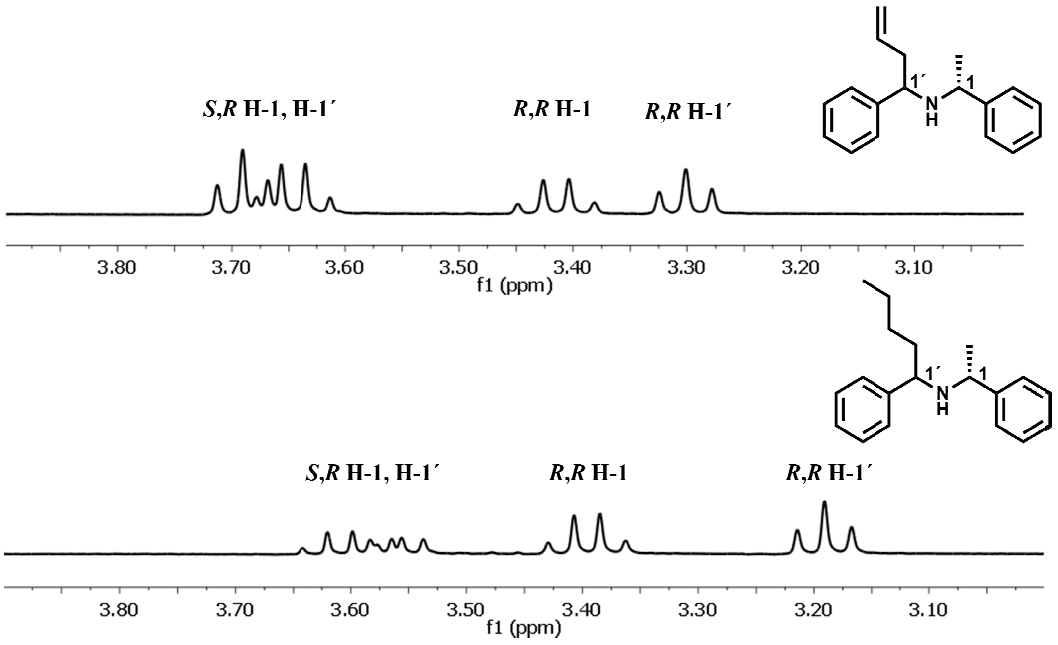


Figure 2. ^{1}H-NMR spectra of diastereomeric mixtures of the amines deriving from addition of allyl- (top) and butyl metal (bottom) reagents to (*R*)-*N*-benzylidene-1-phenylethylamine.

The d.e., in turn, was determined by GC-MS analysis of the crude reaction mixtures were the (*R,R*)-diastereomers were always eluted first.

The addition of *n*-BuLi, allyl-ZnBr and allyl-BBN to the same chiral imine gave different stereochemical outcomes indicating that the sense and degree of disteroselectivity is affected by the nature of the metal and the presence of a Lewis acid. Thus, as concluded by Alvaro *et al.*, the 1,3-

asymmetric induction in organometallic reactions of imines carrying the same chiral auxiliary cannot be predicted by a single stereochemical model.[7]

Generally, the step that controls the asymmetric induction is the preliminary coordination of the metal or Lewis acid to the imine nitrogen which determines the orientation of the chiral auxiliary. In fact, NMR experiments conducted on complexes formed between several imines with metal salts showed that, when the metal is relatively small, the complex retains the conformation present in the free imine called H-eclipsed conformation. Whereas, with bulky metals the complexation forces the chiral auxiliary to rotate of about 180˚ along the N-C* bond, thus the complex assumes the so-called M-eclipsed conformation in which the H-C* bond is eclipsed with the metal (Figure 3).[53]

Figure 3. Possible conformations adopted by (*R*)-*N*-benzylidene-1-phenylethylamine after metal complexation.

According to this model, the diastereoselectivity obtained from the addition of *n*-BuLi to the imine in the presence of $BF_3{\cdot}OEt_2$ (Table 5, entry 1) could be explained by considering that the Lewis acid coordination causes the 180˚C rotation of the auxiliary. Hence the (*R*)-imine·BF_3 complex assumes the M-eclipsed conformation and the reaction proceeds by nucleophilic attack of *n*-BuLi to the less hindered *re*-face through the open transition state **I** (Figure 4).

In contrast, in the case of $TiCl_4$ (Table 5, entry 3) the H-eclipsed conformation is retained in the Ti-imine complex, and allyl-ZnBr preferentially attacks the less crowded *si*-face through the open transition state **II** (Figure 4). When the same reaction is performed in absence of a Lewis acid (Table 5, entry 2) the zinc coordinates the imine nitrogen and the nucleophilic addition takes place through a cyclic transition state.

Due to the low bulkiness of allyl-ZnBr the Zn-imine complex should maintain the H-eclipsed conformation and the *si*-face attack should be favored (Figure 4, transition state **III**). However, the reaction led to the formation of the *S,R* diastereomer with a d.e. of only 9%. It has been suggested that the low diastereoselectivity, usually observed for allylzincation reactions performed in the absence of a Lewis acid, may derive from equilibration of the diastereomeric homoallylic amines.[7]

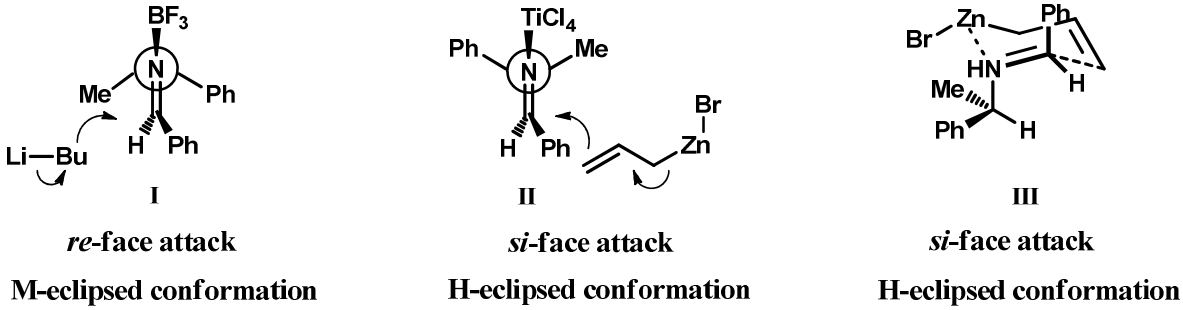
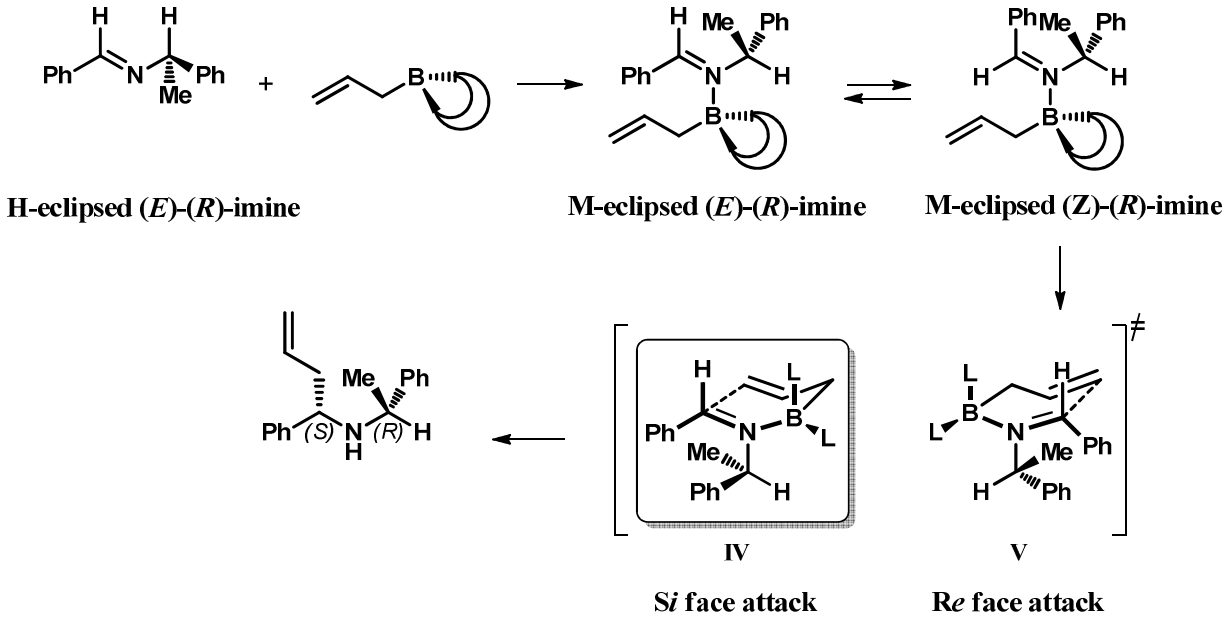


Figure 4. Favorite transition states for the addition of *n*-BuLi and allyl-ZnBr to (*R*)-*N*-benzylidene-1-phenylethylamine according to the model proposed by Alvaro *et al.*

The addition of allyl-BBN to (*R*)-*N*-benzylidene-1-phenylethylamine gave the best result in terms of stereochemical control (80% d.e. of the *S,R* diastereomer). The observed asymmetric induction can be rationalized by assuming that after complexation, due to the bulkiness of the boron reagent, the imine adopts the M-eclipsed conformation. However, in this case the rotation of the N-C* bond is not sufficient to relieve all the steric interactions. In fact, due to severe contacts between the aryl group coplanar to the azomethine group and any of the boron ligands the imine should undergo *E* to the *Z* isomerization of the double bond (Scheme 14).[50] At this point the nucleophilic addition takes place *via* a boat-like transition state in which the phenyl groups assume a *quasi*-parallel orientation and the small hydrogen is oriented toward the boron ligands. The correct sense of asymmetric induction is then given by transition state **IV** in which the phenyl group of the chiral auxiliary is oriented outside.[50]

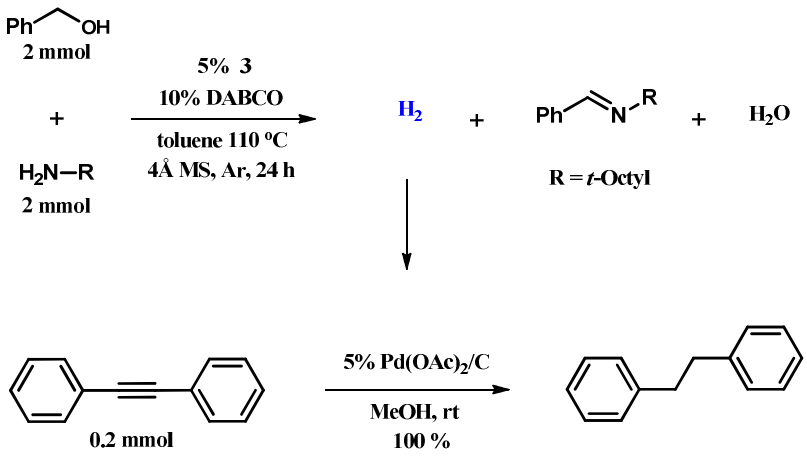


Scheme 14. Stereochemical model for the addition of allyl-BBN to (*R*)-*N*-benzylidene-1-phenylethylamine according to the model proposed by Alvaro *et al.*

1.3.4. Mechanism of the reaction

The imination reaction is believed to proceed *via* alcohol dehydrogenation to form the corresponding aldehyde. The aldehyde is then attacked by the amine to generate a hemiaminal from which the imine is formed by loss of water. Thus, imine formation is accompanied by production of equimolar amounts of hydrogen and water.

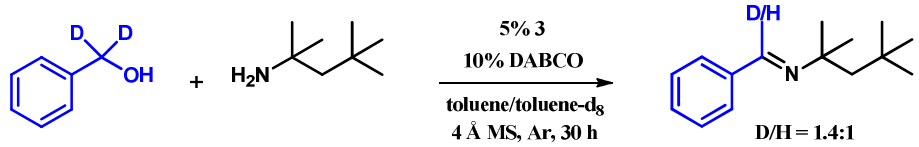
The development of hydrogen during the transformation was confirmed by collecting the gas generated during the reaction and using it for the hydrogenation of diphenylacetylene in a separate flask. In fact, the reaction led to the complete conversion of diphenylacetylene into diphenylethane (Scheme 15).



Scheme 15. Determination of hydrogen development

Formation of hydrogen gas indicates that oxidation of the alcohol into the aldehyde occurs through β-hydride elimination. Therefore, in order to gain more information about this step, different experiments with deuterium-labeled benzyl alcohol were performed.

First, benzyl alcohol-α,α-d_2 ($PhCD_2OH$) and *tert*-octylamine were coupled under the standard imination conditions (Scheme 16). The reaction afforded *N*-benzylidene-*tert*-octylamine as a 1.4:1 mixture of the deuterium-labeled and the unlabeled products.



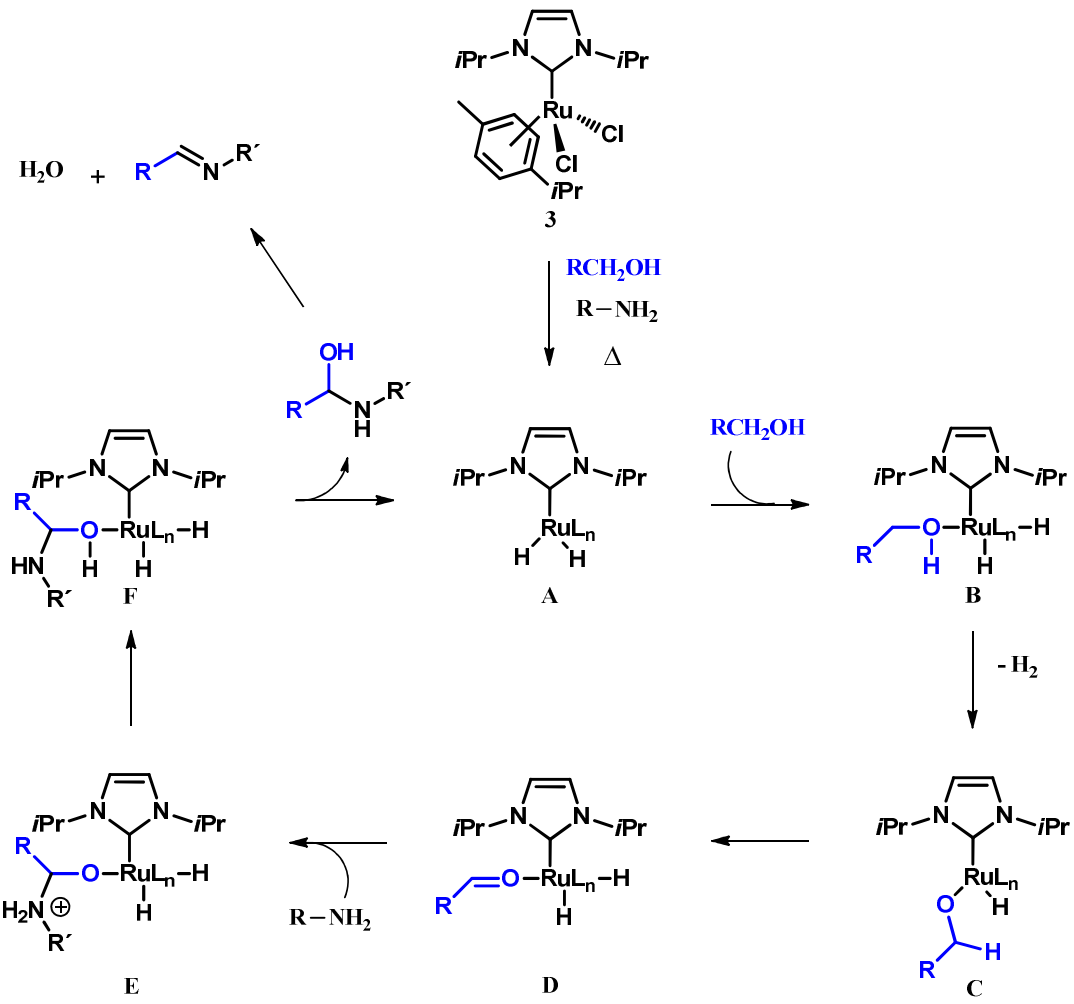
Scheme 16. Imination with benzyl alcohol-α,α-d_2

The same outcome was observed by performing the reaction in toluene-d_8 showing that the hydrogen incorporation into the imine is not the result of a deuterium-hydrogen exchange with the solvent. Furthermore when unlabeled *N*-benzylidene-*tert*-octylamine was treated with $PhCD_2OH$ under the same conditions of Scheme 16, no deuterium incorporation into the imine was observed.

This result shows that the scrambling occurs during the imination reaction and is not due to a competing transformation from the imine. When the imination in Scheme 16 was monitored by ^{1}H-NMR spectroscopy in toluene-d_8, deuterium-hydrogen scrambling in the starting alcohol was observed already after 5 hours. In fact, isolation of the unreacted alcohol at this time showed that it consisted of a mixture containing 56% of $PhCD_2OH$, 34% of PhCDHOH and 10% of $PhCH_2OH$. This indicates that the initial β-hydride elimination is a reversible step and, more importantly, that a ruthenium dihydride species is formed during the catalytic cycle. The same observations have been made for the dehydrogenative ester[35] and amide[41] synthesis from primary alcohols with catalyst **3**.

The role of the β-hydride elimination was further investigated by measuring the kinetic isotope effect (KIE) of the imination reaction. To this end the initial rates for the reactions of both $PhCH_2OH$/*tert*-octyl-NH_2 and $PhCD_2OD$/*tert*-octyl-ND_2 were measured in two separate experiments. The initial rate obtained for the reaction with non-deuterated substrates was 3.04 10^{-5} (± 0.56 10^{-5}) M min^{-1}, whereas the rate with deuterated substrates was 2.69 10^{-5} (± 0.67 10^{-5}) M min^{-1}, giving a KIE of 1.1 (± 0.3). The low value obtained for the KIE indicates that β-hydride elimination is not the rate-limiting step in the imination reaction. This result is in agreement with what observed by Madsen and co-workers for the amidation reaction. In fact, also in this case a low KIE has been observed for the breakage of the alcohol C-H bond.[41]

On the basis of these experiments, and previous studies on the amidation reaction,[40,41] a mechanism for the imination reaction can be proposed (Scheme 17).



Scheme 17. Proposed mechanism for the imination reaction

It has been shown by NMR spectroscopy that the *p*-cymene ligand in complexes like **3** is lost upon reflux in toluene.[36,41,54] Thus, according to this, we hypothesize that the reaction is initiated by loss of the *p*-cymene followed by replacement of the two chlorides with hydride to form complex **A**, were the remaining ligands (L_n) on ruthenium could be DABCO and the amine. This step requires substitution with the alcohol, release of hydrogen chloride, and β-hydride elimination. Thus, small amounts of aldehyde will be formed and converted into the imine by the catalyst initiation.

Formation of ruthenium hydrides by reaction of alcohols and ruthenium(II) chloride complexes has been already reported.[55–57] Furthermore Madsen and co-workers have observed that the initial rate of the amidation reaction performed with complex [RuI_2(I*i*Pr)(*p*-cymene)] is substantially the same

as with complex **3**, suggesting that the halides are not bound the ruthenium centre during the catalytic cycle.[41] These observations together with the deuterium-hydrogen scrambling strongly support the hypothesis that the catalytically active ruthenium species is a dihydride.

Once dihydride complex **A** is formed, the alcohol is coordinated to give complex **B** from which hydrogen gas is liberated by H-transfer to hydride.[58] This lead to the formation of alkoxide complex **C** which is then converted to the aldehyde complex **D** by β-hydride elimination.

At this point the aldehyde may be released from **D** and imine formation would then occur in solution. However, since the imination reaction is sensitive to the steric hindrance of the amine, it is more reasonable that the amine attacks the coordinated aldehyde to form hemiaminal complex **E** as a zwitterion protonated at the nitrogen. So far this mechanism is rather similar to that proposed for the amidation reaction (see pg.13, Scheme 12),[40,41] the only difference is the lack of a strong base.

As mentioned above, according to the Eisenstein computational study, after formation of the hemiaminal complex **E** a proton transfer takes place either between the nitrogen and the hydride or between the nitrogen and the oxygen. Proton transfer to the oxygen generates a neutral hemiaminal which would decoordinate easily from the metal to give imine formation. Whereas, if the proton is transferred to the hydride and hydrogen is liberated the hemiaminal remains coordinated to the ruthenium and undergoes β-hydrogen elimination generating the amide.[42]

The absence of a strong base in the imination reaction may facilitate proton transfer to the oxygen leading to the formation of complex **F** from which the imine is formed after decomplexation of the hemiaminal.

1.3.5 Conclusion

In conclusion, we have developed a procedure for the synthesis of imines from alcohols and amines with concomitant extrusion of water and dihydrogen. The reaction is catalyzed by the complex [$RuCl_2$(I*i*Pr)(*p*-cymene)] (**3**) that is easy to handle and straightforward to synthesise. A mechanism is proposed with a ruthenium dihydride species as the catalytically active component and for which the intermediate aldehyde remains coordinated to the ruthenium during the catalytic cycle.

The imination reaction gives access to a variety of different imines which may be used directly in a subsequent addition reaction. This has been illustrated with the enantiomerically pure (*R*)-*N*-benzylidene-1-phenylethylamine which was reacted with different alkylating and allylating reagents to afford the corresponding secondary amines in good yields and diastereoselectivity (up to 80%).

These results have recently been published as full paper in *Organometallics*.

1.4. Experimental Section

1.4.1. General methods

All experiments were carried out under argon flow using Schlenk flask technique unless specified differently. All chemicals were obtained from Aldrich and used without further purification. Dry solvents were obtained by distillation from sodium and benzophenone under an argon atmosphere.
Imidazolium salts 1,3-dimethylimidazolium iodide (IMe·HI)[43] and 1,3-di-*tert*-butylimidazolium chloride (I*t*Bu·HCl)[46] as well as complexes [$RuCl_2$(I*i*Pr)(*p*-cymene)] (**3**)[40] and [$RuCl_2$(IMe)(*p*-cymene)] (**4**)[36,44] were synthesized following established procedures.
^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Mercury 300 MHz. Chemical shifts (δ) are reported in ppm, using the residual solvent signal in $CDCl_3$ (δ_H 7.26, δ_C 77.0) or TMS as reference, and coupling constant (J) are given in Hz.
Alcohol and amine conversion was obtained on a Shimadzu QP2010S GC-MS instrument equipped with a 30 m x 0.25 m x 0.25 µm film thickness Equity-5 column using nonane as internal standard. During the GC-analysis the injector temperature was at 280˚C, and the temperature program used was: 60˚C, hold 5 min, 20˚C/min to 280˚C, hold 5 min total run time 18 min. The GC was coupled to a mass spectrometer operating in positive EI mode.
LC-HRMS analysis were performed on a Agilent 1100 LC system with a diode array detector (Agilent Technologies, Waldbronn, Germany) and equipped with a 50 mm × 2 mm i. d. 3µm Luna C_{18} (2) column (Phenomenex, Torrance, CA, USA). The LC was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with Lock Mass probe and operated in positive electrospray mode.
Optical rotations were measured on a Perkin-Elmer 241 polarimeter.
Column chromatography separations were carried out on silica gel (pore size 60 Å, 35-70 µm) saturated with Et_3N.

1.4.2. General procedure for imination with ruthenium complexes **3** and **4**

Ruthenium complex (0.05 mmol), DABCO (11.2 mg, 0.1 mmol) and 4 Å molecular sieves (150 mg) were placed in an oven-dried Schlenk flask equipped with a cool finger. Vacuum was applied and the flask was then filled with argon (repeated twice). Freshly distilled toluene or mesitylene (1 mL), alcohol (1 mmol), amine (1 mmol) and nonane (0.2 mmol, internal standard) were added via syringe and the mixture was refluxed with stirring for 24 hours. After cooling to room temperature a sample of 50 μl was taken, transferred to a GC vial, diluted to 1 mL with CH_2Cl_2 and then subjected to GC-MS-analysis. After removal of the solvent, the crude product was purified by silica-gel column chromatography (hexane-ether 10:0 to 9:1 plus 2 volume % of Et_3N) to afford the pure imine.

1.4.3. General procedure for imination with catalysts generated *in situ*

$[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol), DABCO (11.2 mg, 0.1 mmol), imidazolium salt (0.05 mmol), KO*t*Bu (11.2 mg, 0.05 mmol) and 4 Å molecular sieves (150 mg) were placed in an oven-dried Schlenk flask equipped with a cool finger. Vacuum was applied and the flask was then filled with argon (repeated twice). Freshly distilled toluene (1 mL) was added and the mixture was refluxed with stirring for 20 minutes. Benzyl alcohol (108 mg, 1 mmol), *tert*-octylamine (129 mg, 1 mmol) and nonane (0.2 mmol, internal standard) were added via syringe and the mixture was refluxed with stirring for 24 hours. After cooling to room temperature a sample of 50 μl was taken, transferred to a GC vial, diluted to 1 mL with CH_2Cl_2 and then subjected to GC-MS-analysis.

1.4.4. General procedure for determination of hydrogen development

Benzyl alcohol (213 mg, 2 mmol), *tert*-octylamine (262 mg, 2 mmol) and 4Å molecular sieves (300 mg) were placed in an oven-dried Schlenk flask and subjected to imination reaction following the general procedure for imination with ruthenium complex **3**.
A separate flask, containing diphenylacetylene (213 mg, 0.2 mmol), $Pd(OAc)_2$ (3 mg, 0.01 mmol), charcoal (90% wt/Pd) and methanol (1 ml), was equipped with a septum cap, connected to the

Schlenk flask with a needle and the reaction mixture was stirred over night at room temperature. In this way the hydrogen developed during the imination reaction was collected in the separate flask causing the reduction of the alkyne bond.[59] GC-MS analysis of the hydrogenation reaction mixture showed the complete conversion of the alkyne into diphenylethane (EI, Pos; RT = 12.16; $[M]^+$ = 182).

1.4.5. General procedure for determination of deuterium isotope effect

Benzyl alcohol (108 mg, 1 mmol) and *tert*-octylamine (129 mg, 1 mmol) were placed in an oven-dried Schlenk flask and subjected to imination reaction following the general procedure for imination with ruthenium complex **3**. The reaction mixture was refluxed with stirring for 1.5 h. Every 15 minutes the reaction mixture was cooled to room temperature and a sample of 50 μl was taken, transferred to a GC vial diluted to 1 mL with CH_2Cl_2, and then subjected to GC-MS-analysis following the formation of tert-octylbenzaldimine. The same procedure was repeated using benzyl alcohol-α,α-d_2 [60] (110 mg, 1 mmol), *tert*-octylamine (129 mg, 1 mmol) and toluene-d_8 (1 ml) as solvent. In this case, before to start the reaction, the alcohol and the amine were dissolved in methanol-d_4 and then the methanol was evaporated (repeated twice). Each experiment was repeated four times and the initial rate (r) determined. The mean initial rate for the reaction of benzyl alcohol was $r_H = 3.04\ 10^{-5}$ ($\pm$ $0.56\ 10^{-5}$) M min^{-1}. The mean initial rate for the reaction of benzyl alcohol-α,α-d_2 was $r_D = 2.72\ 10^{-5}$ ($\pm$ $0.67\ 10^{-5}$) M min^{-1}. The isotope effect was $K^H/K^D = 1.1$ ($\pm$ 0.3).

1.4.6. General procedure for addition of allylmetal reagents to (*R*)-*N*-Benzylidene-1-phenylethylamine.

- Addition of *n*-butyllitium (*n*-BuLi)

Crude (*R*)-*N*-benzylidene-1-phenylethylamine, synthesized according to the imination procedure with complex **3**, was dissolved in toluene (6 mL). The solution was cooled down to -78˚C and $BF_3{\cdot}OEt_2$ (1.6 mmol, 0.2 mL) was added followed by *n*-BuLi (2 mmol, 0.8 mL). The reaction was stirred for six hours letting the temperature rise to 5˚C. A sample was taken and analyzed by GC-MS showing the presence of trace amount of the imine and formation of the corresponding

secondary amine as a mixture of the two diastereomers (*R,R*/*S,R* 1.7:1). The reaction was quenched by addition of saturated $NaHCO_3$; then the mixture was eluted with CH_2Cl_2 and the organic layer was separated, washed with brine and dried over Na_2SO_4.
After evaporation of the solvent the crude amine was purified by column chromatography (hexane:Et_2O, 9.5:0.5) to afford 120 mg of the pure diastereomeric mixture (45% yield over two steps).

