

# Iridium Catalyzed Carbon-Heteroatom Bond Forming Reactions via Hydrogen Transfer

Method Development and Mechanistic Elucidations

Aitor Bermejo López





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## Method Development and Mechanistic Elucidations

Aitor Bermejo López

Academic dissertation for the Degree of Doctor of Philosophy in Organic Chemistry at Stockholm University to be publicly defended on Friday 23 September 2022 at 09.00 in Magnélisalen, Kemiska övningslaboratoriet, Svante Arrhenius väg 16 B.

### Abstract

The present thesis describes the applicability of two different iridium(III) complexes for C-O and C-N bond forming reactions. The different projects described in this work are united by the use of an iridium catalyst bearing a functionalized N-heterocyclic carbene ligand. These catalysts operate through a hydrogen transfer mechanism to afford the desired products. This approach gives access to a variety of valuable products in a sustainable and atom economical manner, generating water as the only byproduct.

In Chapter 1, a general introduction to catalysis, followed by a more detailed description of organometallic complexes and their use in hydrogen transfer reactions is described. An overview of different mechanistic studies that have been employed within this thesis is also provided.

Chapter 2 describes the use of an alkoxy-functionalized iridium-NHC complex, previously reported by our group, on cyclodehydration reactions (Paper I). A range of cyclic ethers are obtained from the corresponding diol compounds. Mechanistic studies confirmed an unexplored hydrogen transfer pathway to be operating for the majority of the substrates.

In Chapter 3, a new amino-functionalized iridium-NHC catalyst is designed and synthesized, aiming at improving the reactivity compared to previous reports. Then, its outstanding efficiency on carbon-nitrogen bond forming reactions is depicted in different protocols (Papers II, III and IV).

Paper II achieves the base-free and selective mono-N-alkylation of amines with alcohols mostly at room temperature. Mechanistic studies are performed to gain a better understanding of the catalytic cycle by combining experimental and in silico studies.

In Paper III, the use of this catalyst to access N-modified amino acids is described. Excellent group tolerance allowed for the synthesis of more than 100 compounds. Moreover, quantitative yields are obtained in all cases without the need of tedious derivatization/purification steps. In addition, convenient scalability, recyclability and deuterium labelling studies are also presented. Further applicability of these compounds as high-value building blocks for the synthesis of N-modified peptides is demonstrated.

In Paper IV, the catalyst is used for the direct mono-N-alkylation of a range of aminosugars with alcohols. The method is developed to be applied on unprotected carbohydrates, that enables to access these important organic molecules in a direct, and thus sustainable, manner, avoiding unnecessary protection and deprotection steps.

**Keywords:** *Catalysis, N-Heterocyclic carbene, N-Alkylation, Hydrogen transfer, Amino acids, Carbohydrates, Amines.*

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*Student:* Dr. Einstein,  
Aren't these the same  
questions as last year's  
final exam?

*Dr. Einstein:* Yes; But this  
year the answers are  
different.

- Albert Einstein



# Abstract

The present thesis describes the applicability of two different iridium(III) complexes for C–O and C–N bond forming reactions. The different projects described in this work are united by the use of an iridium catalyst bearing a functionalized *N*-heterocyclic carbene ligand. These catalysts operate through a hydrogen transfer mechanism to afford the desired products. This approach gives access to a variety of valuable products in a sustainable and atom-economical manner, generating water as the only byproduct.

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# Populärvetenskaplig sammanfattning

Boken du håller i just detta ögonblick, luften du andas in, parfymen du använde i morse, pillret du tar när du känner dig sjuk, din kropp. Kemikalier finns överallt runtomkring oss. Vi som kemister ägnar våra liv åt att studera hur molekyler interagerar med varandra för att bilda komplexa strukturer. Vi studerar hur de är organiserade i rymden, de krafter som håller ihop dem, och de som bryter isär dem. Vi syntetiserar inte bara naturligt förekommande föreningar, utan även de som aldrig funnits tidigare.

Under mina doktorandstudier har jag fokuserat för att utforska nya metoder att framställa organiska föreningar på ett mer hållbart sätt än de befintliga procedurer som tidigare rapporterats. En annan prioritet för mig har varit att uppnå en god förståelse om hur transformationerna uppstår, att kunna identifiera begränsningarna och kunna förbättra dem ytterligare i framtiden.

I detta avseende har huvudämnet i detta arbete varit baserat på hur alkoholer och aminer kan användas för syntes av mer komplexa föreningar som är av intresse inom flera områden, såsom pesticider, kosmetika, polymerer, och speciellt läkemedel. I enlighet med deras elektroniska egenskaper är alkoholer bra nukleofiler och tenderar att reagera med elektrofila föreningar. Aminogrupper är också elektronegativa och är reaktiva mot elektrofiler. Detta gör att en reaktion mellan en alkohol och en amin inte kan uppstå under normala förhållanden. För att övervinna detta problem beskriver vi ett sätt som består av en första modifiering av alkoholen där vi omvandlar den till en elektrofil, vilket sedan med lätthet reagerar med det andra nukleofila substratet. För att uppnå detta undersöker vi användningen av olika iridiumkatalysatorer. En mer detaljerad beskrivning ges i kapitel 1.

I kapitel 2 beskriver vi cyklodehydreringen av dioler för att bilda cykliska etrar med en bifunktionell iridiumkatalysator. Denna rapport utgjorde den första metoden för att erhålla cykliska etrar *via* väteöverföringsmetodik. Kapitel 3-5 beskriver reaktioner mellan en amin- och en alkoholgrupp. I dessa avsnitt designade vi en ny iridium-baserad katalysator som övervann begränsningarna hos befintliga komplex. I kapitel 3 studeras tillämpningen av denna nya katalysator i reaktioner av aminer och alkoholer. Fördjupad mekanistiska studier presenteras. Kapitel 4 beskrivs syntesen av *N*-modifierade aminosyror. Här har över 100 exempel erhållits i kvantitativa utbyten, och som även undviker användningar av extra derivatiseringssteg och långdragna reningar. Vidare kunde både katalysatorn och lösningsmedlen återvinnas och återanvändas i flera omgångar. I kapitel 5 beskrivs *N*-alkyleringen av ett antal oskyddade aminosocker.



## Previous documents based on this work

This thesis is partly-based on the author's half-time report titled: "*Carbon–Heteroatom Bond-Forming Reactions Mediated by Ir(III) Catalysts. Method Development and Mechanistic Investigations*" (presented on June 21, 2021, Stockholm)

The introduction (Chapter I) has been modified to give a more detailed description of the background of the chemistry presented in this work, as well as of the mechanistic studies used. References have been updated.

Paper I, which was previously presented, has been rewritten and extensively revised. References have been updated.

Papers II and III, which were partially presented in the half-time report, have been completed with the new findings. A major part in Paper III has been included and is described for the first time in this thesis. References have been updated.

Paper IV was not included in the half-time report and has been entirely written for the purpose of this thesis.

# List of publications

This doctoral thesis is based on the following articles, henceforth referred with Roman numerals I-IV in the text:

## Paper I

### **Nonclassical Mechanism in the Cyclodehydration of Diols Catalyzed by a Bifunctional Iridium Complex**

Greco González Miera<sup>#</sup>, Aitor Bermejo López<sup>#</sup>, Elisa Martínez-Castro, Per-Ola Norrby and Belén Martín-Matute.

*Chemistry – A European Journal* **2019**, 25, 2631–2636.

## Paper II

### **A General and “Universal” Catalyst for the Base-Free Selective Mono-*N*-Alkylation of Amines with Alcohols. Insights into the Mechanism**

Aitor Bermejo-López, Man Li, Aditya Dharanipragada, A. Ken Inge, Fahmi Himo and Belén Martín-Matute.

*Manuscript*

## Paper III

### **Selective and Quantitative Functionalization of Unprotected $\alpha$ -Amino Acids Using a Recyclable Homogeneous Catalyst**

Aitor Bermejo-López, Majken Raeder, Elisa Martínez-Castro and Belén Martín-Matute.

*Chem. Accepted*

## Paper IV

### **Direct *N*-alkylation of Unprotected Aminosugars with Alcohols. Fast Access to Highly Functionalized Building Blocks and Biodegradable Surfactants**

Aitor Bermejo-López, Beatriz Saavedra, Kevin Dorst, María Obieta, Patrick Maguire, Göran Widmalm and Belén Martín-Matute.

*Manuscript*

*Related publications by the author not included in this thesis:*

**Selective Synthesis of Imines *via* Photooxidative Amine Cross-Condensation Catalyzed by PCN-222(Pd)**

Aitor Bermejo-López, Sergio Carrasco<sup>#</sup>, Pedro J. Tortajada<sup>#</sup>, Kenji P. M. Kopf, Amparo Sanz-Marco, Mathias S. Hvid, Nina Lock and Belén Martín-Matute.

*ACS Sustainable Chemistry & Engineering* **2021**, 9, 14405–14415.

**Iron-Catalyzed Cross-Coupling of Propargyl Ethers with Grignard Reagents for the Synthesis of Functionalized Allenes and Allenols**

Daniels Posevins, Aitor Bermejo-López and Jan-E. Bäckvall.

*Angewandte Chemie International Edition* **2021**, 60, 22178–22183.

**Iron-Catalyzed Borylation of Propargylic Acetates for the Synthesis of Multisubstituted Allenylboronates**

Aitor Bermejo-López<sup>#</sup>, Wei-Jun Kong<sup>#</sup>, Pedro J. Tortajada, Daniels Posevins, Belén Martín-Matute and Jan-E. Bäckvall.

*Submitted*

**Mechanistic Studies on Iron-Catalyzed Dehydrogenation of Amines Involving Cyclopentadienone Iron Amine Complexes. Evidence for Stepwise Hydride and Proton Transfer**

Srimanta Manna, Joannes Petters, Aitor Bermejo-López, Andrew Ken Inge, Fahmi Himo, and Jan-E. Bäckvall.