- Addition of allylzinc bromide

Crude (*R*)-*N*-benzylidene-1-phenylethylamine, synthesized following the imination procedure with ruthenium complex **3**, was dissolved in anhydrous THF (6 mL) and added drop wise to a THF (5 ml) solution of allylzinc bromide (4 mmol, prepared according to a reported procedure)[61] at -78˚C under Ar atmosphere. The reaction mixture was then stirred for 16 h, while being allowed to reach room temperature. A sample was taken and analyzed by GC-MS showing the complete conversion of the imine and formation of the corresponding homoallylic amine as a mixture of the two diastereomers (*S,R*/*R,R* 1.2:1). The reaction was then quenched by addition of 10% NaOH (20 ml), the organic phase was separated and the water phase was extracted three times with Et_2O (10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated at reduced pressure to leave the crude amine. This was then purified by column chromatography (hexane:Et_2O, 9.5:0.5) to afford 154 mg of the pure diastereomeric mixture (61% yield over two steps).

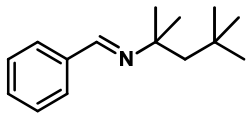
- Addition of B-allyl-9-BBN

B-allyl-9-BBN was generated *in situ* following a modification of the procedure reported by Fang *et al*.[62] An oven-dried Schlenk flask was charged with *B*-methoxy-9-BBN (1.0 M solution in hexane, 3 mL, 3 mmol), then the hexane was removed under reduced pressure and the borinic ester was dissolved in anhydrous Et_2O (6 mL). The solution was cooled to -78˚C and allylmagnesium chloride (2 M solution in THF, 1.5 mL, 3 mmol) was added drop wise. The reaction mixture was warmed to room temperature and then stirred for 30 min followed by evaporation of the solvent. The white solid obtained was suspended in anhydrous hexane (9 mL) and stirred for 3 h at room temperature during which time the borane formed and magnesium salt precipitated. After evaporation of the solvent dry Et_2O (3 mL) was added and the suspension, containing the borane reagent, was cooled to -78˚C. The crude imine, synthesized following the imination procedure with

ruthenium complex 3, was dissolved in anhydrous Et_2O (6 mL) and added drop wise to the borane solution. The reaction mixture was stirred at -78˚C for 1 h and then allowed to reach room temperature over 16 h. A sample was taken and analyzed by GC-MS showing the complete conversion of the imine. The reaction was then quenched at 0˚C by addition of 37% hydrochloric acid (0.8 mL) and stirred for further 12 h at room temperature. Then 10% NaOH was added to the mixture until reaching pH 11, the organic phase was separated and the water phase was extracted three times with Et_2O (10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated at reduced pressure. A sample of the organic phase was taken and analyzed by GC-MS indicating the formation of the corresponding homoallylic amine with diastereoisomeric ratio 9:1 (*S,R*/*R,R*). The crude amine was then subjected to column chromatography (hexane:Et_2O, 9.5:0.5) to afford 134 mg of the pure diastereoisomeric mixture (53.4% yield over two steps).

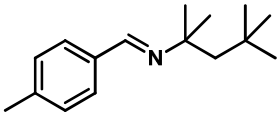
1.4.7. Characterization data

- *N*-benzylidene-*tert*-octylamine



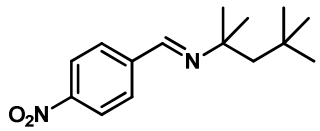
Following the imination procedure with ruthenium complex **3**, the imine was isolated as light yellow oil (174 mg, 80% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.26 (s, 1H, N=CH), 7.78-7.75 (m, 2H, Ar), 7.43-7.40 (m, 3H, Ar), 1.72 (s, 2H, CH_2), 1.35 (s, 6H, 2 x CH_3), 0.98 (s, 9H, 3x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 154.3 (N=CH), 137.3(Ar-quat-C), 129.9, 128.5, 127.8 (Ar), 60.9 (quat-C), 56.5 (CH_2), 32.0 (quat-C), 31.8, 29.6 (CH_3); NMR data in accordance with literature values;[6] **GC-MS** (EI, Pos): **RT** = 12.6 min; $[M\text{-}CH_3]^+$ = 202 *m/z*.

- *N*-4-methylbenzylidene-*tert*-octylamine



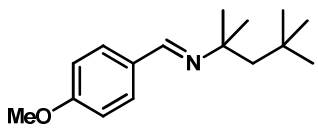
Following the imination procedure with ruthenium complex **3**, the imine was isolated as colorless oil (177 mg, 77% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.21 (s, 1H, N=CH), 7.64 (d, 2H, J = 8.1, Ar), 7.21 (d, 2H, J = 8.1, Ar), 2.38 (s, 3H, CH_3), 1.69 (s, 2H, CH_2), 1.32 (s, 6H, 2 x CH_3), 0.96 (s, 9H, 3 x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 154.2 (-N=CH), 140.0 (Ar-quat-C), 134.8 (Ar-quat-C), 129.1, 127.8 (Ar), 60.8 (quat-C), 56.6 (CH_2), 32.0 (quat-C), 31.7, 29.6, 21.4 (CH_3); **GC-MS** (EI, Pos): **RT** = 13.3 min, $[M\text{-}CH_3]^+$= 216 *m/z*; **HRMS** (ESI, Pos): calcd for $C_{16}H_{25}N$ $[M+H]^+$ = 232.2021, found = 232.2059 *m/z*.

- *N*-4-nitrobenzylidene-*tert*-octylamine



Following the imination procedure with ruthenium complex **3**, the imine was isolated as light brown oil (126 mg, 48% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.30 (s, 1H, N=CH), 8.26 (d, 2H, J = 8.7, Ar), 7.91 (d, 2H, J = 8.7, Ar), 1.71 (s, 2H, CH_2), 1.34 (s, 6H, 2 x CH_3), 0.94 (s, 9H, 3 x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 152.3 (N=CH), 142.7 (Ar-quat-C), 128.5, 123.8, (Ar), 61.9 (quat-C), 56.5 (CH_2), 32.0 (quat-C), 31.7, 29.5 (CH_3);**GC-MS** (EI, Pos): **RT** = 15.2 min, $[M\text{-}CH_3]^+$= 247 *m/z*; **HRMS** (ESI, Pos): calcd for $C_{15}H_{22}N_2O_2$ $[M+H]^+$ = 263.1715, found = 263.1753 *m/z*.

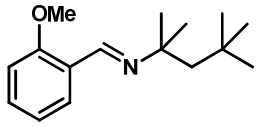
- *N*-4-methoxybenzylidene-*tert*-octylamine



Following the imination procedure with ruthenium complex **3**, the imine was isolated as colorless oil (155 mg, 63% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.18 (s, 1H, N=CH), 7.70 (d, 2H, J =

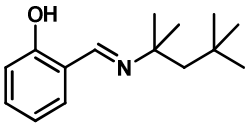
8.7, Ar), 6.93 (d, 2H, J = 8.7, Ar), 3.84 (s, 3H, OMe), 1.68 (s, 2H, CH_2), 1.32 (s, 6H, 2 x CH_3), 0.96 (s, 9H, 3 x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 161.0 (Ar-quat-C), 153.6 (N=CH), 130.4 (Ar-quat-C), 129.3, 113.8 (Ar), 60.6 (quat-C), 56.6 (CH_2), 55.3 (OCH_3), 32.0 (quat-C), 31.8, 29.7 (CH_3); **GC-MS** (EI, Pos): **RT** = 14.2 min, $[M\text{-}CH_3]^+$= 232 *m/z*; **HRMS** (ESI, Pos): calcd for $C_{16}H_{25}NO$ $[M+H]^+$ = 248.1970, found = 248.2010 *m/z*.

- *N*-2-methoxybenzylidene-*tert*-octyl-2-amine



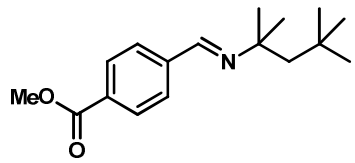
Following the imination procedure with ruthenium complex **3**, the imine was isolated as colorless oil (170 mg, 69% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.67 (s, 1H, N=CH), 7.96 (bd, 1H, Ar), 7.35 (bt, 1H, Ar), 6.98 (bt, 1H, Ar), 6.91 (bd, 1H, Ar), 3.87 (s, 3H, OMe), 1.70 (s, 2H, CH_2), 1.33 (s, 6H, 2 x CH_3), 0.96 (s, 9H, 3 x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 158.6 (Ar-quat-C), 150.4 (N=CH), 131.0, 127.0 (Ar), 125.8 (Ar-quat-C), 120.8, 110.8 (Ar), 61.3 (quat-C), 56.6 (CH_2), 55.4 (OCH_3), 32.0 (quat-C), 31.8, 29.8 (CH_3) ppm; **GC-MS** (EI, Pos): **RT** = 13.8 min, $[M\text{-}CH_3]^+$= 232 *m/z*; **HRM**S (ESI, Pos): calcd for $C_{16}H_{25}NO$ $[M+H]^+$ = 248.1970, found = 248.2008.

- *N*-2-hydroxylbenzylidene-*tert*-octyl-2-amine



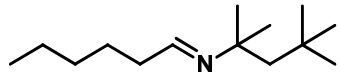
Following the imination procedure with ruthenium complex **3**, the imine was isolated as intense yellow oil (77 mg, 33% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.23 (s, 1H, N=CH), 7.24-7.16 (m, 2H, Ar), 6.86 (d, 1H, J = 7.8, Ar), 6.77 (td, 1H, J_1 = 7.5, J_2 = 0.9, Ar), 1.64 (s, 2H, CH_2), 1.30 (s, 6H, 2 x CH_3), 0.88 (s, 9H, 3 x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 162.2 (Ar-quat-C), 159.5 (N=CH), 131.9, 131.2 (Ar), 118.8 (Ar-quat-C), 117.9, 117.3 (Ar), 60.5 (quat-C), 56.2 (CH_2), 31.9 (quat-C), 31.6, 29.4 (CH_3); **GC-MS** (EI, Pos): **RT** = 13.8 min, $[M\text{-}CH_3]^+$= 218 *m/z*; **HRMS** (ESI, Pos): calcd for $C_{15}H_{23}NO$ $[M+H]^+$ = 234.1813, found = 234.1854 *m/z*.

- *N*-4-carbomethoxybenzylidene-*tert*-octyl-2-amine



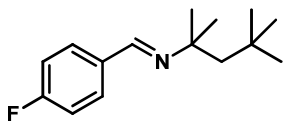
Following the imination procedure with ruthenium complex **3**, the imine was isolated as light yellow solid (162 mg, 59% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.27 (s, 1H, N=CH), 8.07 (d, 2H, J = 8.1, Ar), 7.80 (d, 2H, J = 8.1, Ar), 3.93 (s, 3H, OMe), 1.70 (s, 2H, CH_2), 1.33 (s, 6H, 2 x CH_3), 0.95 (s, 9H, 3 x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.8 (C=O), 153.5 (N=CH), 141.2, 131.1 (Ar-quat-C), 129.7, 127.7 (Ar), 61.5 (quat-C), 56.5 (CH_2), 52.2 (OCH_3), 32.0 (quat-C), 31.7, 29.5 (CH_3); **GC-MS** (EI, Pos): **RT** = 15.1 min, $[M\text{-}CH_3]^+$= 260 *m/z*, **HRMS** (ESI, Pos): calcd for $C_{17}H_{25}NO_2$ $[M+H]^+$ = 276.1919, found = 276.1960 *m/z*.

- *N*-hexylidene-*tert*-octyl-2-amine



Following the imination procedure with ruthenium complex **3**, the imine was isolated as yellow oil (84 mg, 40% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.55 (t, 1H, J = 4.8, N=CH), 2.25-2.19 (m, 2H, CH_2), 1.59 (s, 2H, CH_2), 1.52-1-45 (m, 2H, CH_2), 1.32-1.28 (m, 4H, 2 x CH_2), 1.18 (s, 6H, 2 x CH_3), 0.91 (bs, 12H, 4 x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 158.6 (N=CH), 60.32 (quat-C), 55.82 (CH_2), 36.39 (CH_2), 31.97 (quat-C), 31.72 (CH_3), 29.55 (CH_3), 29.19, 25.92, 22.46 (CH_2), 13.98 (CH_3); **GC-MS** (EI, Pos): **RT** = 11.1 min, $[M\text{-}CH_3]^+$= 196 *m/z*.

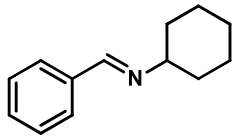
- *N*-4-fluorobenzylidene-*tert*-octyl-2-amine



Following the imination procedure with ruthenium complex **3**, the imine was isolated as colorless oil (169 mg, 72% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.21 (s, 1H, N=CH), 7.76-7.70 (m, 2H,

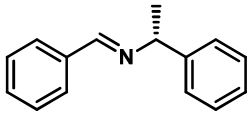
Ar), 7.10 (bt, 2H, Ar), 1.69 (s, 2H, CH_2), 1.32 (s, 6H, 2 X CH_3), 0.96 (s, 9H, 3 x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 163.8 (d, J_{C-F} = 248.0, Ar-quat-C), 152.9 (N=CH), 133.6 (d, J_{C-F} = 2.85, Ar-quat-C), 129.6 (d, J_{C-F} = 8.4, Ar), 115.5 (d, J_{C-F} = 21.6, Ar), 60.9 (quat-C), 56.5 (CH_2), 32.0 (quat-C), 31.7, 29.6 (CH_3); **GC-MS** (EI, Pos): **RT** = 12.5 min, $[M-CH_3]^+$ = 220 *m/z*, **HRMS** (ESI, Pos): calcd for $C_{15}H_{22}FN$ $[M+H]^+$ = 236.1770, found = 236,1809.

- *N*-benzylidenecyclohexanamine



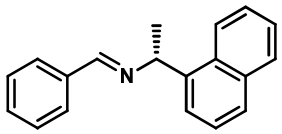
Following the imination procedure with ruthenium complex **3**, the imine was isolated as yellow oil (113 mg, 60% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.32 (s, 1H, N=CH), 7.75-7.71 (m, 2H, Ar), 7.41-7.39 (m, 3H, Ar), 3.24-3.15 (m, 1H, CH), 1.87-1.54 (m, 8H, 4 x CH_2), 1.44-1.26 (m, 2H, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 158.6 (N=CH), 136.5 (Ar-quat-C), 130.3, 128.5, 127.9 (Ar), 70.0 (CH), 34.3, 25.6, 24.8 (CH_2); NMR data in accordance with literature values;[63] **GC-MS** (EI, Pos): **RT** = 12.8 min, $[M]^+$ = 187 *m/z*.

- (*R*)-*N*-benzylidene-1-phenylethylamine



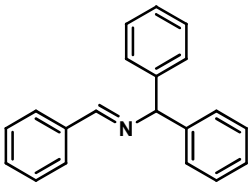
Following the imination procedure with ruthenium complex **3**, the imine was isolated as light yellow oil (132 mg, 63% yield). $[\alpha]_D^{20}$ = -64.6 (c = 1.6, $CHCl_3$) (ref.[14] $[\alpha]_D^{20}$ = -64.7; c 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.30 (s, 1H, N=CH), 7.72-7.69 (m, 2H, 2 x Ar), 7.34-7.24 (m, 8H, Ar), 4.47 (q, 1H, J = 6.6, CH), 1.52 (d, 3H, J = 6.6, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 159.4 (N=C), 145.1, 136.4 (Ar-quat-C), 130.5, 128.5, 128.4, 126.8, 126.6 (Ar), 69.7 (CH), 24.8 (CH_3); NMR data in accordance with literature values;[64] **GC-MS** (EI, Pos): **RT** = 13.9 min, $[M]^+$= 209 *m/z*.

- (*R*)-*N*-benzylidene-1-(1-naphthyl)ethylamine



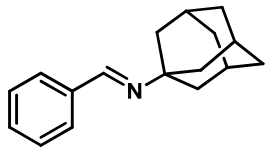
Following the imination procedure with ruthenium complex **3**, the imine was isolated as orange solid (133.4 mg, 51.5% yield). $[\alpha]_D^{20}$ = -242.0 (c = 1.1, $CHCl_3$) (ref.[14] $[\alpha]_D^{20}$ = -250.3; c 1.04, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.45 (s, 1H, N=CH), 8.28 (d, 1H, J = 8.4 Hz, Ar), 7.91-7.67 (m, 5H, Ar), 7.58-7.48 (m, 3H, Ar), 7.44-7.42 (m, 3H, Ar), 5.38 (q, 1H, J = 6.6 Hz, CH), 1.76 (d, 3H, J = 6.6 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 159.6 (N=CH), 141.1, 136.4, 133.9, 130.6 (Ar-quat-C), 130.5, 128.9, 128.5, 128.2, 127.3, 125.7, 125.6, 125.3, 123.9, 123.6 (Ar), 65.5 (CH), 24.5 (CH_3); NMR data in accordance with literature values;[64] **GC-MS** (EI, Pos): **RT** = 16.8 min, $[M]^+$ = 259 *m/z*.

- *N*-benzylidene-1,1-diphenylmethanamine



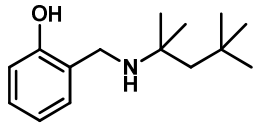
Following the imination procedure with ruthenium complex **3**, the imine was isolated as white solid (108 mg, 40% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.34 (s, 1H, N=CH), 7.78-7.74 (m, 2H, 2 x Ar), 7.34-7.31 (m, 7H, Ar), 7,26-7,21 (bt, 4H, Ar) 7.17-7.12 (m, 2H, Ar), 5.51 (s, 1H, CH); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 160.7 (-N=CH), 143.8, 136.2, 130.7, 128.5, 128.4, 128.4, 127.6, 126.9 (Ar), 77.8 (CH); NMR data in accordance with literature values;[65] **GC-MS** (EI, Pos): **RT** = 16.8 min, $[M]^+$= 271 *m/z*.

- *N*-benzylideneadamantan-1-amine



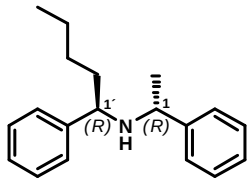
Following the imination procedure with ruthenium complex **3**, the imine was isolated as white solid (169 mg, 70% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.28 (s, 1H, N=CH), 7.77-7.74 (m, 2H, 2 x Ar), 7.41-7.38 (m, 3H, Ar), 2.18 (bs, 3H, 3 x CH), 1.82 (bd, 6H, 3 x CH_2), 1.73 (bs, 6H, 3 x CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 154.8 (N=CH), 137.2 (Ar-quat-C), 130.1, 128.4, 127.8 (Ar), 57.4 (quat-C), 43.1, 36.5, 29.5 (aliphatic -C); NMR data in accordance with literature values;[66] **GC-MS** (EI, Pos): **RT** = 15.6 min, $[M]^+$= 239 *m/z*.

- 2-hydroxylbenzyl-tert-octyl-2-amine



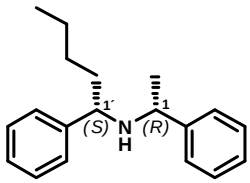
Following the imination procedure with ruthenium complex **3**, the amine was isolated as light brown oil (88 mg, 37% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.15 (bt, 1H, Ar), 7.00 (bd, 1H, Ar), 6-84-6.74 (m, 2H, Ar), 3.94 (s, 2H, CH_2), 1.54 (s, 2H, CH_2), 1.26 (s, 6H, 2 x CH_3), 1.04 (s, 9H, 3 x CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 158.3 (Ar-quat-C), 128.5, 127.9 (Ar), 123.5 (Ar-quat-C), 118.8, 116.4 (Ar), 54.3 (quat-C), 53.4, 45.6 (CH_2), 31.7 (CH_3), 31.6 (quat-C), 28.2 (CH_3); **HRMS** (ESI, Pos): calcd for $C_{15}H_{25}NO$ $[M+H]^+$ = 236,2009, found = 236,2009.

- (*R*)-1-phenyl-N-(*R*)-1-phenylethyl-pentan-1-amine



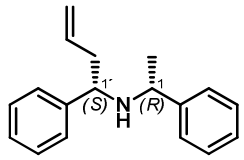
Following the procedure for addition of *n*-BuLi to (*R*)-*N*-benzylidene-1-phenylethylamine, the *R,R* diastereomer was isolated in mixture with the *S,R* diastereomer as colorless oil. The reported ^{1}H and ^{13}C NMR signals were deduced from the spectra of the diastereomeric mixture. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.39-7.19 (m, 10H, Ar), 3.51 (q, 1H, J = 6.6, H-1), 3.31 (t, 1H, J = 7.2, H-1´), 1.73-1.51 (m, 3H), 1.30 (d, 3H, J = 6.6, CH_3), 1.00-1.25 (m, 4H), 0.84 (bt, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 145.9, 144.9 (Ar-quat-C), 128.3, 128.2, 127.2, 126.7, 126.6, 126.5 (Ar), 60.0, 54.8, 38.5, 28.5, 25.1, 22.6, 13.9; NMR data in accordance with literature values;[52] **GC-MS** (EI, Pos): **RT** = 14.7 min, $[M\text{-}CH_3]^+$ = 253 *m/z*.

- (*S*)-1-phenyl-N-(*R*)-1-phenylethyl-pentan-1-amine



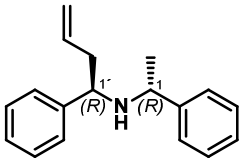
Following the procedure for addition of *n*-BuLi to (*R*)-*N*-benzylidene-1-phenylethylamine, the *S,R* diastereomer was isolated in mixture with the *R,R* diastereomer as colorless oil. The reported ^{1}H and ^{13}C NMR signals were deduced from the spectra of the diastereomeric mixture. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.39-7.19 (m, 10H, Ar), 3.73 (q, 1H, J = 6.6, H-1), 3.68 (m, 1H, H-1´), 1.88-1.70 (m, 3H), 1.37 (d, 3H, J = 6.6, CH_3), 1.27-1.16 (m, 4H), 0.87 (bt, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 145.9, 144.9 (Ar-quat-C), 128.3, 128.2, 127.2, 126.7, 126.6, 126.5 (Ar), 60.2, 54.4, 37.3, 28.4, 25.1, 22.4, 14.0; NMR data in accordance with literature values;[52] **GC-MS** (EI, Pos): **RT** = 14.9 min, $[M\text{-}CH_3]^+$ = 253 *m/z*.

- (*S*)-1-phenyl-*N*-(*R*)-1-phenylethyl-but-3-en-1-amine



Following the procedure for addition of *B*-allyl-9-BBN to (*R*)-*N*-benzylidene-1-phenylethylamine, the pure *S*,*R* diastereoisomer was isolated as light yellow oil (99 mg, 39 % yield). $[\alpha]_D^{20}$ = +3.6 (c = 1.1, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.25-7.12 (m, 10H, Ar), 5.66-5.33 (m, 1H, =CH), 4.98-4-91 (m, 2H, =CH_2), 3.69 (t, 1H, J = 6.6, H-1´), 3.64 (q, 1H, J = 6.6, H-1), 2.37 (bq, 2H, CH_2), 1.53 (s, 1H, NH), 1.25 (d, 3H, J = 6.6, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 146.0, 143.9 (Ar-quat-C), 135.4 (=CH), 128.3, 128.2, 127.1, 126.8, 126.7, 126.5 (Ar), 117.2 (=CH_2), 59.6, 54.5 (CH), 42.1 (CH_2), 22.5 (CH_3); NMR data in accordance with literature values;[50,51] **GC-MS** (EI, Pos): **RT** = 14.4 min, $[M\text{-}CH_3]^+$ = 236 *m/z*.

- (*R*)-1-phenyl-*N*-(*R*)-1-phenylethyl-but-3-en-1-amine



Following the procedure for addition of allylmetal reagents to (*R*)-*N*-Benzylidene-1-phenylethylamine, the *R*,*R* diastereoisomer was isolated in mixture with the *S*,*R* diastereoisomer. The reported ^{1}H NMR signals were deduced from one of the most enriched chromatographic fractions. While ^{13}C NMR signals were deduced from the spectra of the diastereomeric mixture.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27-7.07 (m, 10H, Ar), 5.67-5.48 (m, 1H, =CH), 5.00-4.91 (m, 2H, =CH_2), 3.41 (q, 1H, J = 6.6, H-1), 3.30 (t, 1H, J = 6.9, H-1´), 2.25 (bt, 2H, CH_2), 1.62 (bs, 1H, NH), 1.19 (d, 3H, J = 6.6, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 145.7, 144.2 (Ar-quat), 135.6 (=CH), 128.3, 128.3, 127.2, 126.8, 126.7, 126.5 (Ar), 117.3 (=CH_2), 58.9, 54.8 (CH), 43.3 (CH_2), 24.8 (CH_3); NMR data in accordance with literature values;[51,67] **GC-MS** (EI, Pos): **RT** = 14.2 min, $[M\text{-}CH_3]^+$= 236 *m/z*.

2. Tin-mediated regioselective 6-*O*-glycosylations of unprotected phenyl 1-thio-glycopyranosides

2.1. Introduction

Complex carbohydrates constitute the major class of cell surface molecules and play a crucial role in numerous biological processes such as cell recognition events including cell adhesion, host-pathogen interactions, cancer progression, spermatogenesis, development of the nervous system and serve as protein folding determinants.[68–72]

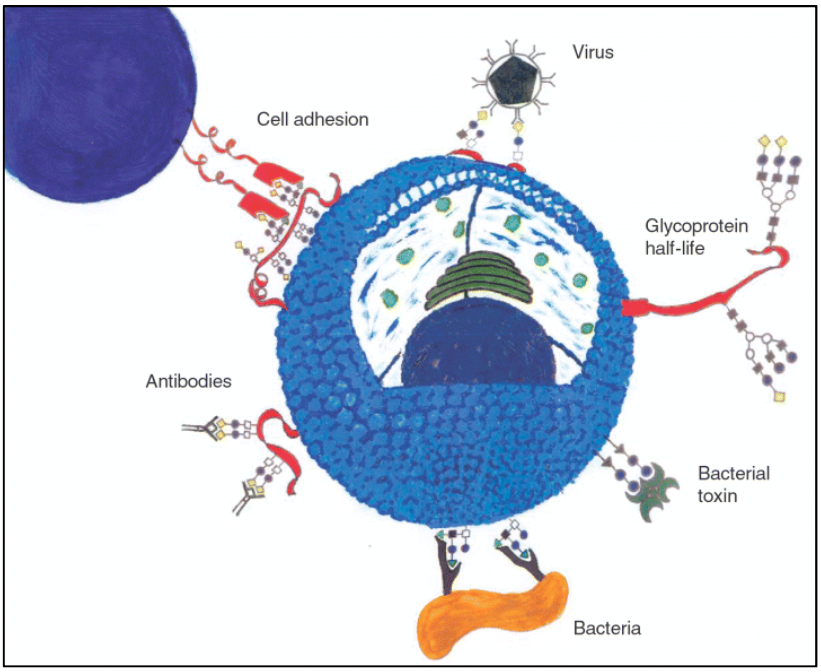


Figure 5. Cell recognition events including cell adhesion and host-pathogen interactions.

The growing interest towards a better understanding of these processes has stimulated a large number of studies in the field of glycobiology and has increased the demand for structurally defined oligosaccharides.[73,74] Due to the fact that complex saccharides are difficult to isolate from natural sources in high purity and sufficient amount; the development of efficient methods for assembling oligosaccharides has become an essential tool for the emerging fields of glycobiology and

glycomics. The assembly of complex glycans can in principle be achieved by following two different strategies: enzymatic and/or chemical synthesis. Enzymatic synthesis can be used for the production of oligosaccharides with absolute regio- and stereoselectivity, but its broad application is often limited by the availability (or costs) of sugar nucleotides, the natural donor molecules of glycosyltransferases and it lacks general flexibility (*i.e.* only natural oligosaccharides with natural linkages can be assembled). Hitherto chemical synthesis is the most powerful and versatile protocol to access complex carbohydrates. In fact, a vast array of glycosylation methods and strategies is available and, as a result, the synthesis of almost any oligosaccharide is virtually possible.[75–80]

However, due to the presence of multiple hydroxyl groups with very similar reactivity, extensive protecting group manipulations are typically required making the assembly of complex oligomers a challenging and time-consuming task.

The so-called "open" glycosylations, in which several hydroxyl groups are left unprotected and in which one hydroxyl group is glycosylated in preference to the others, may offer a solution to this problem in selected cases.[81] For specific substrates the different steric and electronic properties of hydroxyl groups can be directly exploited to perform glycosylations of partially or fully unprotected sugars. This strategy has been used for the synthesis of different oligosaccharides but it requires a case by case optimization.[82–88]

A more general solution to regiochemical control may be to enhance the differences in the reactivity between the hydroxyl groups in carbohydrates. This can be achieved either by activation of the target hydroxyl group or by deactivation of the remaining hydroxyl groups and it has been shown that organo-boron, organo-tin and molybdenum[89] compounds can be exploited to mediate alkylations, esterifications and glycosylations of unprotected sugars.