*Manuscript*

<sup>#</sup> These authors contributed equally to the publication

# Abbreviations

Abbreviations and acronyms in this work are in agreement with the standards of the American Chemical Society guidelines.<sup>1</sup> Additional non-conventional:

API	Active pharmaceutical ingredients
Boc	<i>tert</i> -Butyloxycarbonyl
CCWT	Continuous Cauchy wavelet transform
Cp	Cyclopentadienyl
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
d.r.	Diastereomeric ratio
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DFT	Density functional theory
EDG	Electron-donating group
<i>ee</i>	Enantiomeric excess
EWG	Electron-withdrawing group
EXAFS	Extended X-ray absorption fine structure
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HOBt	Hydroxybenzotriazole
KIE	Kinetic isotope effect
LPPS	Liquid-phases peptide synthesis
MPV	Meerwin-Ponndorf-Verley
NHC	<i>N</i> -Heterocyclic carbene
NMR	Nuclear magnetic resonance
NTf <sub>2</sub>	Bis(trifluoromethanesulfonyl)imide
OTf	Trifluoromethanesulfonate
OTs	<i>p</i> -Toluene sulfonate
r.d.s.	Rate-determining step
r.t.	Room temperature
ROMP	Ring-opening metathesis polymerization
SPPS	Solid-phases peptide synthesis
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TS	Transition state
VTNA	Variable time normalization analysis
WL	White line
XANES	X-Ray absorption near edge spectroscopy
XAS	X-Ray absorption spectroscopy
ZPE	Zero-point energy

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<sup>1</sup>The ACS Style Guide, American Chemical Society, Oxford University Press, New York 2006.

# Table of Contents

Abstract .....	i
Populärvetenskaplig sammanfattning .....	ii
Previous documents based on this work .....	iii
List of publications .....	iv
Abbreviations .....	vi
1. Introduction .....	1
1.1. Catalysis in organic chemistry .....	1
1.1.1. Organometallic catalysis .....	2
1.2. <i>N</i> -Heterocyclic carbenes (NHC) .....	3
1.3. Hydrogen transfer reactions .....	5
1.4. Metal-ligand cooperation, bifunctionality .....	7
1.5. Mechanistic tools in organic chemistry .....	8
1.5.1. Hammett studies .....	9
1.5.2. Deuterium labelling investigations .....	10
1.6. Purpose and objectives of this thesis .....	11
2. C–O Bond Forming Reactions <i>via</i> Hydrogen Transfer. Synthesis of Substituted Tetrahydrofuranes and Tetrahydropyrans from Diols (Paper I) .....	13
2.1. Introduction .....	13
2.2. Cyclodehydration of substituted 1,4- and 1,5 diols .....	14
2.3. Mechanistic studies .....	16
2.4. Proposed mechanism .....	18
2.5. Conclusions .....	19
3. C–N Bond Forming Reactions <i>via</i> Hydrogen Transfer. <i>N</i> -Alkylation with Alcohols Catalyzed by an Iridium(III)-NHC Complex (Papers II, III and IV) .....	20
3.1. Introduction .....	20
3.2. Catalyst design: Synthesis of a new Ir(III)-NHC complex .....	22
3.3. A General and “Universal” Catalyst for the Base-Free Selective Mono- <i>N</i> -Alkylation of Amines with Alcohols. Insights into the Mechanism (Paper II) .....	25
3.3.1. Background and purpose of this work .....	25
3.3.2. Optimization of the reaction conditions and robustness test .....	26
3.3.3. Substrate scope and limitations .....	28
3.3.4. Mechanistic studies .....	31
3.3.4.1. Study of the reaction orders. Variable time normalization analysis .....	33
3.3.4.2. Density functional theory (DFT) .....	34
3.3.4.3. Structural studies: X-ray absorption spectroscopy .....	36
3.3.5. Summary of the mechanistic studies and proposed catalytic cycle .....	37

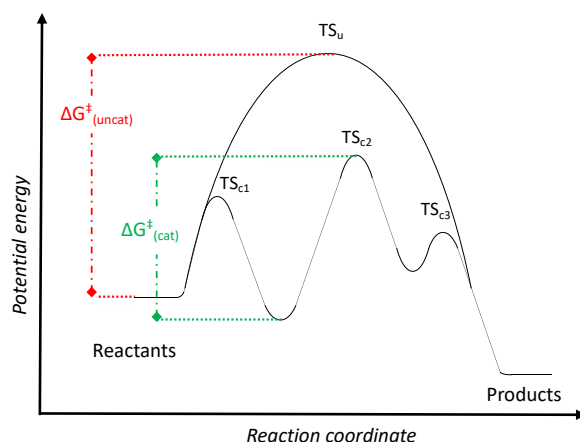
3.3.6.	Conclusions .....	39
3.4.	Selective and Quantitative Functionalization of Unprotected Amino Acids Using a Recyclable Homogeneous Catalyst (Paper III) .....	40
3.4.1.	Background and purpose of this work.....	40
3.4.2.	Optimization of the reaction conditions and robustness test.....	41
3.4.3.	Substrate scope and limitations .....	44
3.4.3.1.	Direct synthesis of non-natural amino acids .....	44
3.4.3.2.	Facile access to mono-methylated amino acids .....	48
3.4.3.3.	Synthesis of biodegradable surfactants .....	49
3.4.3.4.	Synthesis of isotopically labelled <i>N</i> -alkylated amino acids .....	50
3.4.4.	Synthesis of modified peptides .....	51
3.4.5.	Scalability of the reaction .....	54
3.4.6.	Recyclability test .....	54
3.4.7.	Mechanistic investigations and proposed mechanism.....	56
3.4.8.	Proposed mechanism .....	57
3.4.9.	Conclusions .....	58
3.5.	Direct <i>N</i> -Alkylation of Unprotected Amino Sugars with Alcohols. Fast Access to Highly Functionalized Building Blocks and Biodegradable Surfactants (Paper IV) ..	59
3.5.1.	Background .....	59
3.5.2.	Synthesis of the starting materials .....	61
3.5.3.	Optimization of the reaction conditions .....	61
3.5.4.	Substrate Scope and Limitations .....	63
3.5.4.1.	Selective <i>N</i> -alkylation of unprotected amino sugars with alcohols .....	63
3.5.4.2.	Synthesis of carbohydrate-based surfactants.....	67
3.5.5.	Proposed mechanism .....	68
3.5.6.	Conclusions .....	68
4.	Concluding remarks.....	69
5.	Appendix A. Author's contribution list .....	71
6.	Appendix B. Reprint permissions.....	72
7.	Appendix C. Experimental Data.....	73
8.	Acknowledgements.....	74
9.	References .....	76

# 1. Introduction

## 1.1. Catalysis in organic chemistry

Organic chemistry is the scientific study of the synthesis, properties, structure and reactivity of all carbon-containing compounds. It covers not only the study of this specific element, but also its interaction with other elements. The most common ones are nitrogen, oxygen, sulfur, halogens, phosphorus and silicon, as they have high affinity to form chemical bonds with carbon.

A main objective for organic chemists is to develop methodologies that grant access to organic compounds in an efficient way. A good understanding of the reaction mechanism is key to achieve such a goal. Catalysis is defined as a process in which the reaction rate is increased by the assistance of a reagent, commonly known as the catalyst, and that is not itself consumed during the reaction.<sup>1</sup> In the case of catalytic reactions, understanding the mode of action of the catalysts enables the design of better and more efficient processes. This, in turn, can result in new processes that produce reduced amounts of waste and that have a decreased use of dangerous or toxic chemicals, while still providing the desired products in high yields. Indeed, catalysis is one of the “Twelve Principles of Green Chemistry” outlined by Anastas and Warner.<sup>2-4</sup> In every chemical transformation there is an energy barrier ( $\Delta G^\ddagger$ ) that must be overcome for it to proceed. The role of the catalyst can either be lowering such energy barrier or allowing the transformation to occur through different and less energy-requiring pathways (Figure 1). In addition, the use of a catalyst may open a new range of reactions that cannot be achieved efficiently in a non-catalyzed approach.<sup>5,6</sup>

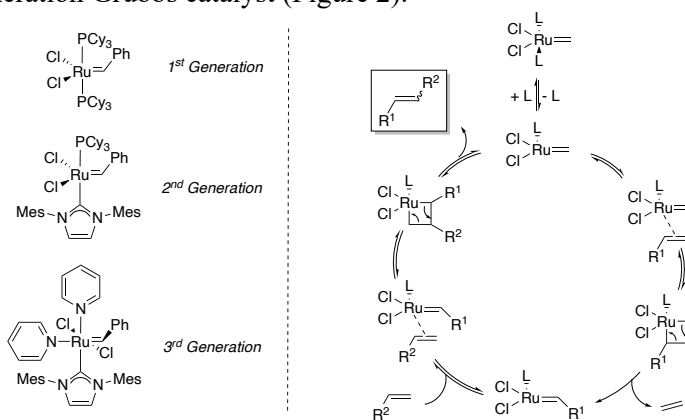


**Figure 1.** Energy profiles of a catalyzed vs an uncatalyzed reaction.

Catalysts can be divided into two main groups depending on the phase they are present in during the reaction. Those are homogeneous and heterogeneous in nature. The former refers to the reactions where the catalyst is present in the same phase as the substrates, whereas the latter variant exists when the catalyst is in a different phase. Due to the high selectivity and efficiency that homogeneous catalysts commonly present,<sup>7,8</sup> advances in synthetic techniques allow for a controlled immobilization of such species, making them more robust, easier to separate and to recycle.<sup>9,10</sup>