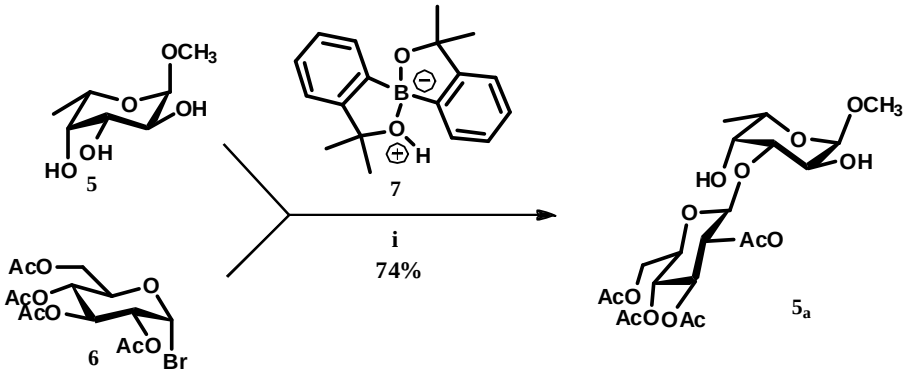
Despite the great potential of these methods only few examples of metal and metalloid mediated glycosylations have been reported over the last twenty years.

2.1.1. Boron mediated glycosylations

It is known that boronic acids are capable to form cyclic boronates with 1,2-*cis*-diols as well as 4,6-diols of hexoses leading to deactivation of the bound oxygen atoms. Thus, they can be utilized as mediators for molecular recognition of carbohydrates. In fact, due to their liability they function as a transient masking rather than a protection for hydroxyl groups. However, in the presence of a base

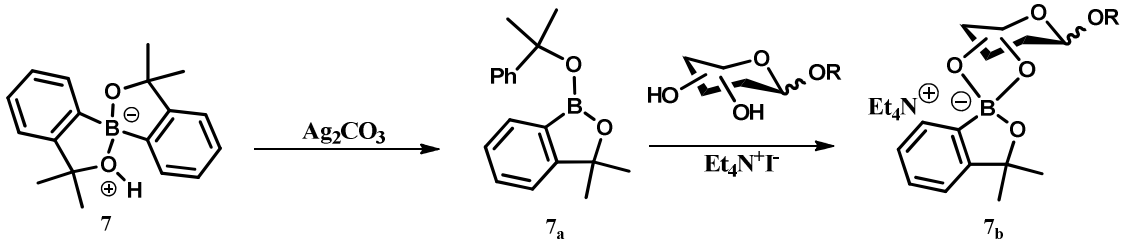
the otherwise inert boron-oxygen bond can be activated leading to reactivity enhancement of the bound oxygen.

Consequently, boronic acids can serve both as activating and deactivating agents.[90–97] Oshima *et al*. have used arylboronic acids as activating agents to perform regiospecific glycosylations of unprotected sugars.[95,98] When methyl α-L-fucoside (**5**) was coupled with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**6**) in the presence of stoichiometric amounts of diarylboronic acid derivative **7**, tetramethylammonium iodide ($Et_4N^+I^-$) and silver carbonate (Ag_2CO_3), the corresponding β(1→3) linked disaccharide was obtained as the sole product (Scheme 18). High regioselectivity was also achieved by using octyl β-D-glucopyranoside (**8**) as the acceptor, where, under the same conditions, exclusively the β(1→6) linked disaccharide was obtained. While using methyl α-D-galactopyranoside (**9**) and methyl α-D-mannopyranoside (**10**) as acceptors, a lower selectivity was observed. In fact, their coupling with donor **6** led to the formation of mixtures of di- and tri-saccharides.



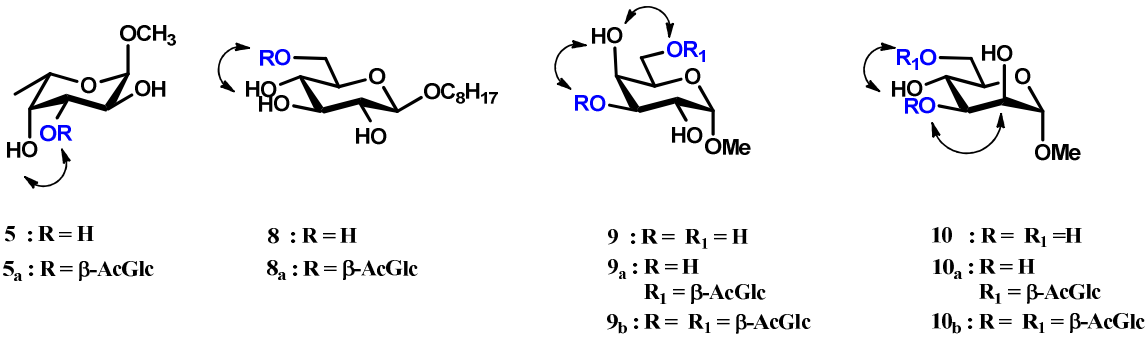
Scheme 18. Regioselective glycosylation of α-L-fucoside **5** *via* arilboronic activation: (i) $Et_4N^+I^-$, Ag_2CO_3, 4Å MS, tetrahydrofuran (THF), 25˚ to 50˚C, 68h.

The observed regioselectivity was explained by considering that in the presence of Ag_2CO_3 the borinate **7** undergoes protonolysis of the boron-carbon bond to give the dimethylbenzyl derivative $\mathbf{7_a}$ which, upon treatment with the acceptor, and in the presence of $Et_4N^+I^-$ undergoes alcohol/sugar exchange to afford the boronate $\mathbf{7_b}$ (Scheme 19).



Scheme 19. Formation of the sugar boronate.

In the case of fucoside **5** the 3,4-boronate complex is formed and the reaction takes place at the less hindered equatorial oxygen. Whereas for glucoside **8**, the boronate is formed at the 4,6-diol leading to glycosylation at the 6-position. The low selectivity observed for mannoside **10** and galactoside **9** is due to the presence of two diol systems able to form a complex with the boron reagent. In the case of the galactoside these are the 3,4- and the 4,6-diols, while in the case of the mannoside these are the 2,3- and the 4,6-diols (Figure 6).



5 : R = H
5a : R = β-AcGlc

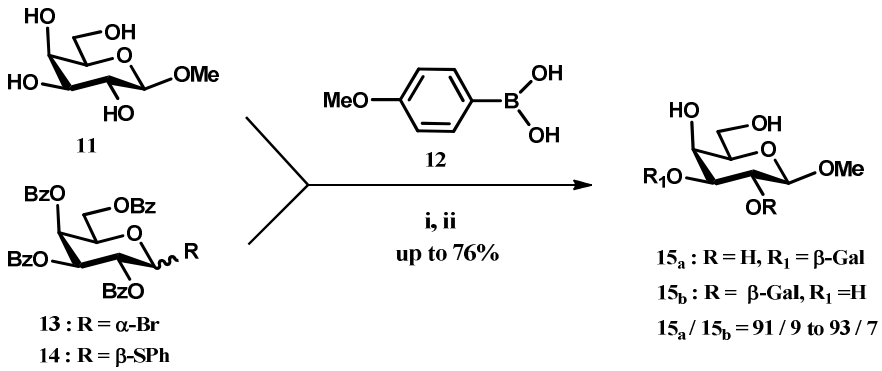
8 : R = H
8a : R = β-AcGlc

9 : R = R_1 = H
9a : R = H, R_1 = β-AcGlc
9b : R = R_1 = β-AcGlc

10 : R = R_1 = H
10a : R = H, R_1 = β-AcGlc
10b : R = R_1 = β-AcGlc

Figure 6. Regioselectivity observed with different acceptors.

As mentioned above boronic acids can also be used to deactivate hydroxyl groups. This was illustrated by Kaji *et al.* for the regioselective glycosylation of different unprotected hexopyranosides with glycosyl bromides and phenyl thioglycoside donors.[96,97] Treatment of methyl β-D-galactopyranoside (**11**) with stoichiometric amounts of *p*-methoxy arylboronic acid **12** followed by the coupling with donors **13** or **14** afforded the corresponding β(1→3)-linked disaccharides as the major products with high regioselectivity (Scheme 20).

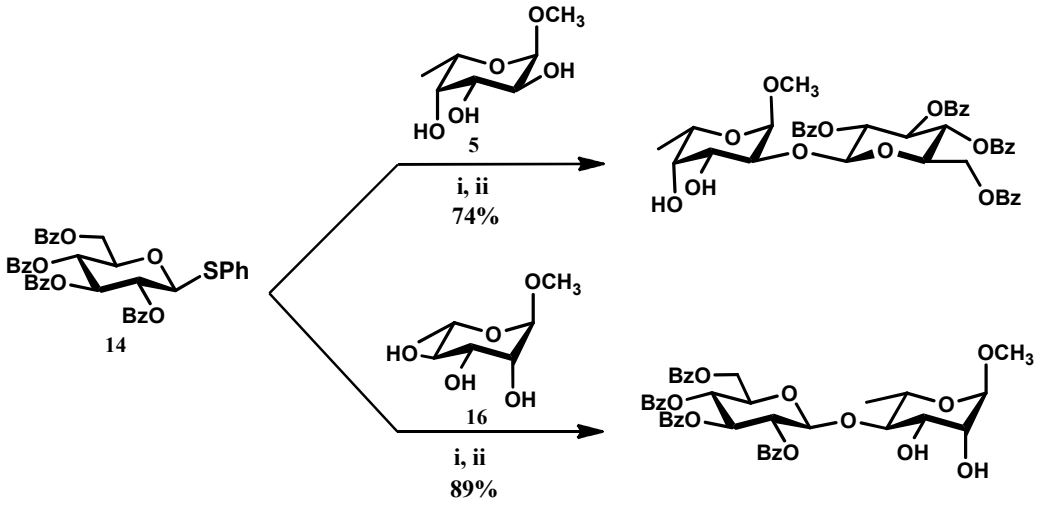


Scheme 20. Glycosylation of galactopyranoside **11** by means of transient masking with **12**: (i) 1,2-DCE : CH_3CN = 1:1, rt, 16h; (ii) Ag(I) silica-allumina, 0˚C, 24h, or NIS / TMSOTf, -30˚C, 2h.

When methyl α-D-galactopyranoside (**9**) was glycosylated under the same conditions lower selectivity was observed. The opposite outcome was achieved for the glycosylation of methyl α-D-glucopyranoside. In fact, in this case the (1→2)-linked disaccharide was obtained in preference to the (1→3)-linked saccharide in a ratio of 7:1. The regioselectivity obtained was explained by considering the formation of a 4,6-boronate intermediate resulting in the masking of the 4,6-hydroxyl groups and leading to glycosylation of the least hindered free hydroxyl group.

The glycosylation of methyl α-L-fucopyranoside (**5**) and methyl α-L-rhamnopyranoside (**16**) with phenyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (**14**) in presence of **12** was also explored (Scheme 21).

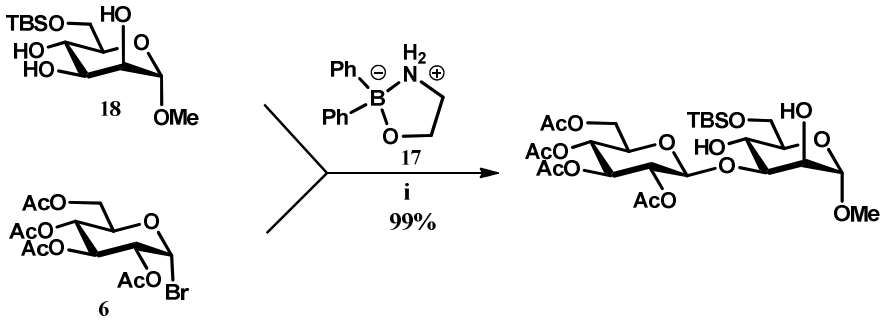
In this case the masking of the *cis*-diol leaves only one hydroxyl group free leading to the formation of the β(1→2)-linked disaccharide in the case of **5** and the β(1→4)-linked disaccharide in the case of **16**.



Scheme 21. Glycosylation of fucopyranoside **5** and rhamnopyranoside **16** by means of transient masking with **12**: (i) arylboronic acid **12**, 1,2-DCE : CH_3CN = 1:1, rt, 16h; (ii) NIS / TMSOTf, -30˚C, 2h.

Borinic acid derivatives are another class of organo boron compounds that has been harnessed for regioselective acylations and glycosylations of carbohydrates. In fact, like boronic acids they are capable of generating adducts with 1,2-*cis*-diols leading to activation of the bound oxygen atoms. Related to this approach Taylor and co-workers have shown that 2-aminoethyl diphenylborinate (**17**) enables the differentiation of secondary hydroxyl groups in a broad range of hexopyranosides. Thus, regioselective acylation and glycosylation of fully unprotected fucosides and rhamnosides as well as of 6-*O* protected mannosides and galactosides have been performed.[99–101]

For instance, the coupling between methyl 6-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranoside (**18**) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**6**) promoted by silver oxide (Ag_2O) in the presence of catalytic amounts of **17** afforded the corresponding β(1-3)-linked disaccharide as sole the product (Scheme 22). The observed regioselectivity was explained to involve the formation of a tetracoordinate borinate adduct with the 1,2-*cis*-diol resulting in the glycosylation of the more reactive equatorial oxygen atom. The advantage of this procedure is that only catalytic amounts of diphenyl borinate ester are needed. On the other end, free primary hydroxyl groups are not tolerated and carbohydrates lacking the 1,2-*cis*-diol motif are not suitable substrates.

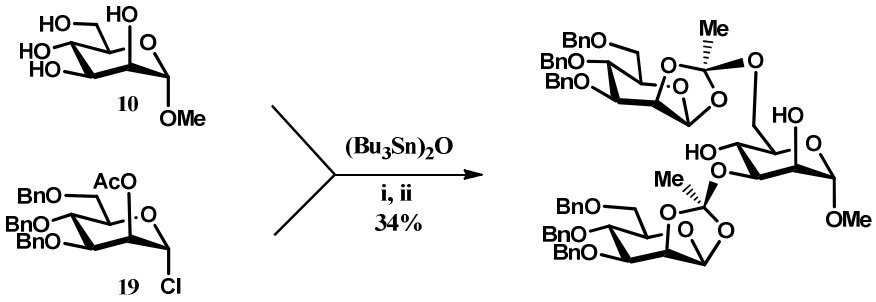


Scheme 22. 3-*O* regioselective glycosylation of mannose derivative **18** promoted by 2-aminoethyl diphenylborinate (**17**): (i) **17** (10 mol%), Ag_2O, CH_3CN, 16h, rt.

2.1.2. Tin mediated glycosylations

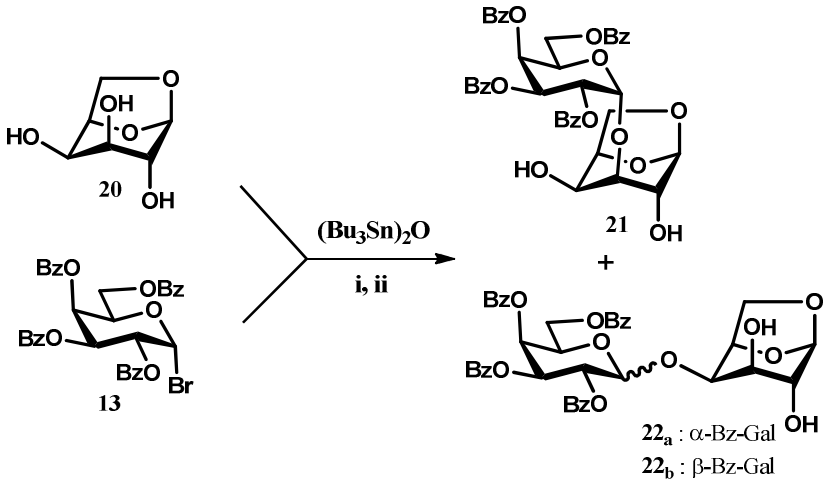
Activation of hydroxyl groups for electrophilic attack can also be achieved by means of organo-tin compounds. Organo-tin derivatives of sugars, such as tributyltin ethers and dibutylstannylene acetals, have been employed as intermediates for regioselective esterifications and alkylations of carbohydrate diols and polyols,[102] as well as in oligosaccharide synthesis.

One of the first accounts regarding the use of organo-tin compounds as mediators in open glycosylations has been given by Ogawa *et al*. who described the regio-controlled activation of the hydroxyl groups of methyl α-D-mannopyranoside (**10**) through tributylstannylation.[103] When **10** was treated with bis(tributyltin)oxide ($(Bu_3Sn)_2O$) in refluxing toluene and then reacted with 2-*O*-acetyl-3,4,6,-tri-*O*-benzyl-α-D-mannopyranosyl chloride (**19**) orthoester formation was observed at the 6-*O* and 3-*O* positions in moderate yield (Scheme 23).



Scheme 23. Glycosylation of **10** *via* $(Bu_3Sn)_2O$ activation: (i) $(Bu_3Sn)_2O$, toluene (reflux), azeotropic removal of water; (ii) donor **19**, toluene, rt.

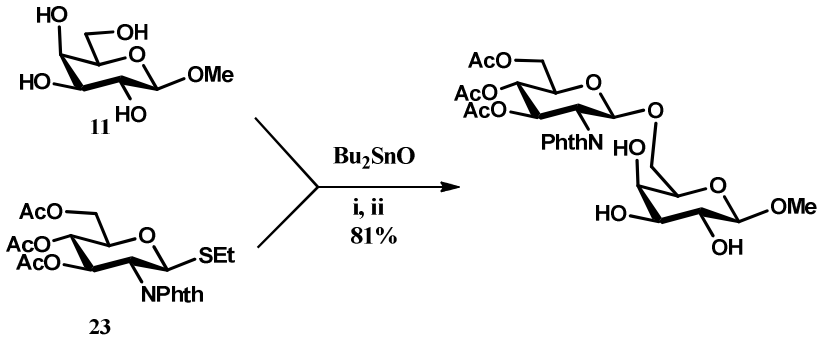
The use of tributyltin ether derivatives of sugars for the synthesis of di- and tri-saccharides has also been reported by Lomas and co-workers. In this case $(Bu_3Sn)_2O$ was investigated as activating agent for the halide assisted glycosylation of 1,6-anhydro-β-D-galactopyranoside (**20**) with 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (**13**) (Scheme 24).[104]



Scheme 24. Glycosylation of **20** *via* $(Bu_3Sn)_2O$ activation: (i) $(Bu_3Sn)_2O$, 4Å MS, toluene, 120˚C, 15h; (ii) donor **13**, $Et_4N^+Br^-$, toluene or CH_2Cl_2, 60˚C or rt, 4 days.

Treatment of **20** with $(Bu_3Sn)_2O$ followed by reaction with donor **13** in the presence of tetraethylammonium bromide ($Et_4N^+Br^-$), afforded a mixture containing the α(1→3)-linked disaccharide **21** and the α/β(1→4)-linked disaccharides $\mathbf{22_a}$ and $\mathbf{22_b}$.

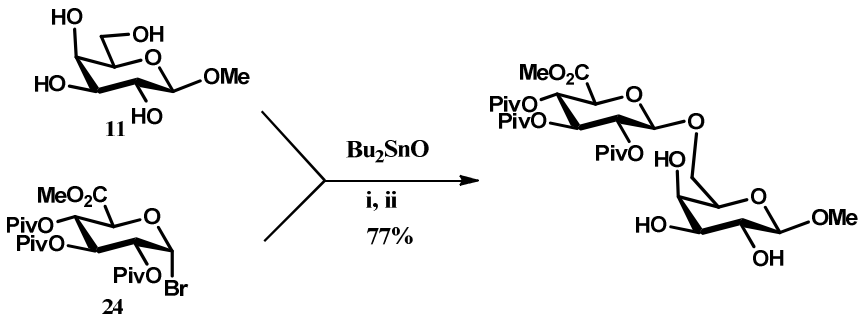
Changes in the solvent and the reaction temperature affected the ratio between the different regio- and stereoisomers. In fact, when the reaction was performed in toluene at 60˚C 14% of **21** and 79% of a 4:1 mixture of disaccharides $\mathbf{22_a}$ and $\mathbf{22_b}$ were obtained. While, when the reaction was carried out in dichloromethane (CH_2Cl_2) at room temperature, 30% of disaccharide **21** and 50% of a 2.5:1 mixture of $\mathbf{22_a}$ and $\mathbf{22_b}$ were formed. The regioselective glycosylation of methyl β-D-lactoside with donor **13** *via* tributyltin ether activation was also attempted. The reaction was performed in toluene under the conditions employed for galactoside **20** and led to the formation of a 4:1 mixture of the α(1→6´)- and the α(1→6)-linked trisaccharides in a considerable yield (74% combined yield).[104]
Higher regioselectivity has been obtained utilizing carbohydrates tin-acetals. They are commonly synthesized by treatment of 1,2-cis diols and 4,6-diols with dibutyltin oxide (Bu_2SnO) in refluxing toluene or methanol.
For instance, Garegg and co-workers have conducted glycosylations of fully unprotected methyl galacto- and glucopyranosides with different thioglycoside and bromide donors via stannylene acetal activation. An illustrative example is given by the glycosylation of methyl β-D-galactopyranoside (**11**) with glucosamine derivative **23**. The reaction afforded exclusively the β(1→6)-linked disaccharide in excellent yields (Scheme 25).[81]



Scheme 25. Glycosylation of **11** *via* Bu_2SnO activation: (i) Bu_2SnO, MeOH, reflux, 2h; (ii) donor **23**, DMTST, 4Å MS, CH_2Cl_2, 0˚C to rt, 10 h.

Another contribution to the use of Bu_2SnO in open glycosylations was given by Kaji and co-workers who investigated the glycosylation of fully unprotected galactosides as well as rhamnosides with glucuronyl bromide donors.[105] When the tin-acetal derivative of galactopyranoside **11** was

coupled with per-*O*-pivaloylated-α-D-glucuronyl bromide (**24**) by means of Ag(I)-silica alumina the corresponding β(1→6)-linked disaccharide was obtained (Scheme 26).

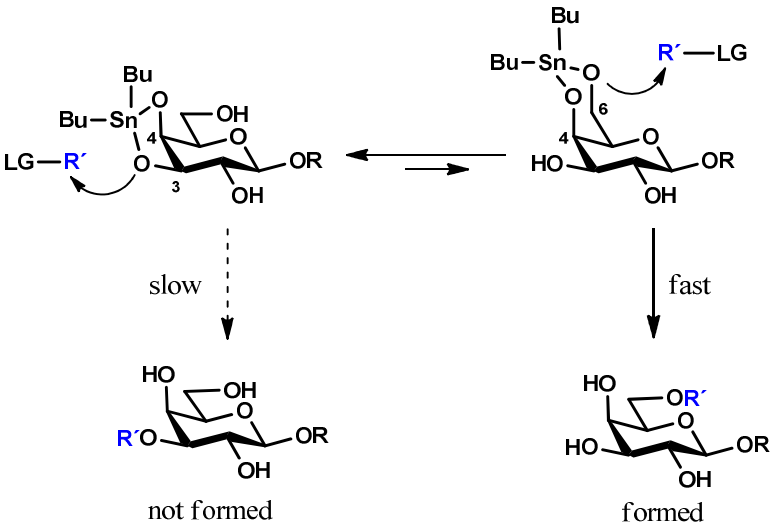


Scheme 26. Glycosylation of **11** *via* Bu_2SnO activation: (i) Bu_2SnO, MeOH, reflux, 3h; (ii) donor **24**, Ag(I)-silica alumina, 3Å MS, CH_2Cl_2, 50°C, 39 h.

Per-*O*-benzoylated-α-D-glucuronyl bromide was also investigated as the donor for the tin-mediated glycosylation of galactoside **11**. The reaction was performed under the same conditions as reported in Scheme 26 to afford, after four days, a 1.6:1 mixture of the β(1→6)-linked disaccharide and the corresponding orthoester in 63% combined yield.

Furthermore, the regioselective coupling between the stannylene acetal of methyl α-L-rhamnopyranoside (**16**) and glucuronyl bromide **24** was achieved to afford the corresponding β(1→3)-linked disaccharide in moderate yield.

It has been hypothesized that the regioselectivity observed for tin-acetal glycosylations could depend on the reactivity of different stannylated structures present in equilibrium (Scheme 27).



Scheme 27. Reactivity of different stannylated structures.

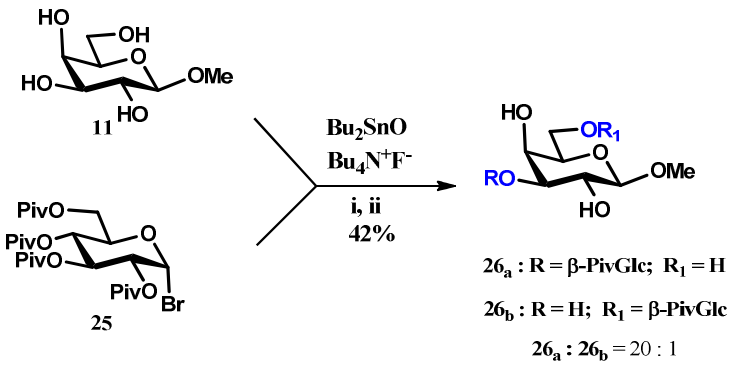
It has been shown that the enhancement of the reactivity of hydroxyl groups in tin mediated reactions depends primarily on the stereochemical arrangement of the hydroxyl groups.[106,107]

For instance, in the case of *galacto*pyranosides and *manno*pyranosides the stannylene acetal formation is most favorable at the *cis-vicinal* glycol to produce a five-membered ring between the axial-equatorial pair, leading to the activation of the equatorial 3-OH.[106] This is true in the case of acylations and alkylations, but not for glycosylation reactions where the 6-OH is the reactive hydroxyl group.

In this regard, it has been observed that dibutylstannylene acetal of lactosides, commonly acylated and allylated at the 3´-*O*-position, upon treatment with *t*-butyldimethylsilyl chloride (TBDMSCl) afforded exclusively the 6´-*O*-TBDMS ether. This result was explained by considering an equilibrium between the major 3´,4´-stannylene acetal and the minor 4´,6´-acetal which is displaced by selective reaction at the most reactive 6´-position (Scheme 27). In fact, TBDMSCl is too bulky to react with the activated 3´-oxygen and reacts instead with the less sterically hindered 6´-oxygen.[108] Plausibly a similar mechanism can also be envisioned in the case of glycosylation reactions.

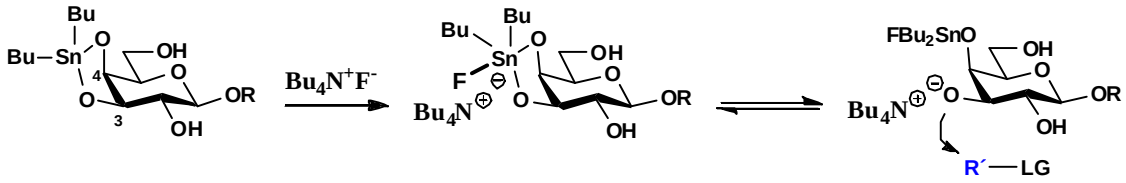
Interestingly, Kaji *et al*. demonstrated that the reactivity of the different stannylated structures can be influenced by addition of a salt such as tetrabutylammonium fluoride ($Bu_4N^+F^-$).[109]

In fact, glycosylation of the tin-acetal derivative of galactopyranoside **11** with per-*O*-pivaloyl-α-D-glucopyranosyl bromide (**25**) in presence of $Bu_4N^+F^-$ afforded a 20:1 mixture of the β-(1→3)- and β-(1→6)-linked dissacharide in 42% combined yield (Scheme 28).



Scheme 28. Regioselectivity shift from β-(1→6)- to β-(1→3)-glycosylation of **11**: (i) Bu_2SnO, MeOH reflux, 3h; (ii) donor **25**, Ag(I)-silica alumina, $Bu_4N^+F^-$, 3Å MS, CH_3CN, 50°C, 24 h.

The shift of regioselectivity was explained considering that, in the presence of a fluoride ion, the major 3,4-stannylene acetal generates a pentacoordinated tin-complex which rearranges to form a reactive alkoxide ion at the 3-position leading to the formation of the (1→3)-linked disaccharide (Scheme 29).



Scheme 29. Mechanism of Bu_2SnO/F^- ion-mediated glycosylation.

2.2. Aim of the project

The possibility to access a large number of structurally defined oligosaccharides is essential for the advance of *glycobiology* and *glycomics*. Even though a vast number of synthetic methods is available, the assembly of complex glycans is still an intricate process and the development of easier and more efficient procedures remains a primary goal. In fact, the major constraint of oligosaccharide synthesis is the extensive use of protecting groups.

In the last two decades several methods that avoid or reduce protecting group manipulations have been developed. These methods exploit the ability of certain metals, such as tin and molybdenum, or metalloids, such as boron, to coordinate diols and enhance the reactivity differences of sugar hydroxyl groups. Particularly, it has been shown that organo-tin compounds can be used to activate specific hydroxyl groups and direct regioselective glycosylations of unprotected monosaccharides.[102–106,108,109] Even though first investigations on tin-mediated open glycosylations have been successful, only a restricted number of substrates have been tested. Therefore more extensive studies are certainly needed to assess the usefulness of this approach.

Herein stannylene-acetal mediated glycosylations are further explored by coupling several fully unprotected phenyl 1-thio-glycopyranoside acceptors with a number of different bromide and thioglycoside donors by means of silver triflate (AgOTf). The promoter system dimethyl disulfide-triflic anhydride is also investigated for the glycosylation of methyl β-D-glucopyranoside (**27**).

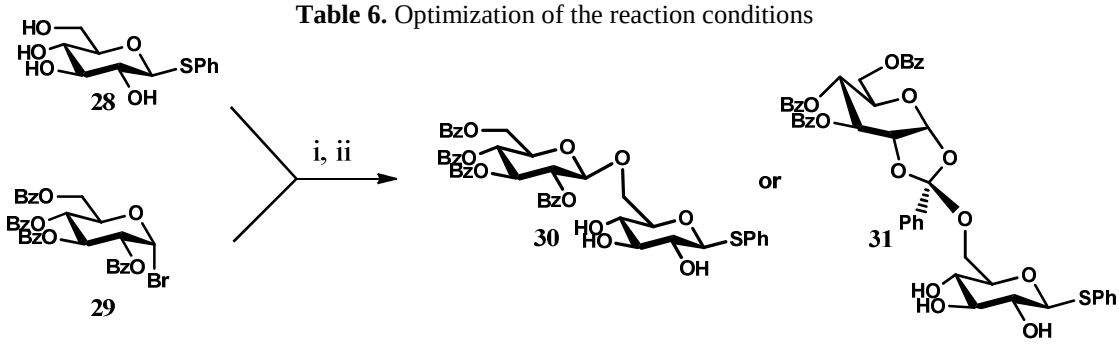
Furthermore the use of bis(acetylacetonato)dioxomolybdenum ($MoO_2(acac)_2$) is examined for the glycosylation of different acceptors.

2.3. Results and discussions

2.3.1. Tin-mediated Koenigs-Knorr glycosylations of unprotected thioglycosides

To the best of our knowledge thioglycosides have never been utilized as acceptors in open glycosylations. Thioglycosides can be easily prepared from per-*O*-acetylated hexopyranoses by treatment with thiols in presence of a hard Lewis acid. Following this procedure the 1,2-*trans* product is predominantly formed as a result of the participation of the acetyl group at the C-2 position.[110] In the absence of a thiophilic agent thioglycosides are very stable. In fact, they can withstand a large range of reaction conditions serving as robust glycosyl acceptors, but at the same time be regioselectively activated to serve as donors. Owing to their versatility and stability we decided to start our investigation with tin-mediated Koenigs-Knorr glycosylations of thioglycosides derived from D-glucose, D-galactose and D-mannose. The reaction conditions were optimized using phenyl 1-thio-β-D-glucopyranoside (**28**) and 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**29**) as test substrates (Table 6).

Table 6. Optimization of the reaction conditions

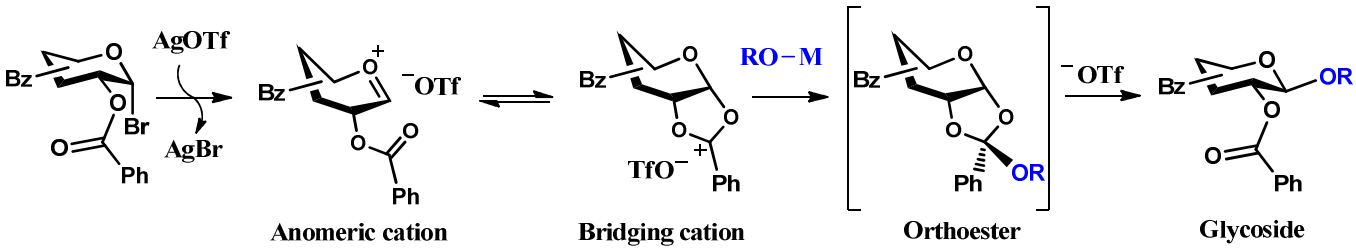


Entry	eq. (D:A)[a]	eq. (P:D)[b]	Additive	Time	Product	Yield[c]
1	1.5	1.5	-	3h[d]	**30**	42%
2	1.5	1.5	*sym*-collidine	3h	**31**	58%
3	1.5	1.5	TMU	3h	several	-
4	1.5	1.5	MS 4Å	6h	**30**	56%
5	1.8	1	MS 4Å	6h	**31**	85%

(i) Acceptor, Bu_2SnO (1.5 eq.), MeOH, reflux, 3h; (ii) Donor, AgOTf, dichloromethane (CH_2Cl_2), −30˚C to −10˚C, Ar atmosphere. [a]Donor:Acceptor Ratio, [b]Promoter:Donor Ratio, [c]Isolated Yield. [d]Longer reaction time (6h) did not improve the yield.

Treatment of **28** with dibutyltin oxide (Bu_2SnO), followed by addition of 1.5 equivalents of donor **29** in the presence of AgOTf led to the formation of the β(1→6) linked disaccharide **30** as the sole product in 42% yield (entry 1). In order to improve the yield a different set of reaction conditions was tested. First, the time was increased from 3 to 6 hours, but no improvement was observed. Then, different additives such as *sym*-collidine, tetramethyl urea (TMU) and molecular sieves (MS) were investigated (Table 1, entries 2-5).

When *sym*-collidine was added to the reaction, orthoester **31** was formed in 58% yield (entry 2). Orthoesters are common by-products of silver-promoted glycosylation reactions, when ester protected glycosyl halides are used as donors. They derive from trapping of the intermediate bridging cation, formed by neighboring group participation, by the nucleophile and it is known that they can rearrange in the presence of triflates to the 1,2-trans-glycosides.[111,112] Hence, this result suggests that during the reaction the orthoester **31** is formed first and successively undergoes a triflate induced rearrangement to glycoside **30** (Scheme 30).[113]



Scheme 30 1,2-trans glycoside formation trough orthoester rearrangement.

When the glycosylation is performed in the presence of *sym*-collidine the triflate, generated during the coupling, is trapped and can no longer induce the rearrangement.

The base 1,1,3,3-tetramethylurea (TMU) was investigated next (entry 3). The use of TMU has been previously reported in Koenigs-Knorr glycosylations with ester-protected glycosyl halides, and it has been shown that 1,2-trans-glycosides were the exclusive products.[114] However, TLC analysis (after three hours) revealed the formation of several products.

An improvement was obtained by carrying out the reaction in presence of MS (entry 4). TLC analysis (after three hours) showed formation of only one product and the presence of trace amounts of unreacted **28**. After six hours no further conversion of the acceptor was observed and thus the

reaction was quenched to afford disaccharide **30** in 58% yield. This improvement can be explained by considering the removal of traces of water, which is released upon tin acetal formation, by the molecular sieves.

A further yield enhancement was obtained by reacting acceptor **28** with 1.8 equivalents of **29** in the presence of molecular sieves (entry 5). In fact, after six hours disaccharide **30** was obtained as the sole product in 85% yield.

In order to determine whether the results obtained are indeed due to tin activation, acceptor **28** was directly coupled with donor **29** in two separate experiments. In the first experiment the coupling was performed under the reaction conditions reported in entry 5. As observed by TLC, almost no reaction occurred and donor decomposition took place. This result could derive from the scarce solubility of the acceptor in the reaction solvent (CH_2Cl_2). Thus, the same experiment was repeated in 1,4-dioxane, a solvent where both donor and acceptor are soluble. After 6h, disaccharide **30** was obtained in only 32% yield, again together with extensive donor decomposition.

These results show that tin complexation increases not only the solubility of the acceptor in CH_2Cl_2 but also its reactivity towards electrophilic attack.

The regioselectivity observed for the glycosylation of phenyl 1-thio-β-D-glucopyranoside (**28**) is in agreement with that observed in previous tin-mediated glycosylations and benzoylations of β-D-glucopyranosides.[81,106] As mentioned in the introduction, the reactivity of the hydroxyl groups in tin-mediated reactions depends primarily on the stereochemical arrangement of the hydroxyl groups.

In the case of *galacto*pyranosides and *manno*pyranosides the stannylene acetal formation is most favorable at the *cis-vicinal* glycol to produce a five-membered ring between the axial-equatorial pair, leading to the activation of the equatorial hydroxyl group. On the contrary, when a *cis-vicinal* glycol system is absent, like in the case of β-D-*gluco*pyranosides, only the most reactive primary hydroxyl group is activated.[106]

With the optimized reaction conditions in place (Table 6, entry 5), our attention turned to other acceptors and donors (Figure 7) in order to investigate the scope of the reaction. Thus, phenyl 1-thio-β-D-glucopyranoside (**28**), phenyl 1-thio-β-D-galactopyranoside (**32**) and phenyl 1-thio-α-D-mannopyranoside (**33**) were coupled with perbenzoylated glucopyranosyl, galactopyranosyl, mannopyranosyl and peracetylated trichloracetamido glucopyranosyl bromide donors (Table 7).

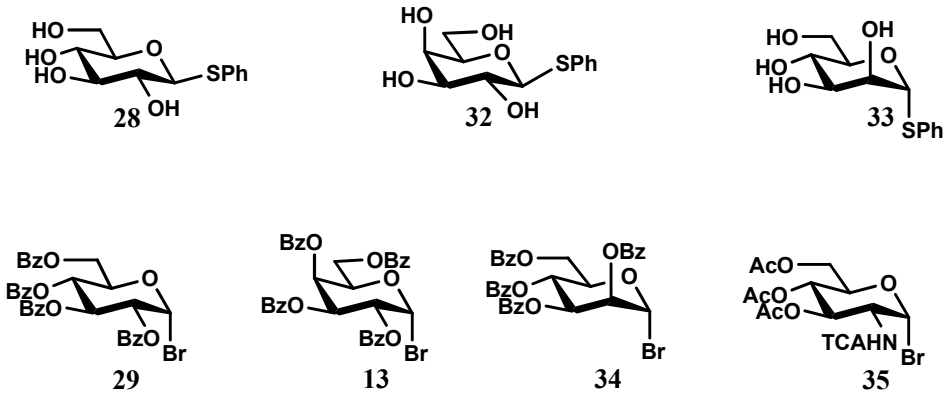
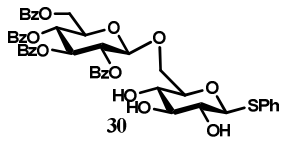
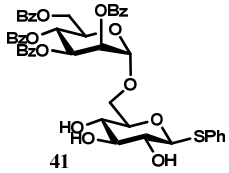
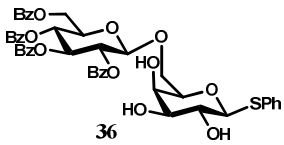
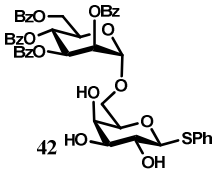
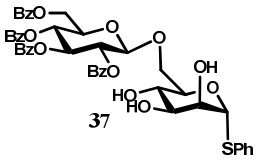
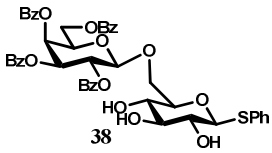
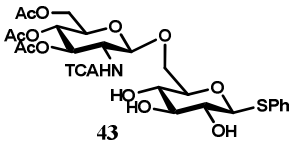
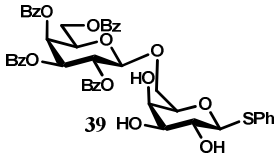
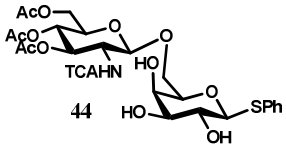
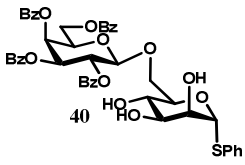
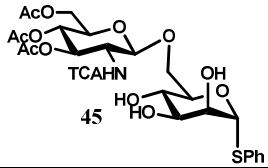


Figure 7. Glycosyl acceptors (**28**, **32**, **33**) and donors (**29**, **13**, **34**, **35**)

The coupling between 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**29**) and acceptors **32** and **33** led to the formation of the corresponding β(1→6) linked disaccharides in 76% and 49% yield, respectively (Table 7, entries 2 and 3). Good yields and high regio- and stereoselectivity were also achieved for the coupling between 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (**13**) with acceptors **28** and **32** (entries 4 and 5), while, in the case of acceptor **33**, a lower yield was obtained (entry 6). 2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**34**) turned out to be an inferior donor under the employed conditions since its coupling with acceptors **28** and **32** afforded disaccharides **41** and **42** in 33% and 23% yield, respectively (entries 7 and 8) whereas, the coupling with acceptor **33** yielded a complex mixture of products (entry 9).

Lastly, 3,4,6,-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-glucopyranosyl bromide (**35**) was investigated for the glycosylation of acceptors **28**, **32** and **33** (entries 10-12). For all three glycosylations a longer reaction time (22 hours) was needed. In fact, TLC analysis after 6 hours showed formation of the desired disaccharides together with two other compounds having a slightly lower polarity. Prolonged treatment led to complete or partial disappearance of the less polar compounds, together with complete consumption of the acceptors to produce disaccharides **43**, **44** and **45** in 52%, 66% and 48% yields. These results could be explained by considering the formation of a mixture containing the oxazoline[115] and orthoester intermediates which slowly react to afford the 1,2-trans-glycoside.

Table 7. Tin mediated Koenigs-Knorr Glycosylations of Unprotected Thiophenyl Pyranosides[a]

Entry	Acceptor	Donor	Product	Yield[b]	Entry	Acceptor	Donor	Product	Yield[b]
1	**28**	**29**	 **30**	85%	7	**28**	**34**	 **41**	33%
2	**32**	**29**	 **36**	76%	8	**32**	**34**	 **42**	23%
3	**33**	**29**	 **37**	49%	9	**33**	**34**	mixture	-
4	**28**	**13**	 **38**	71%	10[c]	**28**	**35**	 **43**	52%
5	**32**	**13**	 **39**	62%	11[c]	**32**	**35**	 **44**	66%
6	**33**	**13**	 **40**	38%	12[c]	**33**	**35**	 **45**	48%

[a](i) Acceptor (0.5 mmol), Bu_2SnO (0.75 mmol), MeOH, reflux, 3h; (ii) Donor (0.9 mmol), AgOTf (0.9 mmol), 4Å MS, CH_2Cl_2, -30˚ to 10˚ C, Ar atmosphere, 6h. [b]Isolated Yield. [c]Reaction time 22h.

The structures of the disaccharides were unequivocally elucidated by ^1H, ^{13}C spectroscopy and mass spectrometry. The position of the interglycosidic linkages was defined by considering the deshielding effect of the ^{13}C-chemical shift.[109] In fact, for all disaccharides the C-6 carbon atoms resonate at a considerably lower magnetic field (between 69.2 and 68.6 ppm), as compared with those of the non-glycosylated acceptors (between 62.7 and 61.2 ppm). Further confirmation was

obtained by HMBC analysis. For all the disaccharides an HMBC correlation between the acceptor H-6 protons and the donor anomeric carbon was observed.

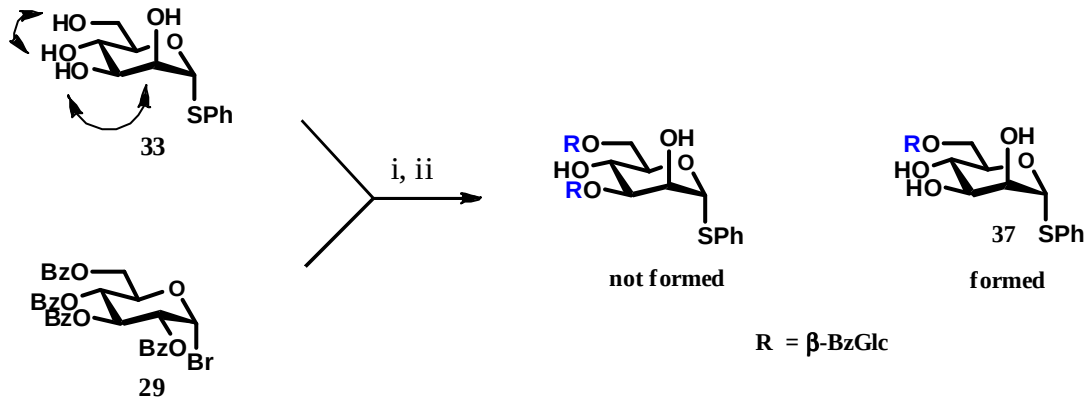
Generally the anomeric configurations of the disaccharides were determined considering the size of the $^{3}J_{H}$ coupling constants between the H-1´ and the H-2´. While in the case of disaccharides **41** and **42** the anomeric configurations were determined from the $^{1}J_{CH}$ coupling constants of the anomeric carbons. The $J_{C\text{-}1',H\text{-}1'}$ were measured to be 173.2 Hz for disaccharide **41** and 171.7 Hz for disaccharide **42**, revealing formation of the α-anomers. In fact, it has been observed that the $^{1}J_{CH}$ values for α-glycosides are around 170 Hz.[116]

All the glycosylations explored led to the formation of the (1→6) linked disaccharide as the sole product. As described in the introduction (see pg. 55-56), in the case of phenyl 1-thio-β-D-galactopyranoside (**32**) and phenyl 1-thio-α-D-mannopyranoside (**33**) the regioselectivity obtained may depend on the reactivity of different stannylated structures present in equilibrium. According to this hypothesis 4,6-*O*-stannylated galactoside and mannoside present in equilibria would react faster than the 3,4-*O*- and 2,3-*O*-stannylated galactoside and mannoside to give the (1→6) linked disaccharide.

2.3.2. Towards the synthesis of trisaccharides

After the successful synthesis of several disaccharides it was decided to extend the investigation to the synthesis of trisaccharides. In a first attempt we explored the possibility to perform a one-pot trisaccharide synthesis by using as acceptor mannoside **33**. In fact, due to the presence of two diol systems (the 2,3- and 4,6-diols) able to form an acetal with tin, treatment of mannoside **33** with twofold excess of Bu_2SnO followed by coupling with a glycoside donor should result in the glycosylation of the 3- and 6-OH groups.

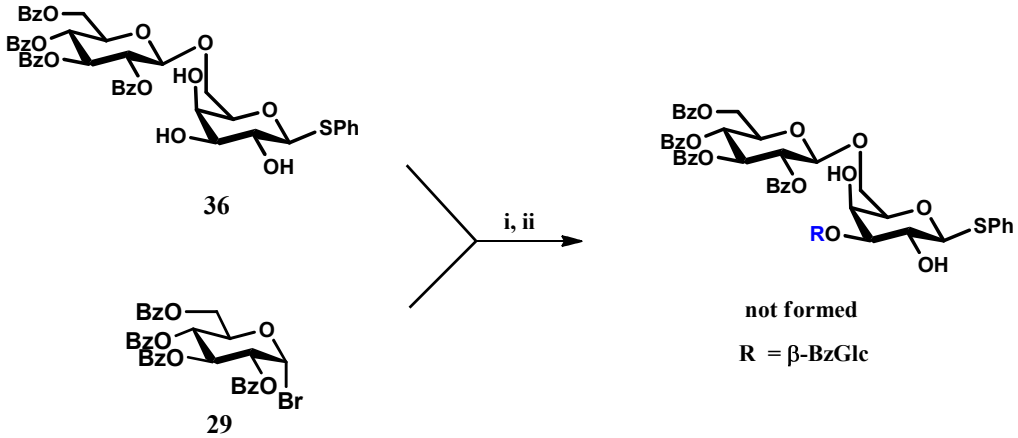
However, when mannoside **33** was treated with 2.5 equivalents on Bu_2SnO and subsequently coupled under standard reaction conditions with 3.5 equivalents of glucosyl bromide **29**, disaccharide **37**, and not the trisaccharide, formed in 36% yield after 24 hours (Scheme 31). A similar result was obtained also coupling **33** with galactoside donor **13**.



Scheme 31. (i) Acceptor, Bu_2SnO (2.5 eq.), MeOH, reflux, 3h; (ii) Donor (3.5 eq.), AgOTf, dichloromethane (CH_2Cl_2), –30˚C to r.t., Ar atmosphere, 24 h.

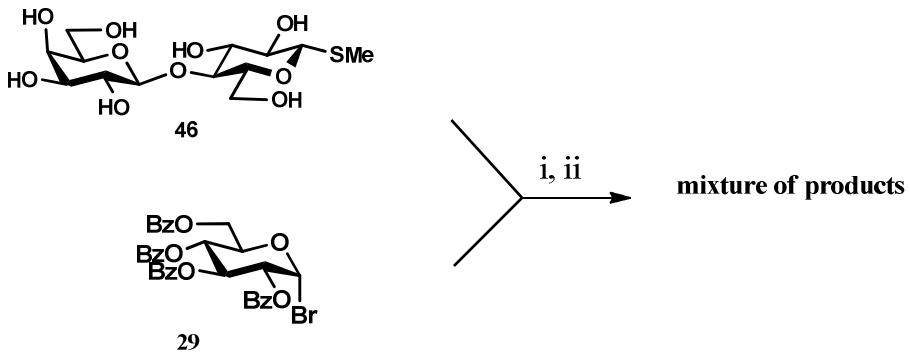
Since the one-pot attempt was not successful in our hands, we next investigated the possibility to use disaccharides as acceptors.

To this end, disaccharide **36** was coupled with glucosyl bromide **29** in two different experiments. In the first experiment the acceptor was directly coupled with the donor under Koenigs-Knorr conditions but no reaction took place, even after an extended reaction time of 24 hours. Thus, the same experiment was repeated by generating the acceptor tin acetal prior to the coupling with the donor. Also in this case no product formation was observed after 24 hours (Scheme 32).



Scheme 32. Method A: (i) AgOTf, dichloromethane (CH_2Cl_2), –30˚C to r.t., Ar atmosphere, 24 h; Method B: (i) Acceptor, Bu_2SnO (2.5 eq.), MeOH, reflux, 3h; (ii) Donor, AgOTf, dichloromethane (CH_2Cl_2), –30˚C to r.t., Ar atmosphere, 24 h.

Yet another approach was examined entailing the use of thiomethyl lactoside **46** as acceptor. Though, when the tin acetal derivative of lactoside **46** was reacted with donor **29** under standard reaction conditions, a complex mixture of products was obtained.



Scheme 33. (i) Acceptor, Bu_2SnO (2.5 eq.), MeOH, reflux, 3h; (ii) Donor, AgOTf, dichloromethane (CH_2Cl_2), –30˚C to r.t., Ar atmosphere, 6 h.

2.3.3. Tin-mediated glycosylation of methyl β-D-glucopyranoside(**27**) with thio-donor **47**

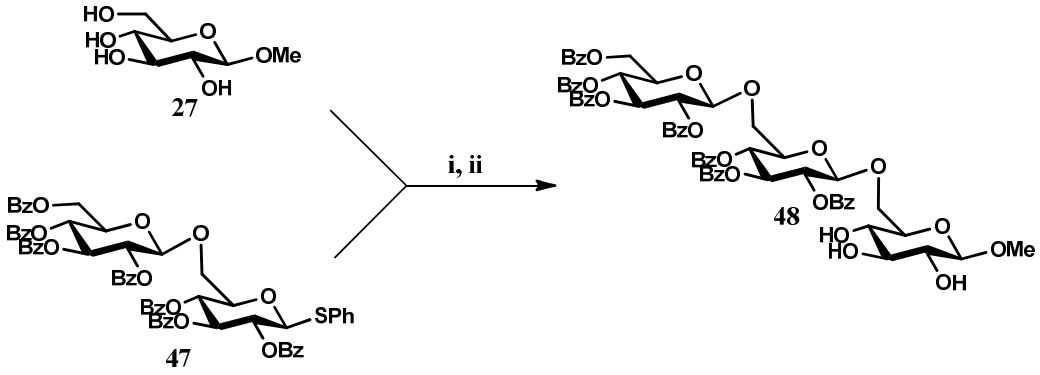
Given that any attempt to synthesize trisaccharides from fully or partially unprotected disaccharide acceptors *via* tin acetal activation failed, it was decided to explore the use of disaccharides as donors.

To this end it was studied whether disaccharide **30** could be directly activated and used as donor for the glycosylation of glucopyranoside **27** (Table 8). Several methods are currently available for the direct activation of thioglycosides. Promoters broadly used include iodonium ions sources such as *N*-iodosuccinimide-triethylsilyl triflate (NIS-TESOTf) and iodonium dicollidine perchlorate (IDCP)[117], methyl triflate (MeOTf)[118], organosulfur compounds such as dimethyl(methylthio)sulfonium triflate (DMTST)[119], diphenyl sulfoxide-triflic anhydride (Ph_2SO-Tf_2O)[120] and dimethyl disulfide-triflic anhydride (Me_2S_2-Tf_2O)[121].

In a first attempt, the perbenzoylated derivative of disaccharide **30** (disaccharide **47**) was coupled with the tin acetal of **27** using NIS-TESOTf as the promoter. However the reaction did not yield the desired trisaccharide but acceptor silylation was observed (Table 8, entry 1).

Recently Fügedi and co-workers have shown that dimethyldisulfide (Me_2S_2) can react with triflic anhydride (Tf_2O) to generate a product similar to DMTST but more reactive since one of the methyl groups would be replaced by the strongly electron-withdrawing trifluoromethanesulfonyl group. In fact, it was reported that when various disarmed thioglycoside donors were coupled with different glycosyl acceptors in the presence of Me_2S_2-Tf_2O oligosaccharides were obtained in high yields.[121] Therefore we decided to examine Me_2S-Tf_2O for the activation of disaccharide **47**. The advantage offered by Me_2S-Tf_2O, compared to promoters like MeOTf and DMTST, is that the use of highly toxic reagents is avoided.

Table 8. Glycosylation of methyl β-D-glucopyranoside with disaccharide **47**



Entry	Promoter	Method	Time	Product	Yield[a]
1	NIS-TESOTf	A	2 h	Silylated Acceptor	-
2	Me_2S_2-Tf_2O	B	3 days	**48**	5%
3[b]	Me_2S_2-Tf_2O	C	1 h	**48**	35%

(i) Acceptor (0.25 mmol), Bu_2SnO (0.37 mmol), MeOH, reflux, 3h; (ii) Method A: Donor (0.37 mmol), acceptor tin-acetal (0.25 mmol), NIS (0.41 mmol), TESOTf (0.074 mmol), 4Å MS, CH_2Cl_2, -30˚C, Ar atmosphere; Method B: Donor (0.37 mmol), acceptor tin-acetal (0.25 mmol), Me_2S_2-Tf_2O (0.39 mmol); CH_2Cl_2, -30˚C, Ar atmosphere, 3 days; Method C: Donor (0.37 mmol) was treated with Me_2S_2-Tf_2O (0.39 mmol) for 10 min, then reacted with acceptor tin-acetal (0.25 mmol) under the conditions described in method B. [a]Isolated yields; [b]longer preactivation and reaction times did not improve the yield.