### 1.1.1. Organometallic catalysis

The use of transition metals in catalysis for the construction of carbon–carbon and carbon–heteroatom bonds has been widely investigated over the past decades. Examples of catalytic reactions mediated by transition metal catalysts include oxidations and reductions, polymerizations, cross-couplings, and carbonylations, to name a few.<sup>11–14</sup> A significant example was reported by Grubbs in 1992, where the ring-opening metathesis polymerization (ROMP) of norbornene was efficiently achieved by a ruthenium complex.<sup>15</sup> The relevance of this work was acknowledged later on and contributed to the Nobel Prize award in Chemistry in 2005. Over the time, the very-well established metathesis catalyst developed by Grubbs was subjected to further modifications with the aim of enhancing the reactivity. Substitution of a tricyclohexylphosphine ligand with an *N*-heterocyclic carbene resulted in a second-generation catalyst, which was less sensitive to air and so, easier to handle (*vide infra*).<sup>16</sup> Further, replacing the phosphine group with two more labile pyridine ligands was proven to drastically increase the rate of the reaction. In some cases, the reaction rates were increased by more than a millionfold. This highly active catalyst derivative is commonly referred to as third-generation Grubbs catalyst (Figure 2).<sup>17</sup>



**Figure 2.** First-, second-, and third-generation Grubbs catalyst (left). General mechanism of olefin metathesis (right).

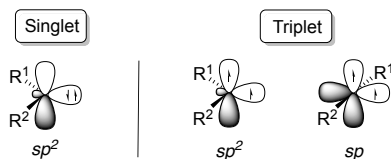


Transition-metal catalysts have proven to be a powerful tool in synthetic organic chemistry. Their coordination capability and ability to change oxidation states offer new pathways to access compounds that would not be accessible otherwise.

## 1.2. *N*-Heterocyclic carbenes (NHC)

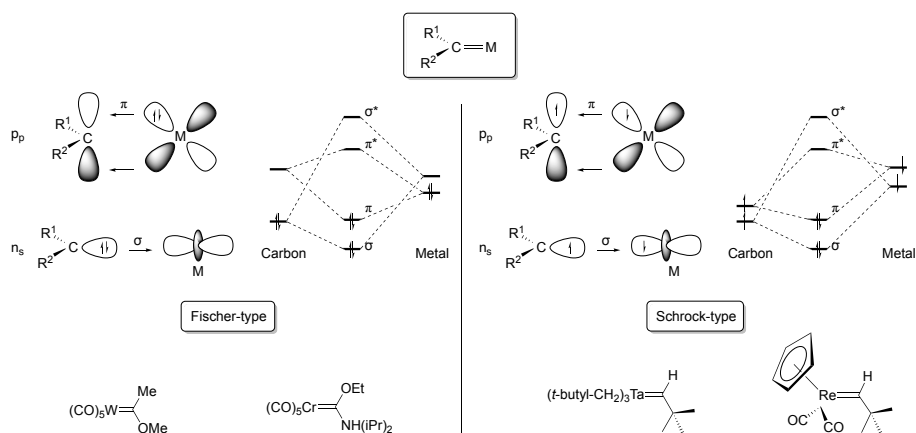
The carbene terminology finds its origins in 1855, when Geuther and Hermann observed a divalent carbon atom-containing intermediate bearing unshared two electrons, that resulted from subjecting chloroform to basic conditions.<sup>18</sup> However, it was not until 1964 when Fischer and Maasböl reported the synthesis and characterization of a methoxymethylcarbene bound to pentacarbonyl tungsten, confirming what would be the first metal-carbene complex ever described (*vide infra*, Figure 4).<sup>19</sup>

Carbenes are classified into singlet and triplet carbenes. They differ from each other in the electronic spins they possess. On the one hand, singlet carbenes present the two electrons in the same molecular orbital (diamagnetic) showing an  $sp^2$  hybridization. On the other hand, triplet carbenes present one electron in each orbital (paramagnetic) and can show a bent or linear conformation ( $sp^2$ - or  $sp$ -hybridization, respectively) (Figure 3).



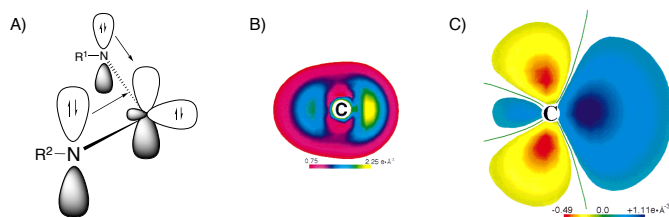
**Figure 3.** Ground electronic states for singlet (left) and triplet (right) carbenes.

Furthermore, carbenes are known to have a high affinity towards transition metals, forming metal-carbene complexes. These complexes can be further divided into two main groups depending on the nucleophilicity character of the carbenoid atom called Fischer-<sup>19</sup> or Schrock-carbenes.<sup>20</sup> The former, presents  $\pi$ -donor substituents bonded to the carbenoid carbon such as alkoxy or alkylated amino groups, making the singlet state more stable. The latter, presents alkyl groups as substituents, making the carbenoid carbon highly nucleophilic (triplet state), and being commonly found with metals bearing higher oxidation states (Figure 4).



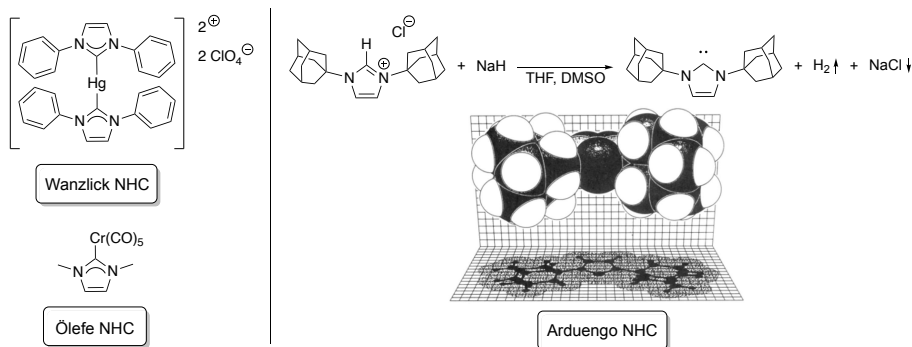
**Figure 4.** Major orbital interactions and bonding in Fischer- and Schrock-carbenes (top). Selected examples of Fischer- and Schrock-carbenes (bottom).

The presence of heteroatoms bonded to the carbenoid carbon may have a direct influence, stabilizing singlet-type carbenes. Indeed, in 1999 Arduengo reported a remarkable study of the electronic distribution within 1,3,4,5-tetramethylimidazol-2-ylidene, an *N*-heterocyclic carbene.<sup>21</sup> Due to the electronic contribution from the p-orbitals of the heteroatoms, the carbenoid carbon is stabilized in a  $sp^2$ -hybridization and singlet state, forcing the electron density of the lone pair to lie on the same orbital of the carbon (Figure 5).



**Figure 5.** A) Stabilization of singlet-type carbenes, B) Carbene lone pair electron density, and C) Electron density profile of the carbenoid carbon.<sup>21</sup>

*N*-Heterocyclic carbenes (NHCs) have become ubiquitous ligands in metal complexes. Although they were reported for the first time in 1968 by Wanzlick<sup>22</sup> and Ölefe,<sup>23</sup> no isolation of such kind of compounds was achieved until 1991, when Arduengo isolated a crystalline imidazole-2-ylidene derivative (Figure 6).<sup>24</sup>



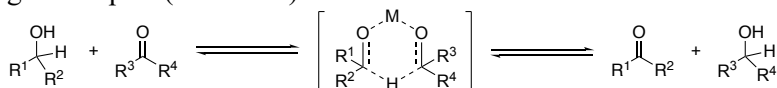
**Figure 6.** First reported NHCs (left) and first isolated NHC (right). Space filling of X-ray structure (bottom right).<sup>24</sup>

In addition to their peculiar electronic properties, NHCs offer the possibility to be functionalized. This feature provides the possibility to design a ligand for a catalyst in the most optimal way to catalyze a target transformation. This versatility has been highlighted by Peris in a review article where NHCs are referred to as “smart ligands”.<sup>25</sup>

### 1.3. Hydrogen transfer reactions

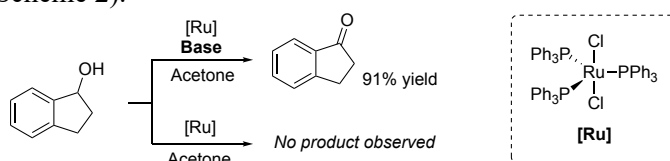
Transfer hydrogenations consist of the addition of hydrogen to a molecule from a source different than H<sub>2</sub>. It is presented as an elegant alternative to direct hydrogenations that does not require hydrogen gas or complex instrumental set ups (*i.e.*, hydrogenation reactors). In this methodology, the hydrogenating agents are easily accessible, inexpensive and easy to handle. Examples of hydrogen donors include abundant alcohols (*i.e.*, 2-propanol) or formic acid.

The first transfer hydrogenation reaction was published in 1925 by Meerwein, Ponndorf and Verley.<sup>26-28</sup> It was demonstrated that stoichiometric amounts of an aluminum alkoxide were able to reduce a ketone to the corresponding alcohol in the presence of a sacrificial secondary alcohol as hydrogen donor. It was suggested that this transformation occurs *via* formation of a six-member ring intermediate where the metal center is coordinated to both substrates. A few years later, the reverse reactivity was reported by Oppenauer, yielding oxidized compounds from the corresponding alcohols by using acetone as hydrogen acceptor (Scheme 1).<sup>29</sup>



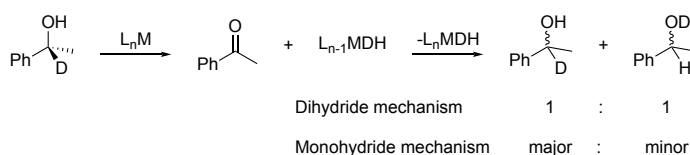
**Scheme 1.** MPV and Oppenauer processes *via* cyclic transition state.