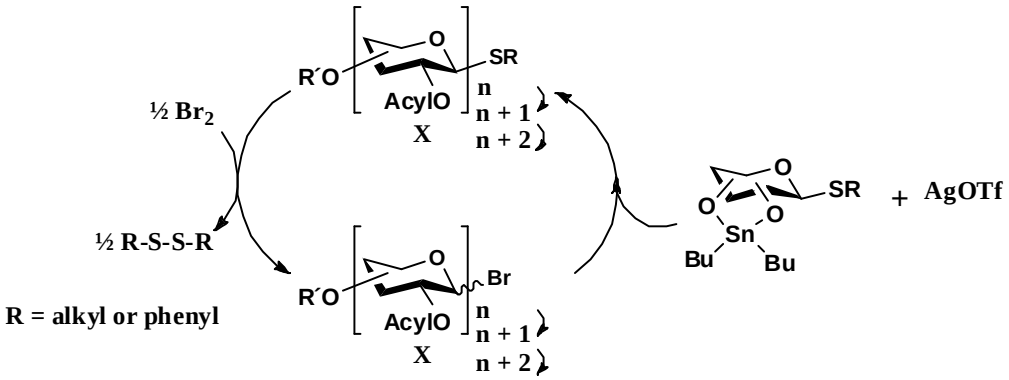
Initially, the coupling was carried out by mixing donor **47** and the stannylene derivative of acceptor **27** together with Me_2S-Tf_2O at -40˚C. This afforded trisaccharide **48** in only 5% yield after three days (Table 8 entry 2). The low yield could derive from tin acetal decomposition. In fact, after three days the presence of a considerable amount of unreacted acceptor was detected by TLC. Thus, a different protocol was attempted entailing the pre-mixing of donor **47** with Me_2S_2-Tf_2O for ten minutes and subsequent addition of the acceptor. This led to complete consumption of **27** and formation of trisaccharide **48** as the sole product in 35% yield after one hour.

Albeit a considerable improvement was obtained, the yield was still not considered fully satisfactory. Therefore the reaction was repeated prolonging both the pre-activation time (from 10 min to 1 h) and the reaction time (from 1 h to 2 h) but a similar yield was obtained.

2.3.4. Tin-mediated glycosylation with perbenzoylated and peracetylated thioglycoside in the presence of bromine

The coupling between thioglycoside **47** and the tin-acetal of methyl glucoside **27** by means of Me_2S-Tf_2O gave the desired product with absolute regio- and stereoselectivity, though only in moderate yield (35%). The low yield obtained could derive from stannylene acetal decomposition due to the harsh reaction conditions. In order to improve the yield it was decided to activate donor **47** following another approach.

It is well known that thioglycosides can be easily converted into glycosyl chlorides or bromides by treatment with chlorine or bromine, and that the obtained glycosyl halide can be further activated with a halophilic reagent.[122–124] The general advantage of this strategy is that a thioglycoside can principally be used as acceptor enabling an iterative oligosaccharide synthesis (Scheme 34).[125,126]

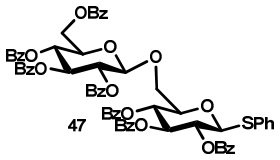
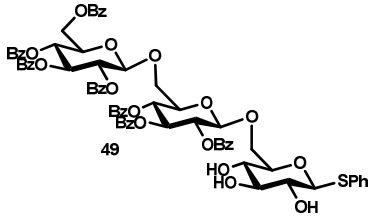
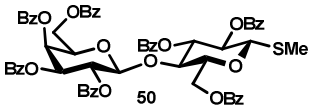
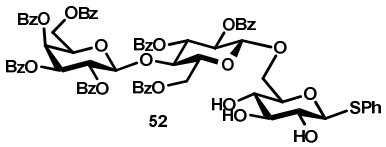
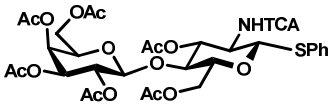
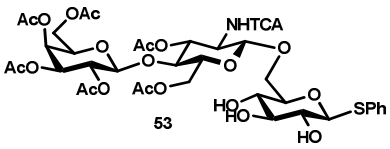


Scheme 34 Iterative oligosaccharide synthesis.[126]

Hence, thioglycoside **47** was first treated with 0.5 equivalents of Br_2 and subsequently coupled with phenyl 1-thio-β-D-glucopyranoside (**28**), by means of AgOTf. The reaction afforded trisaccharide **49** in 40% yield after six hours (Table 3, entry 1).

The same experiment was also performed with disaccharides **50** and **51** to afford trisaccharides **52** and **53** in 46% and 57% yield, respectively (entries 2 and 3). In all the reaction the presence of small amounts of byproducts were observed by TLC but were not further characterized.

Table 9. Iterative tin-mediated glycosylation[a]

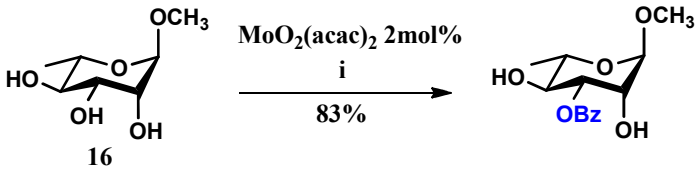
Entry	Acceptor	Donor	Product	Yield[b]
1	**28**	 47	 49	40%
2	**28**	 50	 52	46%
3	**28**	 51	 53	57%

[a](i) Acceptor (0.25 mmol), Bu_2SnO (0.37 mmol), MeOH, reflux, 3h; (ii) Donor (0.5 mmol), Br_2 (0.25 mmol), Ar atmosphere, CH_2Cl_2; (iii) Bromide donor (0.5 mmol), acceptor tin acetal (0.25 mmol), AgOTf (0.5 mmol), 4Å MS, CH_2Cl_2, -40˚ to 10˚C, Ar atmosphere, 6h. [b]Isolated Yield.

As in the case of the disaccharides the structures of the trisaccharides were elucidated by ^1H, ^{13}C spectroscopy and mass spectrometry. The position of the interglycosidic linkages was defined considering the deshielding effect of the ^{13}C-chemical shift[109] and confirmed by HMBC analysis.

2.3.5. Exploring the glycosylation of fully unprotected thioglycosides in presence of $MoO_2(acac)_2$

Very recently Evtushenko has shown that $MoO_2(acac)_2$ can mediate the regioselective benzoylation of different glycopyranosides containing *cis-vicinal* hydroxyl groups.[89] In fact, reaction between methyl α-L-rhamnopyranoside (**16**) and benzoyl chloride in presence of catalytic amounts of $MoO_2(acac)_2$ led to benzoylation of the 3-*O*-hydroxyl position with very high regioselectivity (Scheme 35).



Scheme 35 $MoO_2(acac)_2$ mediated benzoylation of rhamnopyranoside **16**; (i) BzCl, *sym*-collidine, 1,4-dioxane or CH_3CN, rt, 6h.

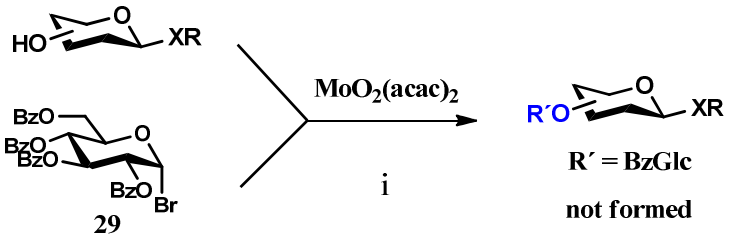
Highly regioselective 3-*O*-benzoylations were also obtained in the case of fucopyranosides and 6-*O*-protected galactopyranosides. In contrast to these results methyl β-D-xylopyranoside did not react under the conditions reported in Scheme 35, indicating that *trans* vicinal hydroxyl groups do not form intermediate complexes with molybdenum.

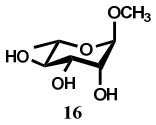
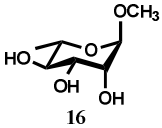
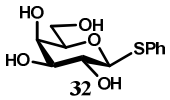
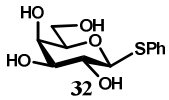
Considering these results, it was decided to explore the possibility of using $MoO_2(acac)_2$ to mediate open glycosylations of fully unprotected rhamosides and galactosides (Table 10).

We started our investigation with the AgOTf-promoted glycosylation of methyl α-L-rhamnopyranoside (**16**) with 2,3,4,6-tetra-*O*-benzoyl-glycopyranosyl bromide (**29**) in presence of a catalytic amount of $MoO_2(acac)_2$. As shown in table 10 entry 1, after 24 hours only donor decomposition was observed. Addition of *sym*-collidine did not change the outcome of the reaction (entry 2).

The same result was also obtained in the case of phenyl 1-thio-β-D-galactopyranoside (**32**) (entry 3). Thus, it was decided to increase the molybdenum loading and to perform the coupling between acceptor **32** and donor **29** in presence of a stoichiometric amount of $MoO_2(acac)_2$. Once again the reaction did not yield the desired product but only donor decomposition.

Table 10. Exploring Molybdenum-Mediated Glycosylations



Entry	Acceptor	$MoO_2(acac)_2$ eq.	Additive	Product
1	 16	0.04	-	n.d.
2	 16	0.04	*sym*-collidine	n.d.
3	 32	0.04	*sym*-collidine	n.d.
4	 32	1	*sym*-collidine	n.d.

(i) Acceptor (0.5 mmol), donor (0.75 mmol), AgOTf (1.12), $MoO_2(acac)_2$, *sym*-collidine (1.12 mmol), CH_3CN, from 0˚C to rt, 24h.

From these results we can conclude that, even though $MoO_2(acac)_2$ seems to be a good catalyst for benzoylations of unprotected sugars, it is not able to mediate open Koenigs-Knorr glycosylations.

2.3.6. Conclusions

In summary the investigation led to a notable improvement and expansion of the regioselective glycosylation of fully unprotected glycoside acceptors via tin activation, and comprised application to a number of attractive structural targets. Tin-mediated Koenigs-Knorr glycosylations of phenyl 1-thio-β-D-glucopyranoside (**28**), phenyl 1-thio-β-D-galactopyranoside (**32**) and phenyl 1-thio-α-D-mannopyranoside (**33**) with different bromide donors afforded the corresponding (1→6) linked disaccharides in good to moderate yields. The disaccharides obtained from the first coupling can be activated as donors for subsequent tin mediated glycosylation reactions, as illustrated in the case of disaccharide **30**. Lactoside derivative **50** and lactosamine derivative **51** were also explored as donors. This method gives easy access to a number of useful di- and trisaccharide building blocks for oligosaccharide synthesis.

In addition $MoO_2(acac)_2$ was also explored as mediator for the glycosylation of α-L-rhamnopyranoside **16** and galactopyranoside **32** with glucosyl bromide **29**. These experiments did not lead to the formation of coupled products showing that $MoO_2(acac)_2$ does not mediate open Koenigs-Knorr glycosylations.

2.4 Experimental Section

2.4.1. General Methods

Chemicals were obtained from Aldrich and ABCR. All reactions were performed under argon (Ar) atmosphere. Molecular sieves (MS) (3 and 4 Å) were flame dried before use. Dichloromethane (CH_2Cl_2) was dried over 3Å MS. Methanol (MeOH) was treated with metallic sodium and, after distillation, dried over 3Å MS. Traces of water from silver triflate (AgOTf) were removed by evaporation with toluene. Phenyl 1-thio-*β*-D-glucopyranoside (**28**)[127], phenyl 1-thio-*β*-D-galactopyranoside (**32**)[128], phenyl 1-thio-*α*-D-mannopyranoside (**33**)[129], methyl 1-thio-lactoside (**46**)[130], 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**29**)[131], 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (**13**)[132], 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**34**)[133], 3,4,6, tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-glucopyranosyl bromide (**35**)[115] and phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-acetyl-2-deoxy-1-thio-2-trichloroacetamido-β-D-glucopyranoside (**51**)[134] were synthesized according to literature procedures. Methyl *β*-D-glucopyranoside (**27**) was purchased from Aldrich and used without further purification.

Thin layer chromatography (TLC) was performed on aluminum plates, percolated with silica gel (Merck 25, 20 X 20 cm, 60 F_{254}). Detection was carried out by UV and by dipping in 20% solution of sulfuric acid in ethanol followed by heating. Flash column chromatography was performed using silica gel (pore size 60 Å, 40-63 μm, Merck).

^1H and ^{13}C NMR spectra were recorded using a Varian Mercury 300 MHz or Varian Unity Inova-500 MHz. Chemical shifts (δ) are reported in ppm, using the residual solvent signal in $CDCl_3$ (δ_H 7.26, δ_C 77.0) or TMS as reference, and coupling constant (J) are given in Hz. Assignment of ^1H and ^{13}C resonances were based on COSY, HSQC and HMBC experiments.

LC-MS analyses were performed on a Waters AQUITY UPLC system equipped with PDA and SQD electrospray MS detector using a thermo accucore C-18 column (2.6μm, 2.1 x 50mm; column temp: 50º C; flow rate: 0.6 mL/min). Eluents A (5mM NH_4Ac in H_2O) and B (5mM NH_4Ac in CH_3CN:H_2O 95:5) were used in a linear gradient (5% B to 100% B) in a total run time of 5 min.

HRMS analyses were performed on a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with Lock Mass probe and operating in positive electrospray mode. Optical rotations were

measured on a Perkin-Elmer 241 polarimeter. Melting points were measured on a Stuart SMP30 apparatus.

2.4.2. Experimental procedures

- Method A: Tin mediated glycosylation with perbenzoylated and peracetylated glycosyl bromide

A suspension of unprotected phenyl 1-thio-hexopyranoside acceptor (0.5 mmol) and dibutyltin oxide (Bu_2SnO) (0.75 mmol) in MeOH (3.0 mL) was refluxed until a clear solution was obtained (3 h). The solvent was evaporated in *vacuo* to give the stannylene derivative as white foam.
The bromide donor (0.9 mmol) and 4Å MS (500 mg) were added to a solution of the stannylene derivative in CH_2Cl_2 (5 mL). The suspension was stirred at -30˚C for 30 min. At this point AgOTf (0.9 mmol) was added and the mixture was stirred in the dark letting the temperature reach 10˚C. After six hours the mixture was filtered, diluted with CH_2Cl_2, washed once with HCl (2 M solution), once with saturated aqueous $NaHCO_3$ and once with water. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by silica-gel column chromatography (toluene : acetone 8:2 → 6:4) to afford the pure disaccharide.

- Method B: Tin mediated glycosylation with perbenzoylated thioglycoside

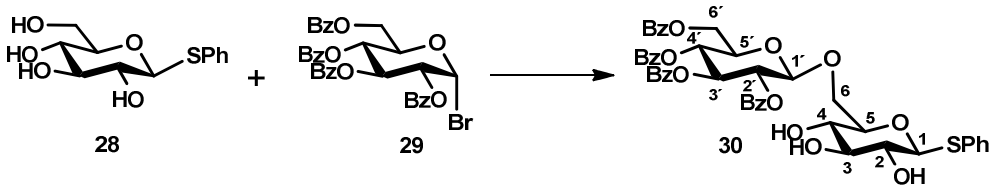
A 1 M solution of Me_2S_2-Tf_2O (1.12 mmol, 1.12 mL, prepared following a reported procedure[121]) in CH_2Cl_2 was added to a suspension of the thioglycoside donor (0.75 mmol) and 4Å MS (1.0 g) in CH_2Cl_2 (2 mL). The mixture was stirred for ten minutes at -40˚C.
At this point the stannylene derivative of the acceptor (0.5 mmol, prepared like reported in method A) was dissolved in CH_2Cl_2 (3 mL) and added *via* syringe to the activated donor at -40˚C. The reaction mixture was stirred for one hour letting the temperature reach -10˚C, quenched by addition of excess triethylamine (9 mmol), diluted with CH_2Cl_2, filtered and sequentially washed with 2M aqueous HCl, saturated aqueous $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$ and concentrated in *vacuo.* The residue was subjected to silica-gel column chromatography (toluene : acetone 8:2 → 6:4) to afford the pure trisaccharide.

- Method C: Tin mediated glycosylation with perbenzoylated and peracetylated thioglycoside in the presence of bromine (Br_2)

Thioglycoside donor (0.5 mmol) was dissolved in CH_2Cl_2 (2 mL) and a 1 M solution of Br_2 in CH_2Cl_2 (0.25 mmol, 0.25 mL) was added at room temperature. The orange solution was stirred in the dark at room temperature until it turned yellow (from 1h to 16h). At this point the solution, containing the donor, was added *via* syringe at -40˚C to a suspension of the stannylene derivative of the acceptor (0.25 mmol, prepared like reported in method A), AgOTf (0.75 mmol) and 4Å MS (250 mg). The mixture was stirred for six hours in the dark letting the temperature reach 10˚C. Then solid were filtered off, and the mixture was first diluted with CH_2Cl_2 and sequentially washed with HCl (2 M solution), saturated aqueous $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by silica-gel column chromatography (toluene : acetone 8:2 → 6:4) to afford the pure trisaccharide.

2.4.3. Characterization data

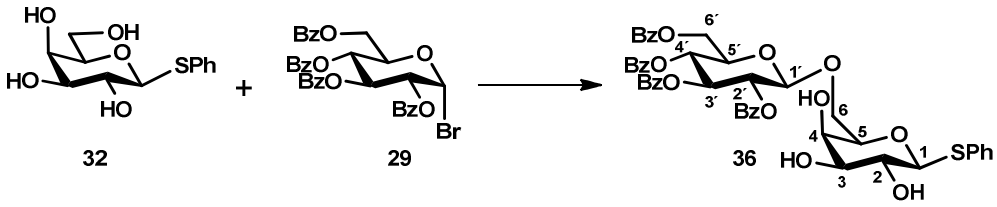
- Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (**30**)



The coupling between **28**[127] and **29**[131] was performed according to method A to afford disaccharide **30** as a white foam (362 mg, yield 85 %). **[α]** $^{25}_{D}$ = + 9.5 (c = 0.8, $CHCl_3$); $\mathbf{R_f}$ = 0.4 (CH_2Cl_2 : MeOH 9:1); ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.94-7.15 (25H, m, Ar), 5.79 (1H, t, J =9.6, H-3´), 5.61 (1H, t, J =9.6, H-4´), 5.44 (1H, t, J = 9.6, H-2´), 4.87 (1H, d, J =7.9, H-1´), 4.61 (1H, dd, J = 12.3, J = 3.0, H-6_a´), 4.39-4.31 (2H, m, H-1, H-6_b´), 4.05-3.95 (2H, m, 5´, H-6_a), 3.79 (1H, dd, J = 11.5, J = 3.0, H-6_b), 3.42-3.29 (3H, m, H-2, H-3, H-4), 3.19 (1H, bt, H-5); ^{13}**C NMR** (75 MHz, $CDCl_3$): 166.3, 165.7, 165.5, 165.1 (4 × C=O), 133-127 (Ar), 101.2 (C-1´), 87.6 (C-1), 78.8 (C-5), 77.6 (C-4), 72.7 (C-3´), 72.1, 71.9 (C-2, C-3), 71.8 (C-5´), 70.3 (C-2´), 69.5 (C-6), 69.2 (C-4´), 62.7

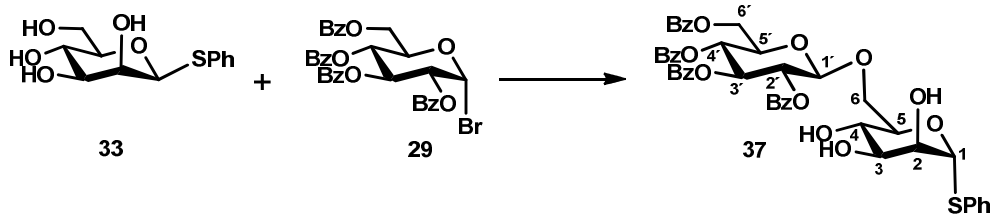
(C-6´); **LC-MS** (ESI, pos): **RT =** 3.61 min; m/z = 868.4 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{46}H_{42}O_{14}S$ $[M + Na]^+$ = 873.2187, found = 873.2177.

- Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-β-D-galactopyranoside (**36**)



The coupling between **32**[128] and **29**[131] was performed according to method A to afford disaccharide **36** as a white foam (326 mg, yield 76 %). **[α]** $^{25}_{D}$ = + 5.1 (c = 0.7, $CHCl_3$); $\mathbf{R_f}$ = 0.4 (CH_2Cl_2 : MeOH 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.99-7.19 (25H, m, Ar), 5.80 (1H, t, J = 9.6, H-3´), 5.61 (1H, t, J = 9.6, H-4´), 5.41 (1H, dd, J = 8.1, J = 9.6, H-2´), 4.86 (1H, d, J = 8.1, H-1´), 4.72 (1H, dd, J = 12.3, J = 3.3, H-6_a´), 4.37-4.29 (2H, m, H-6_b´, H-1), 4.07-4.01 (1H, m, H-5´), 3.98-3.50 (1H, m, H-6_a), 3.91-3.85 (2H, m, H-4, H-3), 3.60-3.50 (2H, m, H-5, H-2), 3.40 (1H, dd, J = 9, J = 3.6, H-6_b); **^{13}C NMR** (75 MHz, $CDCl_3$): 166.4, 165.7, 165.2, 165.1(4 × C=O), 133.5-127.8 (Ar), 101.1 (C-1´), 88.5 (C-1), 77.1 (C-5), 74.3 (C-3), 72.7 (C-5´), 72.4 (C-3´), 71.6 (C-2´), 69.9 (C-4´), 69.2 (C-2), 68.0 (C-4), 67.8 (C-6), 62.4 (C-6´); **LC-MS** (ESI, pos): **RT =** 3.63 min; m/z = 868.4 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{46}H_{42}O_{14}S$ $[M + Na]^+$ = 873.2187, found = 873.2185.

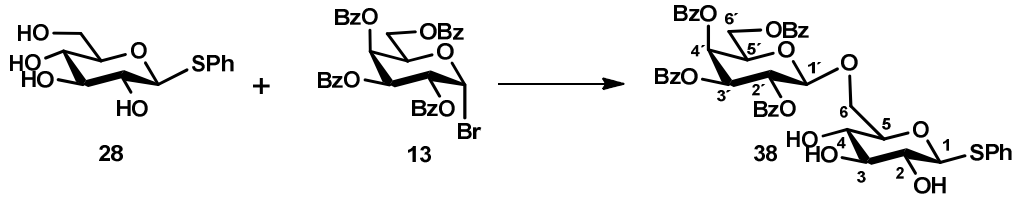
- Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-α-D-mannopyranoside (**37**)



The coupling between **33**[129] and **29**[131] was performed according to method A to afford disaccharide **37** as an amorphous solid (209 mg, yield 49%). **[α]** $^{25}_{D}$ = + 104 (c = 0.5, $CHCl_3$); $\mathbf{R_f}$ = 0.4 (CH_2Cl_2 : MeOH 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 8.03-7.24 (25H, m, Ar), 5.82 (1H, t, J = 9, H-3´), 5.60 (1H, t, J = 9, H-4´), 5.48 (1H, bd, H-2´), 5.42 (1H, bs, H-1), 4.85 (1H, d, J = 8, H-1´),

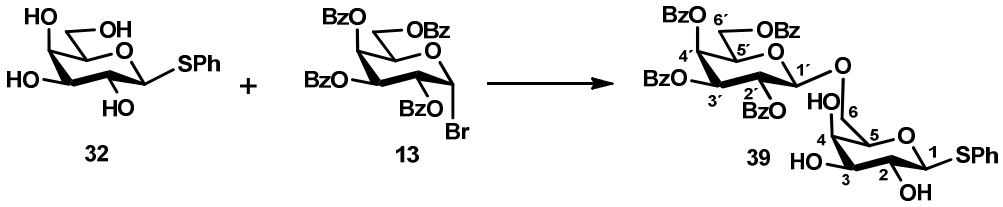
4.58 (1H, dd, J = 12, J = 4, H-6_a´), 4.36 (1H, dd, J = 12, J = 6, H-6_b´), 4.11-4.03 (5H, bm), 3.89 (1H, dd, J = 11.1, J = 5, H-6_b), 3.69-3.63 (2H, m); **^{13}C NMR** (75 MHz, $CDCl_3$): 166.3, 165.7, 165.4, 165.1 (4 × C=O), 133-127 (Ar), 101.0 (C-1´), 87.7 (C-1), 72.6 (C-3´), 72.2 (C-2´), 72.0, 71.9, 71.9, 71.9, 69.4 (C-5´), 69.0 (C-6), 68.3 (C-5), 62.8 (C-6´); **LC-MS** (ESI, pos): **RT =** 3.65 min; m/z = 868.4 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{46}H_{42}O_{14}S$ $[M + Na]^+$ = 873.2187, found = 873.2197.

- Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (**38**)



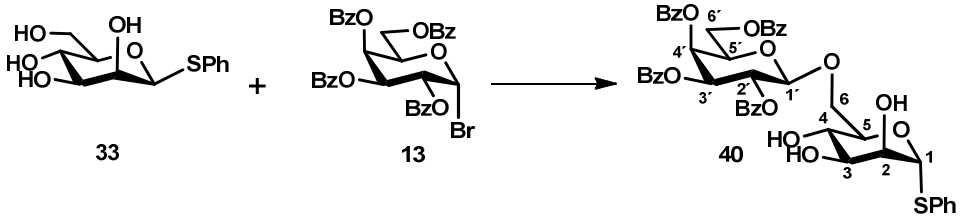
The coupling between **28**[127] and **13**[132] was performed according to method A to afford disaccharide **38** as a glassy solid (303 mg, yield 71%). **[α] $^{25}_{D}$ =** + 37.8 (c = 1, $CHCl_3$); **R_f =** 0.4 (CH_2Cl_2 : MeOH 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 8.00-7.12 (25H, Ar), 5.92 (1H, bs, H-4´), 5.84-5.78 (1H, m, H-2´), 5.52 (1H, dd, J = 10, J = 3, H-3´), 4.86 (1H, d, J = 7.8, H-1´), 4.58 (1H, dd, J = 11.4, J = 6.6, H-$6´_a$), 4.37-4.31 (2H, m, H-$6´_b$, H-1), 4.22-4.10 (2H, m, H-6_a, H-5´), 3.84 (1H, dd, J = 11, J = 6, H-6_b), 3.39-3.30 (3H, m, H-2, H-3, H-5), 3.17 (1H, bt, H-5); **^{13}C NMR** (75 MHz, $CDCl_3$): 166.1, 165.5, 165.4, 165.4 (4 × C=O), 133-128 (Ar), 101.6 (C-1´), 87.8 (C-1), 78.5 (C-5), 77.5 (C-4), 71.6 (C-5´), 71.5, 70.4, 71.4 (C-3´), 69.7 (C-2´), 69.3 (C-6), 68.0 (C-4´), 61.9 (C-6´); **LC-MS** (ESI, pos): **RT =** 3.56 min; m/z = 868.4 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{46}H_{42}O_{14}S$ $[M + Na]^+$ = 873.2187, found = 873.2184.

- Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-1-thio-β-D-galactopyranoside (**39**)



The coupling between **32**[128] and **13**[132] was performed according to method A to afford disaccharide **39** as a glassy solid (266 mg, yield 62 %). **[α]** $^{25}_{D}$ = + 54.2 (c = 0.9, $CHCl_3$); **R_f** = 0.5 (CH_2Cl_2 : MeOH 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.98-7.13 (25H, Ar), 5.91 (1H, d, J = 3.3, H-4´), 5.73-5.67 (1H, m, H-2´), 5.50 (1H, dd, J = 10, J = 3.3, H-3´), 4.86 (1H, d, J = 8.1, H-1´), 4.56 (1H, dd, J = 11.4, J = 6.6, H-6´$_a$), 4.41-4.33 (2H, m, H-6´$_b$ and H-1), 4.22 (1H, t, J = 6.6, H-5´), 4.03-3.92 (1H, m, H-6$_a$), 3.88 (1H, bs, H-6$_b$), 3.60-3.53 (2H, m, H-5 and H-4), 3.42-3.05 (2H, m, H-3 and H-2); **^{13}C NMR** (75 MHz, $CDCl_3$): 166.1, 165.5, 165.4, 165.3 (4 × C=O), 133.6-127.9 (Ar), 101.5 (C-1´), 88.5 (C-1), 74.2 (C-2), 74.2 (C-3), 71.5 (C-3´), 71.5 (C-5´), 69.8 (C-5), 69.6 (C-2´), 68.5 (C-6), 68.2 (C-4), 68.1 (C-4´), 61.9 (C-6´); **LC-MS** (ESI, pos): **RT** = 3.58 min; m/z = 868.4 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{46}H_{42}O_{14}S$ $[M + Na]^+$ = 873.2187, found = 873.2187.

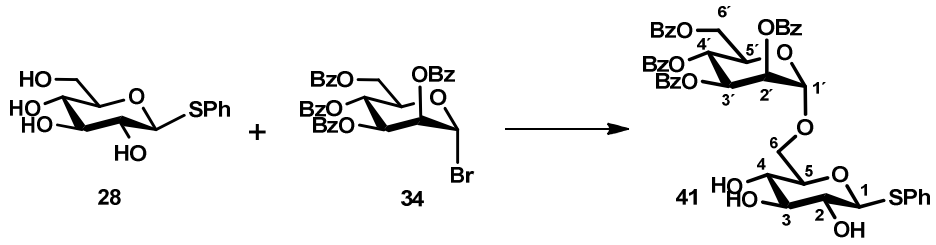
- Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→6)-1-thio-α-D-mannopyranoside (**40**)



The coupling between **33**[129] and **13**[132] was performed according to method A (reaction temperature -70˚C to 10˚) to afford disaccharide **40** as a glassy solid (162 mg, yield 38 %). **[α]** $^{25}_{D}$ = + 120.4 (c = 1, $CHCl_3$); **R_f** = 0.5 (CH_2Cl_2 : MeOH 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 8.00-7.13 (25H, m, Ar), 5.91 (1H, d, J = 3.3, H-4´), 5.73 (1H, m, H-2´), 5.56 (1H, dd, J = 10.8, J = 3.6, H-3´), 5.45 (1H, d, J = 1.2, H-1), 4.83 (1H, d, J = 7.2, H-1´), 4.59 (1H, dd, J = 11.4, J = 6.3, H-6´$_a$), 4.33 (1H, dd, J = 11.4, J = 5.7, H-6´$_b$), 4.26-4.20 (1H, bt, H-5´), 4.15-4.02 (3H, m), 3.92 (1H, dd, J = 12.0, J = 4.2, H-6), 3.66-3.56 (2H, m), 2.63 (3H, bs, 3 × -OH); **^{13}C NMR** (75 MHz, $CDCl_3$): 166.1,

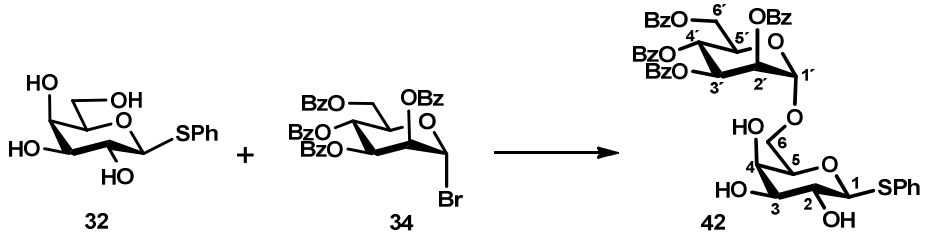
165.6, 165.5, 165.4 (4 × C=O), 133.7-127.4 (Ar), 102.2 (C-1´), 87.8 (C-1), 72.0 (C-3), 71.9, 71.7 (C-5´), 71.5, 71.2 (C-3´), 69.9 (C-2´), 69.4 (C-6), 68.3, 68.0 (C-4´), 61.9 (C-6´); **LC-MS** (ESI, pos): **RT =** 3.56 min; m/z = 868.4 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{46}H_{42}O_{14}S$ $[M + Na]^+$ = 873.2187, found = 873.2191.

- Phenyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (**41**)



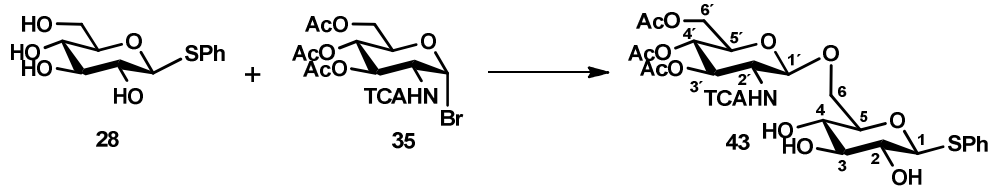
The coupling between **28**[127] and **34**[133] was performed according to method A to afford disaccharide **41** as a white foam (140 mg, yield 33 %). **[α]** $^{25}{}_{D}$ = - 35.9 (c = 1, $CHCl_3$); $\mathbf{R_f}$ = 0.4 (CH_2Cl_2 : MeOH 9:1); ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.10-7.00 (m, 25H, Ar), 6.06 (1H, t, J = 10.2, H-4´), 5.85 (1H, dd, J = 9.6, J = 2.7, H-3´), 5.71 (1H, bs, H-2´), 5.05 (1H, s, H-1´), 4.64-4.49 (m, 3H, H-1, H-5´, H-6_a´), 4.34 (1H, dd, J = 12.6, J = 3.6, H-6_b´), 3.91 (2H, bs, H-6_a, H-6_b), 3.64-3.58 (2H, m, H-3, H-5), 3.54-3.48 (1H, bd, H-4), 3.45-3.37 (1H, m, H-2); ^{13}**C NMR** (75 MHz, $CDCl_3$): 166.2, 165.7, 166.4, 166.3 (4 × C=O), 133.4-127.7 (Ar), 97.4 (J_{C-H} = 173.2, C-1´), 88.2 (J_{C-H} = 156.0, C-1), 78.4 (C-5), 78.1 (C-3), 72.1 (C-2), 70.4 (C-3´), 70.2 (C-4), 70.1 (C-2´), 68.7 (C-5´), 67.2 (C-6), 66.5 (C-4´), 62.6 (C-6´); **LC-MS** (ESI, pos): **RT =** 3.66 min; m/z = 868.4 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{46}H_{42}O_{14}S$ $[M + Na]^+$ = 873.2187, found = 873.2202.

- Phenyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl-(1→6)-1-thio-β-D-galactopyranoside (**42**)



The coupling between **32**[128] and **34**[133] was performed according to method A to afford disaccharide **42** as a white foam (97 mg, yield 23 %). **[α]** $^{25}{}_{D}$ = - 26.5 (c = 0.9, $CHCl_3$); $\mathbf{R_f}$ = 0.3 (CH_2Cl_2 : MeOH 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 8.12-7.15 (m, 25H, Ar), 6.06 (1H, t, J = 9.9, H-3´), 5.85 (1H, dd, J = 10.0, J = 3.0), 5.68 (1H, bs), 5.08 (1H, s, H-1´), 4.64-4.52 (3H, m, H-1, H-6_a´, H-6_a), 4.30 (1H, dd, J = 12.0, J = 4.5, H-6_b´), 4.18-4.15 (1H, m), 4.01 (1H, bs, H-6_b), 3.89-3.85 (1H, m), 3.78 (1H, dd, J = 10.5, J = 5.0), 3.69-3.63 (2H, m); **^{13}C NMR** (75 MHz, $CDCl_3$): 166.2, 165.6, 165.4, 165.3 (4 × C=O), 133.8-128.3 (Ar), 97.4 ($J_{C\text{-}H}$ = 171.7, C-1´), 89.4 ($J_{C\text{-}H}$ = 154.5, C-1), 76.8, 74.7, 70.3, 70.2, 69.8, 68.9 (C-6), 68.7, 67.3, 66.4, 62.6 (C-6´); **LC-MS** (ESI, pos): **RT** = 3.58 min; m/z = 868.4 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{46}H_{42}O_{14}S$ $[M + Na]^+$ = 873.2187, found = 873.2192.

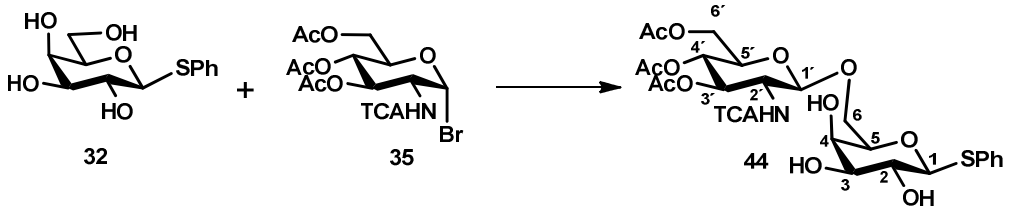
- Phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-trichloroacetamido-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (**43**)



The coupling between **28**[127] and **35**[115] was performed according to method A and stopped after 24 h to afford disaccharide **43** as a white solid (183 mg, yield 52 %). **[α]** $^{25}{}_{D}$ = - 29.3 (c = 0.9, $CHCl_3$); $\mathbf{R_f}$ = 0.3 (CH_2Cl_2 : MeOH 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.54-7.50 (2H, m, Ar), 7.34-7.32 (3H, m, Ar), 7.07 (1H, d, J = 9.3, -NH), 5.28 (1H, t, J = 10.2, H-3´), 5.11 (1H, t, J = 9.9, H-4´), 4.77 (1H, d, J = 8.4, H-1´), 4.50 (1H, d, J = 9.6, H-1), 4.27-4.15 (2H, m, H-6_a´, H-6_b´), 4.10-4.06 (1H, m, H-6_a), 4.03-3.97 (1H, m, H-2´), 3.82 (1H, dd, J = 12.0, J = 5.4, H-6_b), 3.74-3.67 (1H, m, H-5´), 3.57-3.45 (3H, m, H-3, H-5, H-4), 3.31 (1H, t, J=9.9, H-2), 2.08, 2.05, 2.03 (9H, s, 3 × -CH_3); **^{13}C NMR**

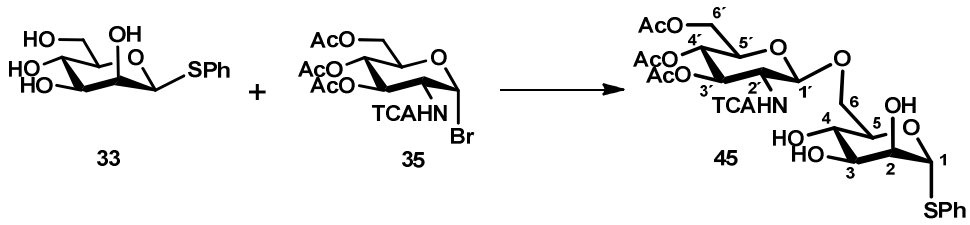
(75 MHz, $CDCl_3$): 171.0, 170.8, 169.49 (3 × C=O), 162.0 (-NH-C=O), 132.7-128.3 (Ar), 100.7 (C-1´), 92.1 (-CCl_3), 87.8 (C-1), 78.7, 77.6, 71.9 (C-5´), 71.7 (C-3´), 71.6 (C-2), 69.8, 68.9 (C-6), 68.3 (C-4´), 61.8 (C-6´), 55.8 (C-2´), 20.8, 20.6, 20.5 (3 × -CH_3); **LC-MS** (ESI, pos): **RT =** 2.42 min; m/z = 722.2 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{26}H_{32}Cl_3NO_{13}S$ $[M + Na]^+$ = 726.0552, found = 726.0556.

- Phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-trichloroacetamido-β-D-glucopyranosyl-(1→6)-1-thio-β-D galactopyranoside (**44**)



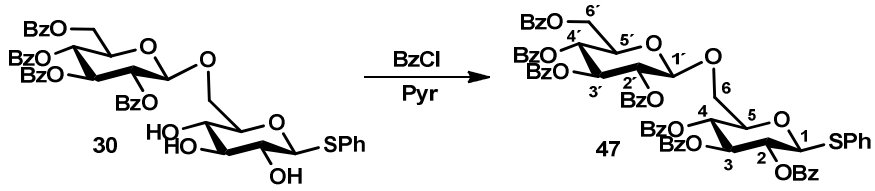
The coupling between **32**[128] and **35**[115] was performed according to method A and stopped after 24 h to afford disaccharide **44** as a white solid (230 mg, yield 66 %). **[α]** $^{25}_{D}$ = - 21.8 (c = 0.01, $CHCl_3$); $\mathbf{R_f}$ = 0.3 (CH_2Cl_2 : MeOH 9:1); ^{1}**H NMR** (300 MHz, $CDCl_3$): 7.52-7.49 (2H, m, Ar), 7.34-7.29 (3H, m, Ar), 6.95 (1H, d, J = 9.3, -NH), 5.24 (1H, t, J = 10.5, H-3´), 5.08 (1H, t, J = 9.9, H-4´), 4.74 (1H, d, J = 7.8, H-1´), 4.52 (1H, d, J = 9.9, H-1), 4.26-4.15 (2H, bm, H-6_a´, H-6_b´), 4.00-3.94 (3H, bm, H-2´), 3.90-3.85 (1H, bm, H-6), 3.75-3.59 (7H, bm, H-5´, H-2), 2.07, 2.04, 2.01 (9H, s, 3 × -CH_3); ^{13}**C NMR** (75 MHz, $CDCl_3$): 171.0, 170.8, 169.5 (3 × C=O), 162.3 (-HN-C=O), 132.7, 132.0, 129.2, 128.1 (Ar), 100.6 (C-1´), 92.1 (-CCl_3), 88.8 (C-1), 77.5, 74.4, 71.9, 71.6 (C-3´), 69.8 (C-5´), 68.7, 68.4 (C-6), 68.3 (C-4´), 61.8 (C-6´), 55.7 (C-2´), 20.8, 20.6, 20.5 (3 × -CH_3); **LC-MS** (ESI, pos): **RT =** 2.40 min; m/z = 722.2 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{26}H_{32}Cl_3NO_{13}S$ $[M + Na]^+$ = 726.0552, found = 726.0540.

- Phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-trichloroacetamido-β-D-glucopyranosyl-(1→6)-1-thio-α-D mannopyranoside (**45**)



The coupling between **33**[129] and **35**[115] was performed according to method A and stopped after 24 h to afford disaccharide **45** as a white solid (170 mg, yield 48 %). **[α]** $^{25}_{D}$ = + 63.2 (c = 0.9, $CHCl_3$); $\mathbf{R_f}$ = 0.3 (CH_2Cl_2 : MeOH 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.38-7.35 (2H, m, Ar), 7.26-7.19 (4H, m, Ar, -NH), 5.49 (1H, s, H-1), 5.23 (1H, t, J = 9.3, H-3´), 5.04 (1H, t, J = 9.6, H-4´), 4.74 (1H, d, J = 9, H-1´), 4.21-4.07 (4H, m, H-6_a´, H-6_b´, H-4, -OH), 4.01-3.82 (3H, m, H-2´, H-6_a, H-6_b), 3.80-3.65 (3H, bm, H-5´, H-2, -OH), 3.63-3.40 (3H, m, H-5, H-3, -OH), 2.00, 1.97, 1.95 (9H, s, 3 × -CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): 170.9, 170.8, 169.4 (3 × C=O), 162.5 (-NH-C=O), 133.7, 131.0, 129.2, 127.5 (Ar), 100.8 (C-1´), 92.2 (-CCl_3), 87.8 (C-1), 72.0 (C-5´), 71.9 (C-5), 71.9, 71.5, 71.5 (C-3´), 68.8 (C-6), 68.3 (C-4´), 68.0, 61.8 (C-6´), 55.8 (C-2´), 21.0, 20.9, 20.8 (3 × -CH_3); **LC-MS** (ESI, pos): **RT** = 2.47 min; m/z = 722.2 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{26}H_{32}Cl_3NO_{13}S$ $[M + Na]^+$ = 726.0552, found = 726.0554.

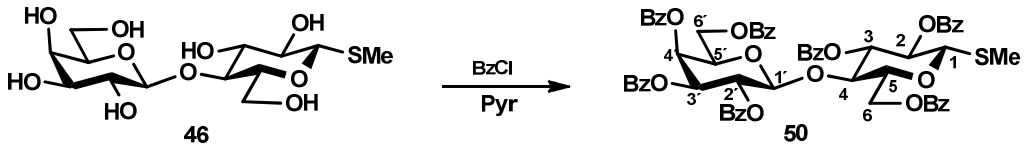
- Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside (**47**)



Disaccharide **30** (2.1 mmol, 1.8 g) was dissolved in pyridine (4.2 mL) and benzoyl chloride (21 mmol, 2.5 mL) was added at 0˚C. The mixture was stirred at room temperature over night; at this point CH_2Cl_2 was added followed by water and, after separation, the organic phase was washed twice with saturated aqueous $NaHCO_3$ and twice with water. The organic layer was dried over

$MgSO_4$ and concentrated in *vacuo* to leave an amorphous solid which was crystallized from toluene/pentane to give the title compound as a white crystalline solid (1.929 g, 80 % yield). **[α]** $^{25}_{D}$ = + 63.2 (c = 0.9, $CHCl_3$); $\mathbf{R_f}$ = 0.7 (toluene :acetone 9:1); **m.p.** = 193-197˚C; **^{1}H NMR** (300 MHz, $CDCl_3$): 8.05-7.15 (40H, m, Ar), 5.79-5.69 (2H, m, H-3´, H-3), 5.52 (1H, t, J = 9.5, H-4´), 5.42 (1H, t, J = 9.0, H-2´), 5.28 (1H, t, J = 9.9, H-2), 5.18 (1H, t, J = 9.6, H-4), 4.88 (1H, d, J = 8.4, H-1´), 4.84 (1H, d, J = 10.2, H-1), 4.52 (1H, dd, J = 12.6, J = 3.0, H-6_a´), 4.33 (1H, dd, J = 12.6, J = 4.8, H-6_b´), 3.99-3.92 (2H, m, H-5´, H-5), 3.89 (2H, bs, H-6_a, H-6_b); **^{13}C NMR** (75 MHz, $CDCl_3$): 166.0, 165.8, 165.6, 165.2, 165.3, 165.1, 164.9 (7 × C=O), 134.5-128.4 (Ar), 100.9 (C-1´), 85.9 (C-1), 78.4 (C-5), 74.0 (C-3), 72.9 (C-3´), 72.2 (C-5´), 71.8 (C-2´), 70.5 (C-2), 69.6 (C-4), 69.5 (C-4´), 68.2 (C-6), 62.8 (C-6´); **LC-MS** (ESI, pos): **RT** = 3.21 min; m/z = 1186.3 $[M + Na]^+$; **HRMS** (ESI, Pos): calculated for $C_{67}H_{54}O_{17}S$ $[M + Na]^+$ = 1185.2974, found = 1185.3017.

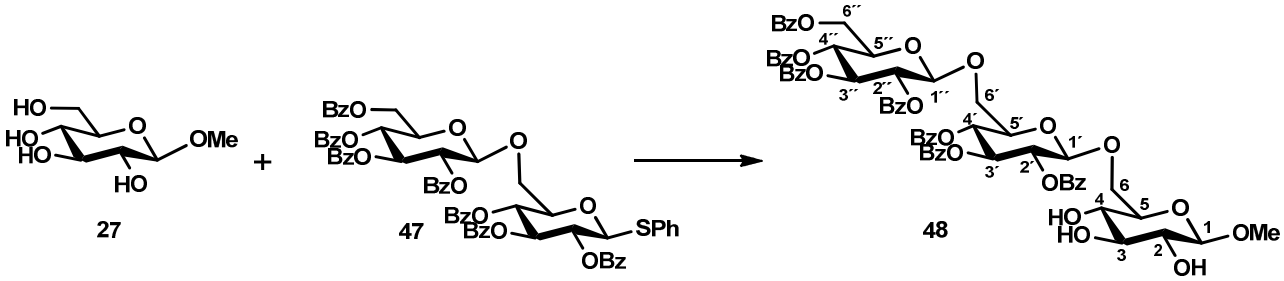
- Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**50**)



Disaccharide **46**[130] (5.4 mmol, 2g) was dissolved in pyridine (5 mL) and benzoyl chloride (54 mmol, 6.3 mL) was added at 0˚C. The mixture was stirred at room temperature over night. At this point CH_2Cl_2 was added followed by water and, after separation, the organic phase was washed twice with saturated aqueous $NaHCO_3$ and twice with water. The organic layer was dried over $MgSO_4$ and concentrated in *vacuo* leaving a residue that was purified by silica-gel column chromatography (toluene : acetone 10 : 0 → 9 : 1) to afford the title compound as a white foam (5.3 g, 89% yield). **[α]** $^{25}_{D}$ = + 52.2 (c = 1.1, $CHCl_3$); $\mathbf{R_f}$ = 0.8 (toluene :acetone 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.95-7.05 (35H, m, Ar), 5.76 (1H, t, J = 9.6, H-3), 5.67-5.62 (2H, m, H-2´, H-4´), 5.43 (1H, t, J = 8.7, H-2), 5.30 (1H, dd, J = 10.2, J = 3.9, H-3´), 4.80 (1H, d, J = 7.5, H-1´), 4.54 (1H, d, J = 9.9, H-1), 4.51-4.39 (2H, m, H-6_a, H-6_b), 4.17 (1H, t, J = 9.9, H-4), 3.85-3.59 (4H, m , H-6_a´, H-6_b´, H-5´, H-5), 2.09 (3H, s, -CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): 165.7, 165.7, 165.4, 165.3, 165.3, 165.2, 164.7 (7 × C=O), 133.6-128.2 (Ar), 100.9 (C-1´), 83.2 (C-1), 75.8 (C-4), 73.9 (C-3), 71.7 (C-3´), 71.3, 69.8, 69.8 67.4 (C-5, C-5´, C-4´, C-2´, C-2), 62.5 (C-6), 60.9 (C-6´), 11.6

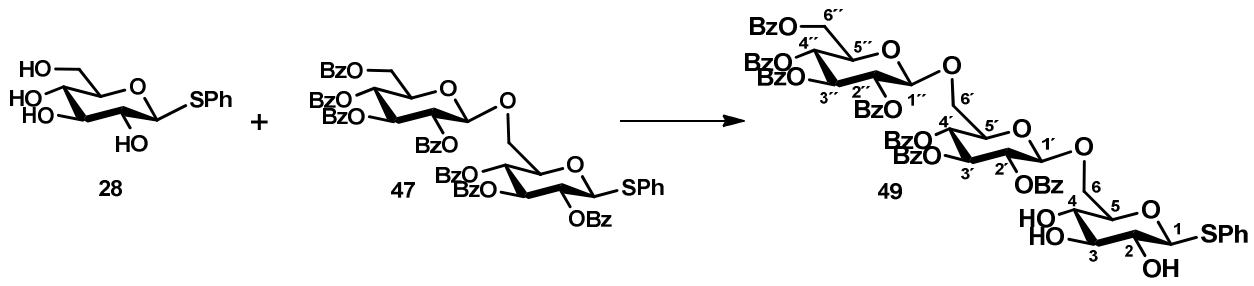
(-CH_3); **MS** (ESI, pos): m/z = 1118.0 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{62}H_{52}O_{17}S$ $[M + Na]^+$ = 1123.2817, found = 1123.2835.

- Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside (**48**)



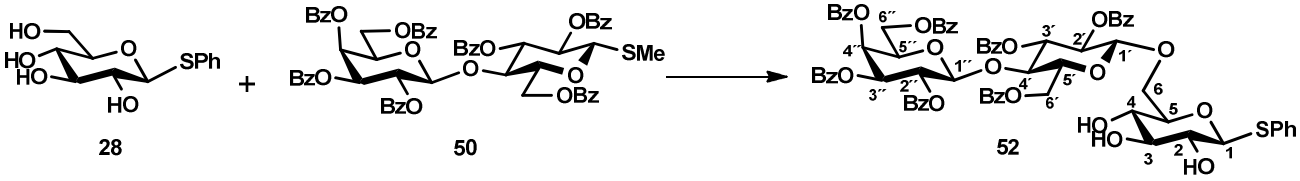
The coupling between **27** and **47** was performed according to method B to afford trisaccharide **48** as white foam (224.5 mg, yield 35 %). **[α]** $^{25}_{D}$ = - 10.2 (c = 1, $CHCl_3$); $\mathbf{R_f}$ = 0.5 (toluene:acetone 1:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.98-7.15 (35H, m, Ar), 5.84 (1H, t, J = 9.3, H-3´´), 5.73 (1H, t, J = 9.9, H-3´), 5.61 (1H, t, J = 10.2, H-4´´), 5.47 (1H, t, J = 9.0, H-2´´), 5.35 (1H, t, J = 9.0, H-2´), 5.23 (1H, t, J = 9.3, H-4´), 5.03 (1H, d, J = 7.8, H-1´´), 4.69 (1H, d, J = 7.5, H-1´), 4.58 (1H, dd, J = 12.6, J = 3.3, H-6´´$_a$), 4.41 (1H, dd, J = 12.6, J = 4.8, H-6´´$_b$), 4.11-4.07 (m, 2H, H-5´´, H-6$_a$), 4.04 (1H, d, J = 7.8, H-1), 3.95-3.84 (3H, m, H-6´$_a$, H-6´$_b$, H-5´), 3.68-3.63 (1H, m, H-6$_b$), 3.50-3.43 (1H, m, H-3), 3.41-3.37 (2H, m, H-5, H-4), 3.29-3.24 (1H, m, H-2), 3.19 (3H, s, -CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): 166.2, 166.1, 165.6, 165.3, 165.2, 165.1, 165.0 (7 × C=O), 133.4-128.2 (Ar), 103.2 (C-1), 101.3 (C-1´´), 100.7 (C-1´), 76.4 (C-3), 74.8 (C-5), 74.4 (C-5´), 73.6 (C-2), 72.8 (C-3´´), 72.5 (C-3´), 72.3 (C-5´´), 71.8 (C-2´´), 71.3 (C-2´), 70.7 (C-4), 69.5 (C-4´), 69.4 (C-4´´), 68.4 (C-6), 68.1 (C-6´), 62.8 (C-6´´), 56.7 (-OMe); **MS** (ESI, pos): m/z = 1270.0 $[M + Na]^+$; **HRMS** (ESI, Pos): calculated for $C_{68}H_{62}O_{23}$ $[M + Na]^+$ = 1269.3574, found = 1269.3647.

- Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (**49**)



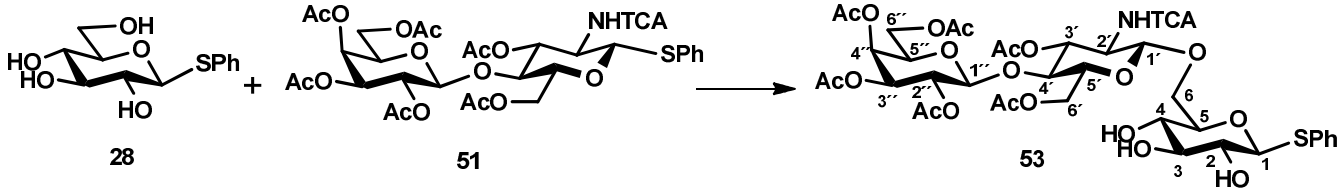
The coupling between **28**[127] and **47** was performed according to method C to afford trisaccharide **49** as a glassy solid (133 mg, yield 40 %). **$[\alpha]^{25}_{D}$** = - 13.7 (c = 1, $CHCl_3$); **R_f** = 0.6 (toluene:acetone 6:4); **^{1}H NMR** (300 MHz, $CDCl_3$): 8.01-7.13 (40H, Ar), 5.87 (1H, t, J = 10.5, H-3´), 5.71 (1H, t, J = 9.6, H-3´´), 5.59 (1H, t, J = 10.2, H-4´), 5.47 (1H, dd, J = 10.5, J = 8.1, H-2´), 5.35 (1H, dd, J = 9.6, J = 8.1, H-2´´), 5.26-5.18 (1H, m, H-4´´), 5.00 (1H, d, J = 8.1, H-1´), 4.67 (1H, d, J = 8.1, H-1´´), 4.54 (1H, dd, J = 12.3, J = 3.0, H-6´$_a$), 4.45 (1H, d, J = 9.9, H-1), 4.38 (1H, dd, J = 12.3, J = 4.8, H-6´$_b$), 4.11-3.78 (6H, bm, H-5´´, H-5´, H-6´´$_a$, H-6´´$_b$, H-6$_a$, H-6$_b$), 3.71-3.66 (1H, m, H-5), 3.55-3.41 (3H, bm, H-3, H-4, -OH), 3.28 (1H, t, J = 9.3, H-2); **^{13}C NMR** (75 MHz, $CDCl_3$): 166.1, 166.0, 165.6, 165.4, 165.2, 165.1, 165.0 (7 × C=O), 133.5-127.8 (Ar), 101.4 (C-1´), 100.7 (C-1´´), 88.2 (C-1), 78.6, 77.8, 74.3, 72.7 (C-3´), 72.6 (C-3´´), 72.2 (C-2´), 71.9 (C-2´´), 71.8 (C-2), 71.5, 70.3 (C-4´), 69.6 (C-4´´), 69.4, 68.6 (C-6´, C-6), 68.3, 62.8 (C-6´´); **MS** (ESI, pos): m/z = 1348.0 $[M + Na]^+$; **HRMS** (ESI, Pos): calculated for $C_{73}H_{64}O_{22}S$ $[M + Na]^+$ = 1347.3502, found = 1347.3566.

- Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (**52**)



The coupling between **28**[127] and **50** was performed according to method C to afford trisaccharide **52** as a glassy solid (152 mg, yield 46 %). **[α]** $^{25}{}_{D}$ = + 23.5 (c = 1, $CHCl_3$); $\mathbf{R_f}$ = 0.7 (toluene:acetone 1:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.96-7.05 (40H, m, Ar), 5.72-5.63 (3H, m, H-2´´, H-3´, H-4´´), 5.38-5.30 (2H, m, H-2´, H-3´´), 4.82 (1H, d, J = 8.1, H-1´´), 4.70 (1H, d, J = 8.1, H-1´), 4.58-4.52 (1H, bd, H-6´$_a$), 4.38 (1H, dd, J = 12.9, J = 4.2, H-6´$_b$), 4.33 (1H, d, J = 9.3, H-1), 4.17 (1H, t, J = 9.6, H-4´), 3.95 (1H, bd, H-6$_a$), 3.84 (1H, t, J = 6.0, H-5), 3.76-3.70 (1H, bd, H-6$_b$), 3-69-3.63 (3H, m, H-5´, H-6$_a$´´, H-6$_b$´´), 3.40-3.29 (3H, m, H-3, H-4, H-5´´), 3.14 (1H, t, J = 9.0, H-2); **^{13}C NMR** (75 MHz, $CDCl_3$): 165.9, 165.6, 165.4, 165.3, 165.3, 165.2, 164.8 (7 × C=O), 133.5-128.2 (Ar), 101.0 (C-1´´), 100.9 (C-1´), 87.8 (C-1), 78.6, 77.6, 75.8 (C-4´), 73.1 (C-5´), 72.7, 71.8, 71.7 (C-2), 71.7, 71.3 (C-5´), 70.5, 69.9, 69.0 (C-6), 67.5, 62.0 (C-6´), 60.9 (C-6´´); **MS** (ESI, pos): m/z = 1343.0 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{73}H_{64}O_{22}S$ $[M + Na]^+$ = 1347.3502, found = 1347.3559.

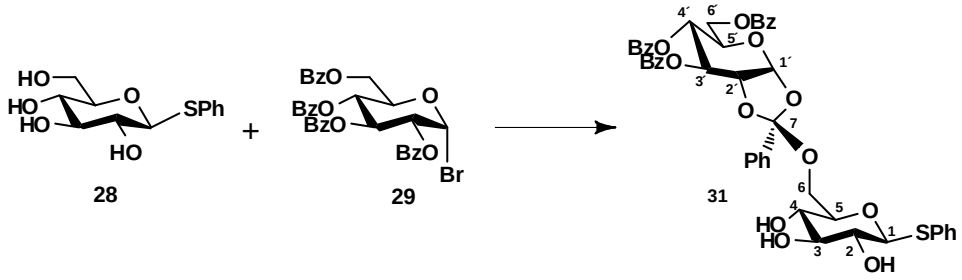
- Phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-acetyl-2-deoxy-trichloroacetamido-β-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (**53**)



The coupling between **28**[127] and **51**[134] was performed according to method C to afford trisaccharide **53** as a glassy solid (141 mg, yield 57 %). **[α]** $^{25}{}_{D}$ = - 14.4 (c = 1, $CHCl_3$); $\mathbf{R_f}$ = 0.5 (toluene:acetone 4:6); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.53-7.14 (6H, m, Ar, -NH), 5.34 (1H, d, J = 3.6), 5.19-5.07 (2H, m, H-3´), 4.96 (1H, dd, J = 11.1, J = 3.6), 4.63 (1H, d, J = 8.1, H-1´), 4.57-4.49

(3H, m, H-1´´, H-1), 4.12-3.76 (10H, m), 3.62-3.38 (5H, m), 3.36-3.28 (1H. bt, H-2), 2.14, 2.10, 2.05, 2.04, 1.96 (18H, 6 × -CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): 170.7, 170.6, 170.4, 170.1, 170.0, 169.3 (6 X C=O), 162.3 (HN-C=O), 101.2 (C-1´), 100.8 (C-1´´), 92.2 (-CCl_3), 87.8 (C-1), 78.9, 77.7, 75.9, 72.8, 71.9, 71.8, 70.7, 70.6, 69.8, 69.1, 68.6, 66.6, 61.8, 60.6, 55.4, 20.9, 20.7, 20.6, 20.5 (6 × -CH_3); **LC-MS** (ESI, pos): **RT =** 1.75 min; m/z = 1011.3 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{38}H_{48}Cl_3NO_{21}S$ $[M + Na]^+$ = 1014.1397, found = 1014.1431.

- 3,4,6-Tri-*O*-benzoyl-1,2-(phenyl 1-thio-β-D-glucopyranosid-6-yloxy-1-benzylidene)-α-D-glucopyranose (**31**)



The coupling between **28**[127] and **29**[131] was performed according to method A in presence of sym collidine (1.12 mmol), the reaction was stopped after 3h to afford 280 mg of a mixture containing 90 % of ortho-ester **31** and 10 % of sym collidine. **R_f =** 0.4 (CH_2Cl_2 : MeOH 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): 7.90-6.99 (25H, m, Ar), 6.71 (Ar, sym collidine), 5.91 (1H, d, J = 4.5, H-1´), 5.67 (1H, s, H-3´), 5.39 (1H, d, J = 9.0, H-4´), 4.73 (1H, bs, H-2´), 4.45-4.24 (3H, m, H-1, H-6_a´, H-6_b´), 4.06-4.00 (1H, m, H-5), 3.80-3.16 (9H, m, H-2, H-3, H-4, H-5, H-6_a, H-6_b), 2.39 (2 × -CH_3, sym collidine), 2.17 (-CH_3, sym collidine); **^{13}C NMR** (75 MHz, $CDCl_3$): 165.9, 165.1, 164.4 (3 × C=O), 134.6-120.9 (Ar, C-7), 97.6 (C-1´), 87.4 (C-1), 77.8, 77.7, 77.5, 71.8, 71.5 (C-2´), 70.2, 68.8 (C-3´), 68.3 (C-4´), 67.3 (C-5´), 63.9; **LC-MS** (ESI, pos): **RT =** 3.50 min; m/z = 868.4 $[M + H_2O]^+$; **HRMS** (ESI, Pos): calculated for $C_{46}H_{42}O_{14}S$ $[M + Na]^+$ = 873.2187, found = 873.2198.

3. Final Remarks

The work described in this thesis covers the method development of two new and distinct metal-mediated synthetic approaches for the coupling of primary alcohols with either amines or carbohydrates. These methods hold promise to become attractive alternatives to existing standard methodology, be it either due to environmental friendliness, or the quicker access to highly relevant structures.

In the first chapter a new method for the dehydrogenative couplings of alcohols and amines to form imines has been presented. The reaction is catalyzed by the ruthenium *N*-heterocyclic carbene complex [$RuCl_2$(I*i*Pr)(p-cymene)] (**3**) in the presence of the ligand DABCO and molecular sieves. This method can be applied to a variety of primary alcohols and amines and can be combined with a subsequent addition reaction. This work has been published as full paper in *Organometallics*, and represents a significant contribution to the development of more environmentally benign methods for oxidative couplings. In fact, the possibility to synthesize imines *via* dehydrogenative coupling of alcohols and amines is becoming of great interest. The growing interest for this transformation has resulted in the development of different catalyst systems within a very short time and the process is still ongoing.[27–30]

The second chapter is focused on tin mediated regioselective 6-*O*-glycosylations of unprotected glycopyranosides acceptors. The development of efficient synthetic methods for assembling oligosaccharides has become an essential tool for the emerging fields of glycobiology and glycomics. Even though a vast number of synthetic methods is available, the assembly of complex glycans is still an intricate process and the development of easier and more efficient procedures remains a primary goal. The major constraint of oligosaccharide synthesis is the extensive use of protecting groups. Thus, approaches to reduce the number of steps connected to chemical synthesis are highly important. In this thesis thioglycosides deriving from D-glucose, D-galactose and D-mannose were coupled with different bromide donors to afforded the corresponding (1→6) linked disaccharides in good to moderate yields. Furthermore, it has been shown that these disaccharides can act as glycosyl donors for subsequent tin mediated glycosylation reactions. The successful synthesis of a collection of di- and tri-saccharides has been described. These results will be submitted as full paper to *European Journal of Organic Chemistry*.

References

[1] D. Srimani, A. Sarkar, *Tetrahedron Lett.* **2008**, *49*, 6304–6307.

[2] R. I. Kureshy, K. J. Prathap, S. Agrawal, N. H. Khan, S. H. R. Abdi, R. V. Jasra, *Eur. J. Org. Chem.* **2008**, 3118–3128.

[3] A. R. Shaffer, J. A. R. Schmidt, *Organometallics* **2008**, *27*, 1259–1266.

[4] N. S. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 3734–3735.

[5] J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760.

[6] J. Alender, P. Morgan, J. Timberlake, *J. Org. Chem.* **1983**, *48*, 755–756.

[7] G. Alvaro, D. Savoia, *Synlett* **2002**, 651–673.

[8] P. R. Girling, T. Kiyoi, A. Whiting, *Org. Biomol. Chem.* **2011**, *9*, 3105–3121.

[9] H. W. Moore, G. Hughes, K. Srinivasachar, M. Fernandez, N. V. Nguyen, D. Schoon, A. Tranne, *J. Org. Chem.* **1985**, *50*, 4231–4238.

[10] K. F. Schmidt, *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1924**, *57*, 704–706.

[11] A. J. Sisti, S. R. Milstein, *J. Org. Chem.* **1974**, *39*, 3932–3936.

[12] F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, J. M. de los Santos, *Tetrahedron* **2007**, *63*, 523–575.

[13] Y. Maeda, T. Nishimura, S. Uemura, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399–2403.

[14] J. Larsen, K. A. Jørgensen, *J. Chem. Soc. Perkin Trans. 2* **1992**, 1213–1217.

[15] L. Aschwanden, T. Mallat, F. Krumeich, A. Baiker, *J. Mol. Catal. A: Chem.* **2009**, *309*, 57–62.

[16] B. Zhu, M. Lazar, B. Trewyn, R. Angelici, *J. Catal.* **2008**, *260*, 1–6.

[17] S.-I. Murahashi, T. Naota, H. Taki, *J. Chem. Soc. Chem. Commun.* **1985**, 613–614.

[18] J. S. M. Samec, A. H. Ell, J.-E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 2327–2334.

[19] K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed* **2003**, *42*, 1479–1483.

[20] S.-I. Murahashi, Y. Okano, H. Sato, T. Nakae, N. Komiya, *Synlett* **2007**, 1675–1678.

[21] G. Chu, C. Li, *Org. Biomol. Chem.* **2010**, *8*, 4716–4719.

[22] A. Grirrane, A. Corma, H. Garcia, *J. Catal.* **2009**, *264*, 138–144.

[23] L. Blackburn, R. J. Taylor, *Org. Lett.* **2001**, *3*, 1637–1639.

[24] S. Sithambaram, R. Kumar, Y. Son, S. Suib, *J. Catal.* **2008**, *253*, 269–277.

[25] H. Sun, F.-Z. Su, J. Ni, Y. Cao, H.-Y. He, K.-N. Fan, *Angew. Chem. Int. Ed. Chem.* **2009**, *48*, 4390–4393.

[26] M. S. Kwon, S. Kim, S. Park, W. Bosco, R. K. Chidrala, J. Park, *J. Org. Chem.* **2009**, *74*, 2877–2879.

[27] B. Gnanaprakasam, J. Zhang, D. Milstein, *Angew. Chem. Int. Ed* **2010**, *49*, 1468–1471.

[28] Y. Shiraishi, M. Ikeda, D. Tsukamoto, S. Tanaka, T. Hirai, *Chem. Commun.* **2011**, *47*, 4811–4813.

[29] M. A. Esteruelas, N. Honczek, E. O, M. Valencia, *Organometallics* **2011**, *30*, 2468–2471.

[30] J. W. Rigoli, S. A. Moyer, S. D. Pearce, J. M. Schomaker, *Org. Biomol. Chem.* **2012**, *10*, 1746–1749.

[31] C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790–792.

[32] V. Dragutan, I. Dragutan, L. Delaude, A. Demonceau, *Coord. Chem. Rev.* **2007**, *251*, 765–794.

[33] S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612–3676.

[34] F. E. Ferna, M. C. Puerta, P. Valerga, *Organometallics* **2012**, *31*, 6869–6879.

[35] A. Sølvhøj, R. Madsen, *Organometallics* **2011**, *30*, 6044–6048.

[36] Y. Zhang, C. Chen, S. C. Ghosh, Y. Li, S. H. Hong, *Organometallics* **2010**, *29*, 1374–1378.

[37] S. C. Ghosh, S. Muthaiah, Y. Zhang, X. Xu, S. H. Hong, *Adv. Synth. Catal.* **2009**, *351*, 2643–2649.

[38] S. Muthaiah, S. C. Ghosh, J.-E. Jee, C. Chen, J. Zhang, S. H. Hong, *J. Org. Chem* **2010**, *75*, 3002–3006.

[39] L. U. Nordstrøm, H. Vogt, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 17672–17673.

[40] J. H. Dam, G. Osztrovszky, L. U. Nordstrøm, R. Madsen, *Chem. Eur. J.* **2010**, *16*, 6820–6827.

[41] I. S. Makarov, P. Fristrup, R. Madsen, *Chem. Eur. J.* **2012**, *18*, 15683–15692.

[42] A. Nova, D. Balcells, N. D. Schley, G. E. Dobereiner, R. H. Crabtree, O. Eisenstein, *Organometallics* **2010**, *29*, 6548–6558.

[43] W. A. Herrmann, C. Köcher, L. J. Goossen, G. R. J. Artus, *Chem. Eur. J.* **1996**, *2*, 1627–1636.

[44] W. Chen, F. Liu, *J. Organomet. Chem.* **2003**, *673*, 5–12.

[45] H. M. J. Wang, I. J. B. Lin, *Organometallics* **1998**, *17*, 972–975.

[46] E. A. Mistryukov, *Mendeleev Commun.* **2006**, *16*, 258–259.

[47] A. J. Arduengo, R. Krafczyk, R. Schmuzler, *Tetrahedron* **1999**, *55*, 14523–14534.

[48] P. Fristrup, M. Kreis, A. Palmelund, P.-O. Norrby, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 5206–5215.

[49] M. Soroka, J. Zygmunt, *Synthesis* **1988**, 370 – 372.

[50] G. Alvaro, C. Boga, D. Savoia, A. Umani-Ronchi, *J. Chem. Soc., Perkin Trans. 1* **1996**, 875–882.

[51] C. Cimarelli, G. Palmieri, E. Volpini, *Tetrahedron: Asymmetry* **2002**, *13*, 2011–2018.

[52] C. Cimarelli, G. Palmieri, E. Volpini, *J. Org. Chem* **2003**, *68*, 1200–1206.

[53] G. Alvaro, D. Savoia, M. R. Valentinetti, *Tetrahedron* **1996**, *52*, 12571–12586.

[54] L. Delaude, S. Delfosse, A. Richel, A. Demonceau, A. F. Noels, *Chem. Comm.* **2003**, 1526–1527.

[55] E. Solari, S. Gauthier, R. Scopelliti, K. Severin, *Organometallics* **2009**, *28*, 4519–4526.

[56] A. Aranyos, G. Csjernyik, K. J. Szabó, J.-E. Bäckvall, *Chem. Comm.* **1999**, 351–352.

[57] E. Mizushima, M. Yamaguchi, T. Yamagishi, *Chem. Lett.* **1997**, 237–238.

[58] S. L. Chatwin, M. G. Davidson, C. Doherty, S. M. Donald, R. F. R. Jazzar, S. A. Macgregor, G. J. McIntyre, M. F. Mahon, M. K. Whittlesey, *Organometallics* **2006**, *25*, 99–110.

[59] F. X. Felpin, E. Fouquet, *Chem. Eur. J.* **2010**, *16*, 12440–12445.

[60] J. Barluenga, F. J. Fañanás, R. Sanz, C. Marcos, M. Trabada, *Org. Lett.* **2002**, *4*, 1587–1590.

[61] M. Taniguchi, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 645–653.

[62] G. Y. Fang, O. a Wallner, N. Di Blasio, X. Ginesta, J. N. Harvey, V. K. Aggarwal, *J. Am. Chem. Soc.* **2007**, *129*, 14632–14639.

[63] G. Pelletier, W. S. Bechara, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 12817–12819.

[64] H. Yamada, T. Kawate, A. Nishida, M. Nakagawa, *J. Org. Chem* **1999**, *64*, 8821–8828.

[65] D. J. Vyas, R. Fröhlich, M. Oestreich, *Org. Lett.* **2011**, *13*, 2094–2097.

[66] I. A. Cliffe, R. Crossley, R. G. Shepherd, *Synthesis* **1985**, 1138–1140.

[67] K. Pachamuthu, Y. D. Vankar, *J. Organomet. Chem.* **2001**, *624*, 359– 363.

[68] I. Bucior, M. M. Burger, *Curr. Opin. Struct. Biol.* **2004**, *14*, 631–637.

[69] S. Hakomori, *Arch. Biochem. Biophys.* **2004**, *426*, 173–181.

[70] C. R. Bertozzi, L. L. Kiessling, *Science* **2001**, *291*, 2357–2364.

[71] L.-X. Wang, J. V Lomino, *ACS Chem. Biol.* **2012**, *7*, 110–122.

[72] L. L. Kiessling, R. A. Splain, *Annu. Rev. Biochem.* **2010**, *79*, 619–653.

[73] M. C. Galan, D. Benito-Alifonso, G. M. Watt, *Org. Biomol. Chem.* **2011**, *9*, 3598–3610.

[74] T. J. Boltje, T. Buskas, G.-J. Boons, *Nature Chem.* **2009**, *1*, 611–622.

[75] X. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed* **2009**, *48*, 1900–1934.

[76] M. Weishaupt, S. Eller, P. H. Seeberger, *Methods Enzymol.* **2010**, *478*, 463–484.

[77] C.-H. Hsu, S.-C. Hung, C.-Y. Wu, C.-H. Wong, *Angew. Chem. Int. Ed.* **2011**, *50*, 11872–11923.

[78] Y. Wang, X.-S. Ye, L.-H. Zhang, *Org. Biomol. Chem.* **2007**, *5*, 2189–2200.

[79] B. Fraser-reid, J. C. Lopez, *Top. Curr. Chem.* **2011**, *301*, 1–29.

[80] A. V. Premathilake, A. V. Demchenko, *Top. Curr. Chem.* **2011**, *301*, 189–221.

[81] P. J. Garegg, J.-L. Maloisel, S. Oscarson, *Synthesis* **1995**, 409–414.

[82] R. K. P. Kartha, M. Kiso, A. Hasegawa, H. J. Jennings, *J. Chem. Soc. Perkin Trans. 1* **1995**, 3023–3026.

[83] B. Yu, B. Li, G. Xing, Y. Hui, *J. Comb. Chem.* **2001**, *3*, 404–406.

[84] A. Steinmann, J. Thimm, J. Thiem, *Eur. J. Org. Chem.* **2007**, *2007*, 5506–5513.

[85] C. Uriel, A. M. Gómez, J. C. López, B. Fraser-Reid, *Org. Biomol. Chem.* **2012**, *10*, 8361–8370.

[86] H. Tanaka, Y. Nishida, K. Kobayashi, *J. Carbohydr. Chem.* **2000**, *19*, 413–418.

[87] B. Becker, R. H. Furneaux, F. Reck, O. A. Zubkov, *Carbohydr. Res.* **1999**, *315*, 148–158.

[88] S. Figueroa-Pérez, V. Verez-Bencomo, *J. Carbohydr. Chem.* **1998**, *17*, 851–868.

[89] E. V. Evtushenko, *J. Carbohydr. Chem.* **2010**, *29*, 369–378.

[90] R. J. Ferrier, *J. Chem. Soc.* **1961**, 2325–2330.

[91] R. J. Ferrier, A. J. Hannaford, W. G. Overend, B. C. Smith, *Carbohydr. Res.* **1965**, *1*, 38–43.

[92] J. S. Brimacombe, F. Hunedy, A. Husain, *Carbohydr. Res.* **1969**, *10*, 141–151.

[93] Y. Shiomi, M. Saisho, K. Tsukagoshi, S. Shinkai, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2111–2117.

[94] K. Oshima, E. Kitazono, Y. Aoyama, *Tetrahedron Lett.* **1997**, *38*, 5001–5004.

[95] K. Oshima, Y. Aoyama, *J. Am. Chem. Soc.* **1999**, *121*, 2315–2316.

[96] E. Kaji, T. Nishino, K. Ishige, Y. Ohya, Y. Shirai, *Tetrahedron Lett.* **2010**, *51*, 1570–1573.

[97] T. Nishino, Y. Ohya, R. Murai, T. Shirahata, D. Yamamoto, K. Makino, E. Kaji, *Heterocycles* **2012**, *84*, 1123–1140.

[98] K. Oshima, T. Yamauchi, M. Shimomura, S. Miyauchi, Y. Aoyama, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1319–1324.

[99] D. Lee, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 3724–3727.

[100] C. Gouliaras, D. Lee, L. Chan, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 13926–13929.

[101] D. Lee, C. L. Williamson, L. Chan, M. S. Taylor, *J. Am. Chem. Soc.* **2012**, *134*, 8260–8267.

[102] B. T. Grindley, A. G. Davies, M. Gielen, K. H. Pannell, E. R. T. Tiekink, *Tin Chemistry-Fundamentals, Frontiers, and Applications*, Wiley, **2008**.

[103] T. Ogawa, M. Matsui, *Carbohydr. Res.* **1978**, *64*, C3–C9.

[104] C. Cruzado, M. Bernabe, M. Martin-lomas, *Carbohydr. Res.* **1990**, *203*, 296–301.

[105] E. Kaji, N. Harita, *Tetrahedron Lett.* **2000**, *41*, 53–56.

[106] Y. Tsuda, M. E. Haque, K. Yoshimoto, *Chem. Pharm. Bull.* **1983**, *31*, 1612–1625.

[107] M. E. Haque, T. Kikuchi, K. Yoshimoto, Y. Tsuda, *Chem. Pharm. Bull.* **1985**, *33*, 2243–2255.

[108] D. A. Leigh, R. P. Martin, J. P. Smart, A. M. Truscello, *J. Chem. Soc. Chem. Commun.* **1994**, 1373–1374.

[109] E. Kaji, K. Shibayama, K. In, *Tetrahedron Lett.* **2003**, *44*, 4881–4885.

[110] R. J. Ferrier, R. H. Furneaux, *Carbohydr. Res.* **1976**, *52*, 63–68.

[111] D. Crich, Z. Dai, S. Gastaldi, *J. Org. Chem* **1999**, *64*, 5224–5229.

[112] W. Wang, F. Kong, *J. Org. Chem* **1998**, *63*, 5744–5745.

[113] B. J. E. Wallace, L. R. Schroeder, *J. Chem. Soc., Perkin Trans. 2* **1977**, 795–802.

[114] S. Hanessian, J. Banoub, *Carbohydr. Res.* **1977**, *53*, C13–C16.

[115] G. Blatter, J. M. Beau, J.-C. Jacquinet, *Carbohydr. Res.* **1994**, *260*, 189–202.

[116] K. Bock, C. Pedersen, *J. Chem. Soc. Perkin Trans. 2* **1974**, 293–297.

[117] G. H. Veeneman, J. H. Van Boom, *Tetrahedron Lett.* **1990**, *31*, 275–278.

[118] H. Lönn, *Carbohydr. Res.* **1985**, *139*, 115–121.

[119] P. Fügedi, P. J. Garegg, *Carbohydr. Res.* **1986**, *149*, C9–C12.

[120] J. D. C. Codée, R. E. J. N. Litjens, R. den Heeten, H. S. Overkleeft, J. H. van Boom, G. A. van der Marel, *Org. Lett.* **2003**, *5*, 1519–1522.

[121] J. Tatai, P. Fűgedi, *Org. Lett.* **2007**, *9*, 4647–4650.

[122] P. Fügedi, P. J. Garegg, H. Lönn, T. Norberg, *Glycoconjugate J.* **1987**, *4*, 97–108.

[123] J. Kihlberg, D. A. Leigh, D. R. Bundle, *J. Org. Chem* **1990**, *55*, 2860–2863.

[124] S. Kaeothip, J. P. Yasomanee, A. V. Demchenko, *J. Org. Chem* **2012**, *77*, 291–299.

[125] S. Koto, T. Uchida, S. Zen, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2520–2523.

[126] S. Yamago, T. Yamada, O. Hara, H. Ito, Y. Mino, J. Yoshida, *Org. Lett.* **2001**, *3*, 3867–3870.

[127] M. S. Motawia, C. E. Olsen, K. Enevoldsen, J. Marcussen, B. L. Møller, *Carbohydr. Res.* **1995**, *277*, 109–123.

[128] H. Sugimura, K. -i. Watanabe, *Synth. Commun.* **2001**, *31*, 2313–2321.

[129] S. Ekholm, F., M. Poláková, J. Pawlowicz, A., R. Leino, *Synthesis* **2009**, 567–576.

[130] K. Leontein, M. Nilsson, T. Norberg, *Carbohydr. Res.* **1985**, *144*, 231–240.

[131] S. A. Mitchell, M. R. Pratt, V. J. Hruby, R. Polt, *J. Org. Chem* **2001**, *66*, 2327–2342.

[132] I. A. Ivanova, A. J. Ross, A. J. Ferguson, A. V Nikolaev, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1743–1753.

[133] M. Dowlut, D. G. Hall, O. Hindsgaul, *J. Org. Chem.* **2005**, *70*, 9809–9813.

[134] I. Bajza, G. Dekany, K. Agoston, I. F. Perez, J. Boutet, M. Hederos, F. Horvath, P. Kovacs-Penzes, L. Kroeger, C. Roehrig, *A Method For Preparation Of The Tetrasaccharide Lacto-N-Neotetraose (LNNT) Containing N-Acetyllactosamine*, **2011**, U.S. Patent WO 2011100980 A1 20110825.

Appendix − Publication

"Dehydrogenative Synthesis of Imines from Alcohols and Amines Catalyzed by a Ruthenium N-Heterocyclic Carbene Complex" A. Maggi, R. Madsen, *Organometallics* **2012**, *31*, 451-455.

ORGANOMETALLICS

Article

pubs.acs.org/Organometallics

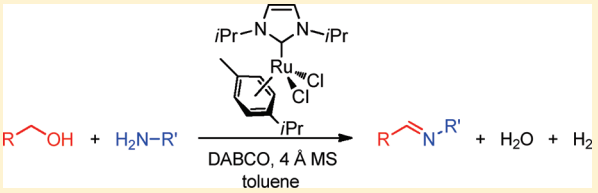
Dehydrogenative Synthesis of Imines from Alcohols and Amines Catalyzed by a Ruthenium N-Heterocyclic Carbene Complex

Agnese Maggi and Robert Madsen*

Department of Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

Supporting Information

ABSTRACT: A new method for the direct synthesis of imines from alcohols and amines is described where hydrogen gas is liberated. The reaction is catalyzed by the ruthenium N-heterocyclic carbene complex [$RuCl_2$(I*i*Pr)(*p*-cymene)] in the presence of the ligand DABCO and molecular sieves. The imination can be applied to a variety of primary alcohols and amines and can be combined with a subsequent addition reaction. A deuterium labeling experiment indicates that the catalytically active species is a ruthenium dihydride. The reaction is believed to proceed by initial dehydrogenation of the alcohol to the aldehyde, which stays coordinated to ruthenium. Nucleophilic attack of the amine affords the hemiaminal, which is released from ruthenium and converted into the imine.



INTRODUCTION

The imine is an important functional group in organic chemistry and is often used for the synthesis of amines by various addition reactions.[1] Imines are usually prepared by condensation of an aldehyde or a ketone with a primary amine but can also be formed by oxidation of secondary amines,[2] oxidative condensation of primary amines,[3] and the aza-Wittig reaction.[4] In addition, imines can be prepared by coupling of alcohols and amines in the presence of an oxidant.[5]

Recently, new dehydrogenative reactions have been developed for the coupling of alcohols and amines where hydrogen gas is liberated and no stoichiometric additives are necessary. These procedures constitute more environmentally benign methods for oxidative couplings and produce a minimum of waste. Ruthenium pincer complexes have been shown to mediate the coupling to form both amides[6] and imines,[7] depending on the structure of the ligand. An osmium pincer complex has been shown to catalyze the formation of imines,[8] while the heterogeneous catalysts Ag/Al_2O_3[9] and Pt/TiO_2[10] mediate the formation of amides and imines, respectively. We have shown that ruthenium N-heterocyclic carbene complexes can catalyze the synthesis of amides from primary alcohols and amines with the extrusion of hydrogen gas.[11] Following our initial findings, several ruthenium N-heterocyclic carbene and related complexes have been shown to mediate the amidation.[12] Among these, the reaction is most efficiently performed with ruthenium complex **1** (Figure 1) in the presence of tricyclohexylphosphine (PCy_3) and potassium *tert*-butoxide.[12c,d]

During the study of the mechanism of this reaction, we observed that imines in some cases were formed to a significant degree[12d] and we speculated whether the conditions could be altered into a dehydrogenative imine synthesis. Herein, we describe a new ruthenium-catalyzed synthesis of imines from primary alcohols and amines where hydrogen gas is liberated (Scheme 1).