Since then, the hydrogen transfer methodology has attracted the attention of the scientific community. Environmental concerns in chemistry have increased the demand for “greener” methods. Another important feature relies on the easy accessibility and the abundance of alcohols, some of them available from renewable feedstock,<sup>30</sup> making transfer hydrogenation a very attractive approach. Nowadays, the use of transition metal complexes as catalyst for this transformation is very well-established, increasing significantly the overall atom-economy of the reaction.<sup>31,32</sup> A very early example reported by Henbest in 1967 showed the affinity of an iridium complex towards the transfer hydrogenation from 2-propanol to  $\alpha,\beta$ -unsaturated ketones.<sup>33</sup> A few years later, Sasson and Blum showed that a ruthenium complex  $\text{RuCl}_2(\text{PPh}_3)_3$  was also active in a very similar catalytic system.<sup>34</sup> Further studies proved that the addition of base enhanced this kind of reactivity, becoming in some cases an essential additive for some reactions to work (Scheme 2).<sup>35,36</sup>



**Scheme 2.** Effect of base in a transition-metal catalyzed Oppenauer-type oxidation.

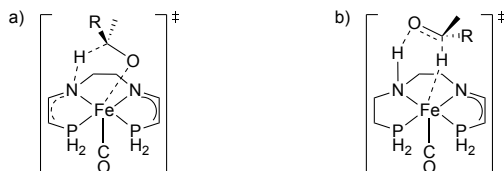
Transfer hydrogenation reactions, such as that shown in Scheme 2, commonly involve the formation of metal-hydride species as key intermediates, as depicted in the general mechanism shown in Scheme 3. Depending on whether the proton and the hydride maintain their identity throughout the catalytic cycle, these transformations may follow a dihydride- or monohydride mechanism.<sup>36</sup> In the former, the proton and the  $\alpha$ -hydrogen from the alcohol donor are both transferred to the metal center forming a metal dihydride, while in the latter their identity are maintained. Simple deuterium-labelling experiments can be performed to identify the major pathway through which the reaction proceeds (Scheme 3).<sup>37</sup>



**Scheme 3.** Deuterium-labelling experiment monohydride vs dihydride mechanisms.

A second mechanism classification relies on the way the substrate interacts with the metal catalyst. In those instances when the alcohol substrate directly coordinates to the metal center through the oxygen atom are referred to as inner-sphere mechanisms, whereas the outer-sphere pathways do not involve

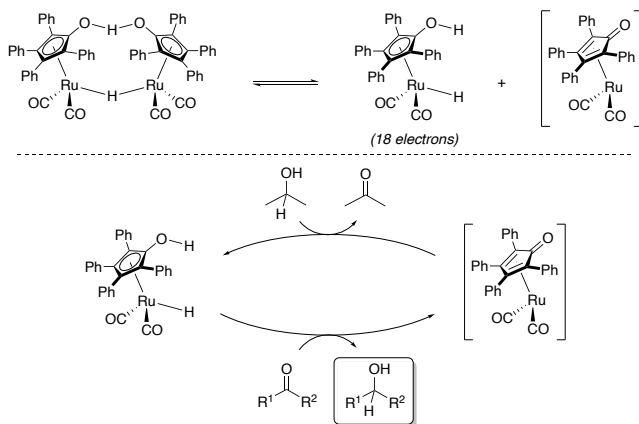
any direct interaction between the alcohol oxygen and the metal center (Figure 7).<sup>36,38</sup> Whether one or the other is followed will depend on different factors, such as the catalyst structure and the reaction conditions, and in some cases it may even dictate the outcome of the reaction.<sup>39</sup> When the catalyst operates through an outer-sphere mechanism, a 6-membered ring is formed in the transition state, where both the hydrogen and the proton may be transferred simultaneously (Figure 7, b).<sup>40</sup>



**Figure 7.** Inner-sphere (left) and Outer-sphere (right) transition states of a transfer hydrogenation reaction catalyzed by an iron(II) (bis)eneamido complex.

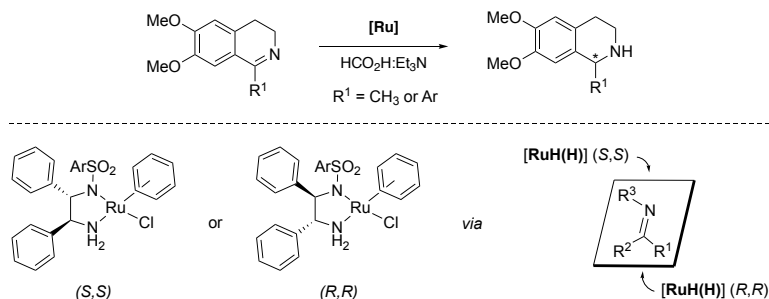
## 1.4. Metal-ligand cooperation, bifunctionality

Traditionally, metal-based catalysts present the metal center as the only active site. However, the catalyst can be designed to bear a ligand that can participate in bond activation steps. This mode of action is denominated “metal-ligand cooperation” or “bifunctionality”. The design of bifunctional catalysts raised tremendous interest in the scientific community after Shvo reported in 1986 for the first time a very efficient catalyst used for hydrogenating ketones.<sup>41</sup> In this piece of work, the authors showed the activity of a dinuclear ruthenium complex that dissociates into an 18-electron complex, which behaves as reducing agent, and its oxidized analogue. The former is regenerated upon dehydrogenation of 2-propanol (Scheme 4).