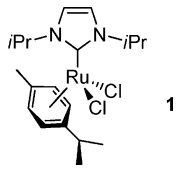
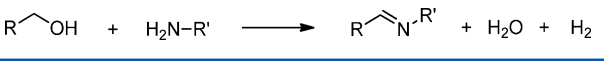


Figure 1. Structure of ruthenium N-heterocyclic carbene complex **1**.

Scheme 1. Dehydrogenative Imine Synthesis



RESULTS AND DISCUSSION

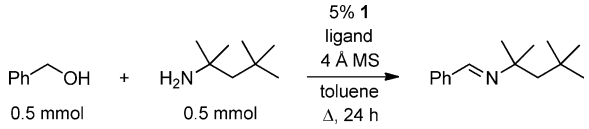
For the initial studies equimolar amounts of benzyl alcohol and *tert*-octylamine were selected as test substrates (Table 1). It was quickly discovered that imine formation occurred in the absence of potassium *tert*-butoxide. The reaction was performed with 5% of complex **1** in refluxing toluene under a flow of argon. Molecular sieves were added to secure continuous removal of water during the reaction. Under these conditions a 40% yield of the imine was obtained after 24 h with 55% conversion of the alcohol (Table 1, entry 1). Only about 3% of the ester from self-condensation of the alcohol[13] was observed as a byproduct, and no secondary amine or amide could be detected.

Imines are usually easy to reduce, and it is noteworthy that the C═N bond is not saturated under the reaction conditions. To improve the conversion of the alcohol, different ligands

Received: November 8, 2011
Published: December 7, 2011

   dx.doi.org/10.1021/om201095m | *Organometallics* 2012, 31, 451–455

Table 1. Optimizing Imine Formation



entry	ligand	amt of ligand (%)	BnOH conversn (%)[a]	imine yield (%)[a]
1	none		55	40
2	PCy_3	5	67	60
3	DABCO	5	80	65
4	dppe	5	42	41
5	xantphos	5	36	32
6	phenanthroline	5	52	44
7	PPh_3	10	17	17
8	pyridine	10	48	44
9	PCy_3	10	84	71
10	DABCO	10	83	81
11[b]	DABCO	10	83	74[c]
12[d]	DABCO	10	89	82
13[e]	DABCO	10	48	34
14[f]	DABCO	10	40	31
15[g]	none		56	35[h]

[a]Determined by GC with nonane as internal standard. [b]Without molecular sieves. [c]9% of secondary amine was also formed. [d]With $[RuCl_2(IMe)(p\text{-cymene})]$ (5%). [e]With $[RuCl_2(p\text{-cymene})]_2$ (2.5%), I*i*Pr·HCl (5%), and KO*t*Bu (5%). [f]With $[RuCl_2(p\text{-cymene})]_2$ (2.5%), I*t*Bu·HCl (5%), and KO*t*Bu (5%). [g]With $[RuCl_2(p\text{-cymene})]_2$ (2.5%). [h]15% of the secondary amine was also formed.

were investigated as additives. With 5% of PCy_3 or 1,4-diazabicyclo[2.2.2]octane (DABCO) the alcohol conversion increased (Table 1, entries 2 and 3), while bidentate ligands as well as PPh_3 and pyridine gave lower conversions (entries 4–8). A further improvement could be achieved by increasing the amount of ligand to 10% (entries 9 and 10), and since DABCO gave the best result, this ligand was selected for general use. With DABCO only a trace amount (~2%) of the secondary amine from reduction of the imine was observed as a byproduct. When the experiment in entry 10 was repeated in the absence of molecular sieves, the same conversion of benzyl alcohol was observed, but the amount of secondary amine had increased to 9% (entry 11). Hence, the molecular sieves do not influence the rate of the imination, but instead the selectivity is affected by the continuous removal of water.

The importance of the ruthenium complex was also investigated. First, the isopropyl wingtips in **1** were replaced by methyl groups and the reaction performed with the complex $[RuCl_2(IMe)(p\text{-cymene})]$ (Table 1, entry 12). This gave a slightly higher conversion than with **1**, but the product imine was obtained together with 6% of the corresponding secondary amine. Due to the lower selectivity, the methyl-substituted complex $[RuCl_2(IMe)(p\text{-cymene})]$ does not constitute a better precatalyst than the isopropyl-substituted **1**. In our amidation reaction it was possible to generate the ruthenium N-heterocyclic carbene complex in situ from $[RuCl_2(p\text{-cymene})]_2$, 1,3-diisopropylimidazolium chloride (I*i*Pr·HCl), and potassium *tert*-butoxide.[11] This was also attempted for the imination reaction, but a significantly lower conversion was observed as compared to the experiment with complex **1** (entries 10 and 13). The use of the more sterically hindered 1,3-di-*tert*-butylimidazol-2-ylidene as the carbene ligand gave even lower conversion (entry 14). The importance of the carbene ligand was confirmed by performing the reaction in the absence of this ligand, where a significant amount of the corresponding secondary amine was formed as a byproduct (entry 15). Thus, for general use complex **1** in the presence of DABCO and molecular sieves presents the optimum catalyst system for the imination. The formation of hydrogen during the transformation was confirmed by collecting the argon–hydrogen gas mixture from the reaction and using it for hydrogenating an alkyne in a separate flask.

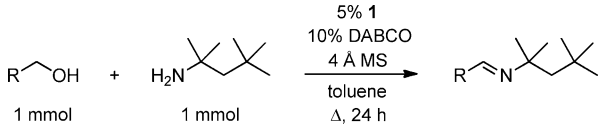
With the optimized catalyst system in place, our attention then turned to other alcohols and amines in order to investigate the scope of the imination. First, different alcohols were studied in the reaction with *tert*-octylamine (Table 2). Para-substituted benzyl alcohols with methyl, methoxy, and fluoro substituents participated well in the imine formation, and only trace amounts of the corresponding secondary amines were detected in these reactions (entries 1–4). The methoxy group could also be tolerated in the ortho position without affecting the yield of the imine (entry 5). Notably, a small amount of anisole was observed in entries 3 and 5, which presumably arises from decarbonylation of the intermediate aldehyde.[14] A methyl ester in the para position gave a slightly lower yield, and with this substrate the reaction was accompanied by significant formation of both the secondary amine and the secondary amide (entry 6). *p*-Chloro- and *p*-bromobenzyl alcohol were poor substrates due to considerable dehalogenation as a side reaction (results not shown).

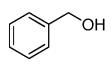
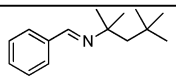
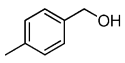
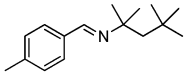
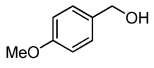
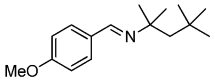
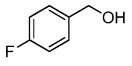
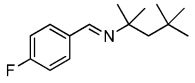
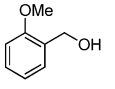
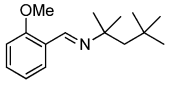
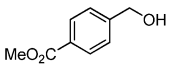
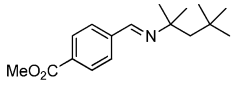
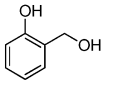
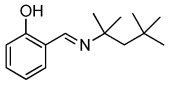
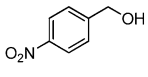
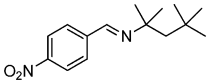
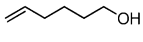
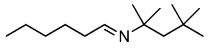
o-Hydroxybenzyl alcohol was also an inferior substrate since the product was obtained as a 1:1 mixture of the desired imine and the corresponding secondary amine (Table 2, entry 7). *p*-Nitrobenzyl alcohol gave the imine in moderate yield due to competing reduction of the nitro group (entry 8). Hex-5-enyl alcohol was converted into the imine with complete reduction of the olefin (entry 9). In this reaction the imine was the only product detected and the moderate yield is presumably due to the poor stability of alkylimines toward purification by flash column chromatography.

In addition to *tert*-octylamine other primary amines were also investigated as substrates, and in this case the reaction was performed with benzyl alcohol (Table 3). Cyclohexylamine gave the imine in 60% isolated yield and with only a trace

dx.doi.org/10.1021/om201095m | *Organometallics* 2012, 31, 451–455

Table 2. Imination of Alcohols with *tert*-Octylamine

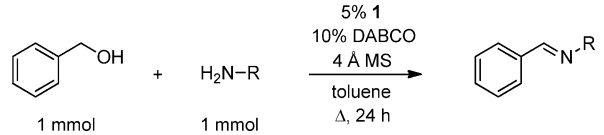


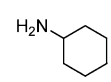
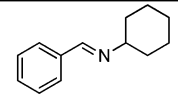
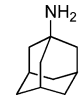
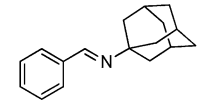
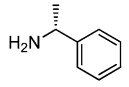
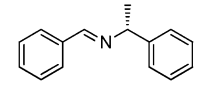
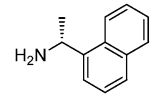
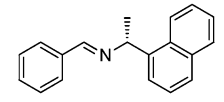
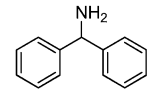
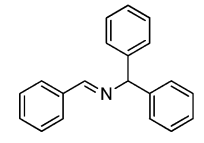
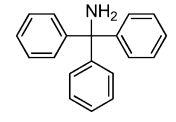
entry	alcohol	imine	amine conv. (%)[a]	imine yield (%)[b]
1			82	80
2			90	77
3			70	63[c]
4			80	72
5			75	69[c]
6[d]			93	59[e]
7			-	33[f]
8			77	48[g]
9			84	40

[a]Determined by GC with nonane as internal standard. [b]Isolated yield. [c]3% of anisole was also formed. [d]Performed in mesitylene at 163 °C with PCy_3 instead of DABCO. [e]14% of secondary amine, 17% of amide, and 3% of methyl benzoate were also formed. [f]37% of secondary amine was also formed. [g]15% of *N*-(*p*-aminobenzylidene)-*tert*-octylamine was also formed.

amount of the secondary amine (entry 1). 1-Adamantylamine afforded the product in 70% yield together with 10% of the secondary amine (entry 2). Optically pure (*R*)-1-phenylethylamine and (*R*)-1-(1-naphthyl)ethylamine gave the corresponding imines without any sign of racemization (entries 3 and 4). The more hindered benzhydrylamine reacted very slowly and only gave 40% yield after 2 days (entry 5). Further steric hindrance inhibited the imination almost completely, as seen with tritylamine, where only a trace amount of the imine was observed together with benzyl benzoate from self-condensation of the alcohol (entry 6). These experiments indicate that the amine has to attack the ruthenium complex in order for the imination to proceed.[15] Aniline reacted very sluggishly with benzyl alcohol and only gave the imine in low yield together with several byproducts (result not shown). Reacting benzyl alcohol with complex **1** in refluxing toluene in the absence of an amine gave about 10% of benzaldehyde after 2 h, as judged by GC-MS analysis, and this did not change upon prolonged treatment, where small amounts of benzyl benzoate were also observed.

Table 3. Imination of Amines with Benzyl Alcohol

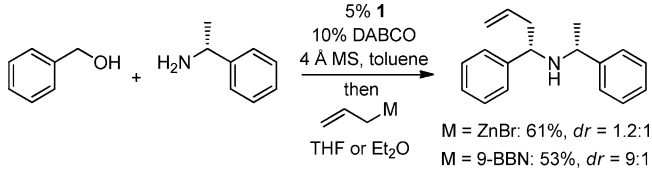


entry	amine	imine	BnOH conv. (%)[a]	imine yield (%)[b]
1			75	60
2			82	70[c]
3			77	63[c]
4			70	52[d]
5[e]			73	40[f]
6[g]		-	75	-

[a]Determined by GC with nonane as internal standard. [b]Isolated yield. [c]10% of secondary amine was also formed. [d]7% of secondary amine was also formed. [e]Reacted for 48 h. [f]5% of secondary amine was also formed. [g]Reacted for 52 h.

The imination reaction provides access to a variety of imines which may be used directly in a subsequent addition reaction. This was illustrated with the enantiomerically pure imine from Table 3, entry 3, which has previously been reacted with a variety of nucleophiles.[1b] After the imine was formed from benzyl alcohol and (*R*)-1-phenylethylamine, the solvent was replaced with THF or Et_2O followed by addition of an allylating agent (Scheme 2). With allylzinc bromide the

Scheme 2. Sequential Imination and Allylation



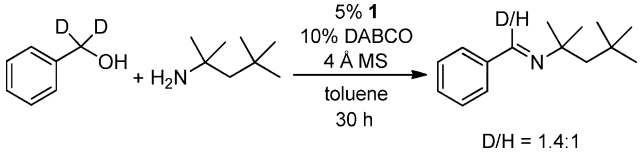
addition product was obtained in 61% overall yield from benzyl alcohol, but with almost no diastereoselectivity. With the more hindered *B*-allyl-9-BBN the product was isolated in 53% yield and with a diastereomeric ratio of 9:1.[16]

To obtain more information about the mechanism of the imination, two experiments with deuterium-labeled benzyl alcohol were performed. First, benzyl alcohol-α,α-d_2 was reacted with *tert*-octylamine under the standard conditions

dx.doi.org/10.1021/om201095m | *Organometallics* 2012, 31, 451−455

(Scheme 3). Interestingly, the product imine was obtained as a 1.4:1 mixture of the deuterium-labeled imine and the

Scheme 3. Imination with Benzyl Alcohol-α,α-d_2



nonlabeled product, as shown by GC-MS analysis. This result was observed in both toluene and toluene-d_8 and is not a result of a deuterium−hydrogen exchange with the solvent. A control experiment showed that the scrambling occurred during the imination reaction and not by a competing transformation from the imine. When the product H-imine from Table 2, entry 1, was treated with $PhCD_2OH$ under the same conditions as in Scheme 3, no deuterium incorporation in the imine was observed.

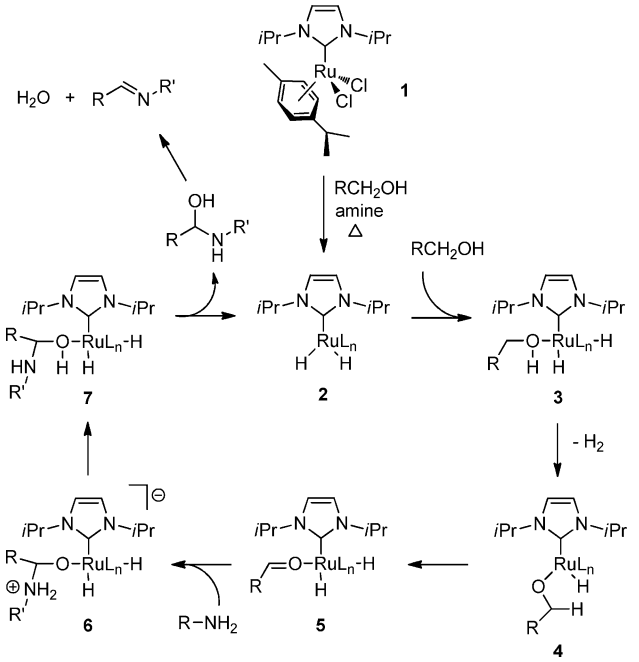
When the imination in Scheme 3 was monitored by ^1H NMR in toluene-d_8, deuterium−hydrogen scrambling in the starting alcohol was observed already after 5 h. Reisolating the alcohol at this time showed that it consisted of $PhCD_2OH$ (56%), PhCDHOH (34%), and $PhCH_2OH$ (10%). This indicates that the initial β-hydride elimination to form benzaldehyde is a reversible reaction and, more importantly, the catalytically active ruthenium species is a dihydride. The same observation was made in our very recent dehydrogenative ester synthesis from primary alcohols with complex **1**.[13]

The influence of the β-hydride elimination was further probed by measuring the primary kinetic isotope effect. The initial rate was determined both with $PhCH_2OH$/*tert*-octyl-NH_2 and with $PhCD_2OD$/*tert*-octyl-ND_2, which gave a kinetic isotope effect (k_H/k_D) of 1.1 ± 0.3. This negligible value indicates that β-hydride elimination from the alcohol is not the rate-determining step in the imination mechanism.

On the basis of these experiments and our previous studies on the amidation,[12d] we propose the imination mechanism in Scheme 4. It has previously been shown by NMR that the *p*-cymene ligand in complexes such as **1** is lost upon reflux in toluene.[17] This is followed by replacement of the two chloride ligands with hydride through substitution with the alcohol, release of hydrogen chloride, and β-hydride elimination. The formation of ruthenium hydrides in this way has been established for other ruthenium(II) chloride complexes.[18] By this catalyst initiation small amounts of the aldehyde will be formed and converted into the imine after reaction with the amine. The catalytically active species is believed to be dihydride **2**, which coordinates the alcohol to afford complex **3**. Hydrogen gas is then liberated by hydrogen transfer to hydride, as demonstrated earlier.[19] This gives rise to alkoxide complex **4**, which is then converted into aldehyde complex **5** by β-hydride elimination. It is possible that the aldehyde is released from **5** and imine formation then occurs with the amine in solution. However, since the imination is sensitive to the steric demands of the amine, it seems more reasonable that the amine attacks the coordinated aldehyde to afford hemiaminal **6** (as the zwitterion protonated at nitrogen).

This is, so far, fairly similar to the mechanism proposed for the amidation with complex **1**.[12d] The major difference, however, is the lack of a strong base in the imination, and the more acidic environment may affect the stability of complex

Scheme 4. Proposed Mechanism for Imination



6. Recently, Crabtree and Eisenstein performed a computational study on a similar hemiaminal bonded to a ruthenium(II) hydride in order to determine whether the amide or the imine would be formed.[20] They showed that the amide is formed after hydrogen transfer to hydride, while imine formation requires hydrogen transfer to oxygen.[20] Under the more acidic conditions of the imination, hydrogen transfer to oxygen may be more facile, e.g. through an outer-sphere proton transfer, which would afford complex **7** and then the imine after decomplexation of the hemiaminal. In this way, the fate of the intermediate hemiaminal determines whether the amide or the imine is formed in the coupling. The scrambling observed in Scheme 3 can be explained by the observation that ruthenium dihydride complexes are able to scramble hydrogen and deuterium when exposed to hydrogen/deuterium gas.[21] In combination with a reversible β-hydride elimination, this provides a route by which O−H or N−H hydrogens can be scrambled into the α positions of the alcohol.

In summary, we have presented a new method for the direct synthesis of imines from primary alcohols and amines in which water and hydrogen gas are formed as the only byproducts. The reaction is catalyzed by the ruthenium N-heterocyclic carbene complex **1**, which is easy to handle and straightforward to prepare. A mechanism is proposed with a ruthenium dihydride species as the catalytically active component.

EXPERIMENTAL SECTION

General Information. Toluene was distilled from sodium and benzophenone under an argon atmosphere. Column chromatography was performed on silica gel 60 (0.035−0.070 mm) saturated with Et_3N. NMR chemical shifts were measured with TMS or the residual solvent signal in $CDCl_3$ (δ_H 7.26 ppm, δ_C 77.0 ppm) as internal reference.

General Procedure for Imination. Ruthenium complex **1**[12d] (22.9 mg, 0.05 mmol), DABCO (11.2 mg, 0.1 mmol), and 4 Å molecular sieves (150 mg) were placed in an oven-dried Schlenk flask equipped with a cold finger. Vacuum was applied, and the flask was then filled with argon (repeated twice). Toluene (1 mL), alcohol (1 mmol), amine (1 mmol), and nonane (0.2 mmol as internal standard)

dx.doi.org/10.1021/om201095m | *Organometallics* 2012, 31, 451−455

were added by syringe, and the mixture was refluxed with stirring under a flow of argon for 24 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The residue was purified by silica gel column chromatography (hexane/Et_2O 10/0 → 9/1 with 2% Et_3N) to afford the imine.

N-(4-Methylbenzylidene)-tert-octylamine (Table 2, Entry 2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.64 (d, 2H, J = 8.1 Hz), 7.21 (d, 2H, J = 8.1 Hz), 2.38 (s, 3H), 1.69 (s, 2H), 1.32 (s, 6H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 140.0, 134.8, 129.1, 127.8, 60.8, 56.6, 32.0, 31.7, 29.6, 21.4; HRMS m/z calcd for $C_{16}H_{26}N$ 232.2021 $[M + H]^+$, found 232.2059.

N-(4-Methoxybenzylidene)-tert-octylamine (Table 2, Entry 3): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.70 (d, 2H, J = 8.7 Hz), 6.93 (d, 2H, J = 8.7 Hz), 3.84 (s, 3H), 1.68 (s, 2H), 1.32 (s, 6H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 153.6, 130.4, 129.3, 113.8, 60.6, 56.6, 55.3, 32.0, 31.8, 29.7; HRMS m/z calcd for $C_{16}H_{26}NO$ 248.1970 $[M + H]^+$ found 248.2010.

N-(4-Fluorobenzylidene)-tert-octylamine (Table 2, Entry 4): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.76−7.70 (m, 2H), 7.10 (bt, 2H), 1.69 (s, 2H), 1.32 (s, 6H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (d, J_{C-F} = 248.0 Hz), 152.9, 133.6 (d, J_{C-F} = 2.85 Hz), 129.6 (d, J_{C-F} = 8.4 Hz), 115.5 (d, J_{C-F} = 21.6 Hz), 60.9, 56.5, 32.0, 31.7, 29.6; HRMS m/z calcd for $C_{15}H_{23}FN$ 236.1770 $[M + H]^+$, found 236.1809.

N-(2-Methoxybenzylidene)-tert-octylamine (Table 2, Entry 5): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.96 (bd, 1H), 7.35 (bt, 1H), 6.98 (bt, 1H), 6.91 (bd, 1H), 3.87 (s, 3H), 1.70 (s, 2H), 1.33 (s, 6H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 150.4, 131.0, 127.0, 125.8, 120.8, 110.8, 61.3, 56.6, 55.4, 32.0, 31.8, 29.8; HRMS m/z calcd for $C_{16}H_{26}NO$ 248.1970 $[M + H]^+$, found 248.2008.

N-(4-Carbomethoxybenzylidene)-tert-octylamine (Table 2, Entry 6): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.07 (d, 2H, J = 8.1 Hz), 7.80 (d, 2H, J = 8.1 Hz), 3.93 (s, 3H), 1.70 (s, 2H), 1.33 (s, 6H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 153.5, 141.2, 131.1, 129.7, 127.7, 61.5, 56.5, 52.2, 32.0, 31.7, 29.5; HRMS m/z calcd for $C_{17}H_{26}NO_2$ 276.1919 $[M + H]^+$, found 276.1960.

N-(4-Nitrobenzylidene)-tert-octylamine (Table 2, Entry 8): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.26 (d, 2H, J = 8.7 Hz), 7.91 (d, 2H, J = 8.7 Hz), 1.71 (s, 2H), 1.34 (s, 6H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 142.7, 128.5, 123.8, 61.9, 56.5, 32.0, 31.7, 29.5; HRMS m/z calcd for $C_{15}H_{23}N_2O$ 263.1715 $[M + H]^+$, found 263.1753.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text and figures giving experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

* E-mail: rm@kemi.dtu.dk.

■ ACKNOWLEDGMENTS

We thank the Danish Council for Independent Research−Technology and Production Sciences for financial support.

■ REFERENCES

(1) (a) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541−2569. (b) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651−673.

(2) (a) Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4568−4571. (b) So, M.-H.; Liu, Y.; Ho, C.-M.; Che, C.-M. *Chem. Asian J.* **2009**, *4*, 1551−1561. (c) Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745−747. (d) Wang, J.-R.; Fu, Y.; Zhang, B.-B.; Cui, X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2006**, *47*, 8293−8297. (e) Samec, J. S. M.; Éll, A. H.; Bäckvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 2327−2334.

(3) (a) Liu, L.; Zhang, S.; Fu, X.; Yan, C.-H. *Chem. Commun.* **2011**, *47*, 10148−10150. (b) Lang, X.; Ji, H.; Chen, C.; Ma, W.; Zhao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3934−3937. (c) Patil, R. D.; Adimurthy, S. *Adv. Synth. Catal.* **2011**, *353*, 1695−1700. (d) Chu, G.; Li, C. *Org. Biomol. Chem.* **2010**, *8*, 4716−4719. (e) Yuan, Q.-L.; Zhou, X.-T.; Ji, H.-B. *Catal. Commun.* **2010**, *12*, 202−206.

(4) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523−575.

(5) (a) Jiang, L.; Jin, L.; Tian, H.; Yuan, X.; Yu, X.; Xu, Q. *Chem. Commun.* **2011**, *47*, 10833−10835. (b) Sun, H.; Su, F.-Z.; Ni, J.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4390−4393. (c) Kwon, M. S.; Kim, S.; Park, S.; Bosco, W.; Chidrala, R. K.; Park, J. *J. Org. Chem.* **2009**, *74*, 2877−2879. (d) Kim, J. W.; He, J.; Yamaguchi, K.; Mizuno, N. *Chem. Lett.* **2009**, *38*, 920−921. (e) Sithambaram, S.; Kumar, R.; Son, Y.-C.; Suib, S. L. *J. Catal.* **2008**, *253*, 269−277. (f) Blackburn, L.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 1637−1639.

(6) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790−792.

(7) Gnanaprakasam, B.; Zhang, J.; Milstein, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 1468−1471.

(8) Esteruelas, M. A.; Honczek, N.; Oliván, M.; Oñate, E.; Valencia, M. *Organometallics* **2011**, *30*, 2468−2471.

(9) Shimizu, K.-i.; Ohshima, K.; Satsuma, A. *Chem. Eur. J.* **2009**, *15*, 9977−9980.

(10) Shiraishi, Y.; Ikeda, M.; Tsukamoto, D.; Tanaka, S.; Hirai, T. *Chem. Commun.* **2011**, *47*, 4811−4813.

(11) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672−17673.

(12) (a) Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H. *Organometallics* **2011**, *30*, 4174−4179. (b) Prades, A.; Peris, E.; Albrecht, M. *Organometallics* **2011**, *30*, 1162−1167. (c) Chen, C.; Hong, S. H. *Org. Biomol. Chem.* **2011**, *9*, 20−26. (d) Dam, J. H.; Osztrovszky, G.; Nordstrøm, L. U.; Madsen, R. *Chem. Eur. J.* **2010**, *16*, 6820−6827.

(13) Sølvhøj, A.; Madsen, R. *Organometallics* **2011**, *30*, 6044−6048.

(14) Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 5206−5215.

(15) In benzene solution tritylamine reacts readily with aldehydes to form the corresponding imines; see: Soroka, M.; Zygmunt, J. *Synthesis* **1988**, 370−372.

(16) Addition of *B*-allyl-9-BBN to the pure imine gave a diastereomeric ratio of 97/3; see: Alvaro, G.; Boga, C.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 875−882.

(17) (a) Zhang, Y.; Chen, C.; Ghosh, S. C.; Li, Y.; Hong, S. H. *Organometallics* **2010**, *29*, 1374−1378. (b) Delaude, L.; Delfosse, S.; Richel, A.; Demonceau, A.; Noels, A. F. *Chem. Commun.* **2003**, 1526−1527.

(18) (a) Solari, E.; Gauthier, S.; Scopelliti, R.; Severin, K. *Organometallics* **2009**, *28*, 4519−4526. (b) Aranyos, A.; Csjernyik, G.; Szabó, K. J.; Bäckvall, J.-E. *Chem. Commun.* **1999**, 351−352. (c) Mizushima, E.; Yamaguchi, M.; Yamagishi, T. *Chem. Lett.* **1997**, 237−238.

(19) Chatwin, S. L.; Davidson, M. G.; Doherty, C.; Donald, S. M.; Jazzar, R. F. R.; Macgregor, S. A.; McIntyre, G. J.; Mahon, M. F.; Whittlesey, M. K. *Organometallics* **2006**, *25*, 99−110.

(20) Nova, A.; Balcells, D.; Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H.; Eisenstein, O. *Organometallics* **2010**, *29*, 6548−6558.

(21) Burling, S.; Kociok-Köhn, G.; Mahon, M. F.; Whittlesey, M. K.; Williams, J. M. J. *Organometallics* **2005**, *24*, 5868−5878.