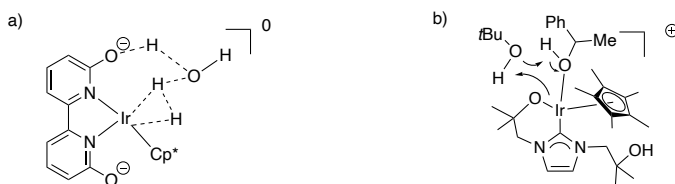
**Scheme 4.** Shvo's catalyst mediated transfer hydrogenation reaction.

As shown above in Scheme 4, the carbonyl group in the tetraphenyl-substituted Cp ligand of the dissociated dimer played an active role in the reaction process acting as Lewis base in the alcohol oxidation step (*vide supra*, Scheme 3). This mode of action is referred to as metal-ligand cooperation and it was introduced for the first time by Noyori in 1996 when he together with Ikariya reported the reduction of various aromatic ketones and imines *via* hydrogen transfer in an stereoselective manner (Scheme 5).<sup>42,43,44,11,45</sup>



**Scheme 5.** Asymmetric transfer hydrogenation of imines by Noyori.

It is worth mentioning that there are other aspects apart from the catalyst that are to be taken into account in these processes. Indeed, additives, conditions and even the solvent may have a tremendous influence. In some instances, reports describing the active role of protic solvents facilitating the oxidation of the alcohol substrate, or simply stabilizing one or more transition states are found (Figure 8).<sup>46,47</sup>



**Figure 8.** Two examples of TS stabilization by solvent assistance a) water, b) *tert*-butanol.

## 1.5. Mechanistic tools in organic chemistry

The study of the reaction mechanism is a primary topic for organic chemists. It covers how a reacting system progresses from starting materials to products, and having a good insight to it is crucial for the development of new and improved methodologies. In the search for an ideal case where the effect of all present compounds and all the intermediates involved are identified, several different but yet closely related experimental tools can be employed.

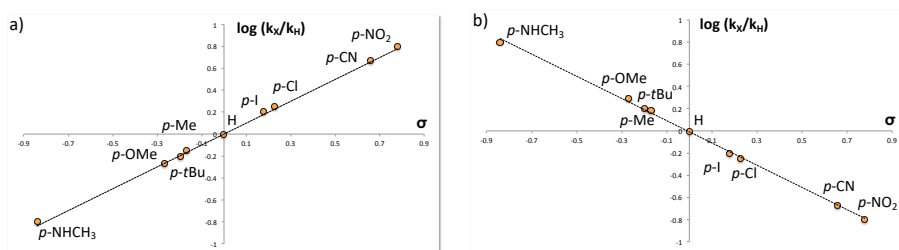
### 1.5.1. Hammett studies

The electronic nature of the substrate may translate to a difference in reaction rate. In 1937, Louis Hammett reported how the acidity of benzoic acids was affected depending on the electronic properties of a variety of substituents in either *para*- or *meta*- positions in the aromatic ring.<sup>48,49</sup> The author observed an empirical relationship in the form of a linear trend between the electronic nature of the substituents and the reaction rates. These results allowed him to assign a constant value (sigma,  $\sigma$ ) for each substituent. Setting the non-substituted substrate as reference ( $\sigma = 0$ ), electron-donating groups (EDG) are found to have negative sigma values ( $\sigma < 0$ ), while electron-withdrawing ones (EWG) present positive sigma values ( $\sigma > 0$ ).<sup>50</sup> Interestingly, it was observed that the same study could be extended to other chemical transformations, maintaining the linearity. Lastly, by adding a new variable (rho,  $\rho$ ) the sigma values assigned could be used as reference and as a tool to the study of the effect of the substituents in a given transformation (eqn. (1)). This new factor is named reaction constant and it shows the sensitivity of the reaction towards the electronic nature of the substituents. In cases where the transformation involves formation of carbocations, a different set of sigma values ( $\sigma^+$ ) are used.

(1)

$$\text{Log } (k_x / k_H) = \rho \sigma$$

Interestingly, different scenarios can be observed when plotting the logarithm of the ratio of the reaction rates vs the already tabulated sigma values. Commonly, linear trends with either a positive or negative slope are obtained. In the former situation, the fact that electron-poor substrates react faster indicates that electron density is built in the rate-limiting transition state (TS). In the latter case, the opposite situation would be taking place (Figure 9 a) and b), respectively).<sup>51,52</sup>



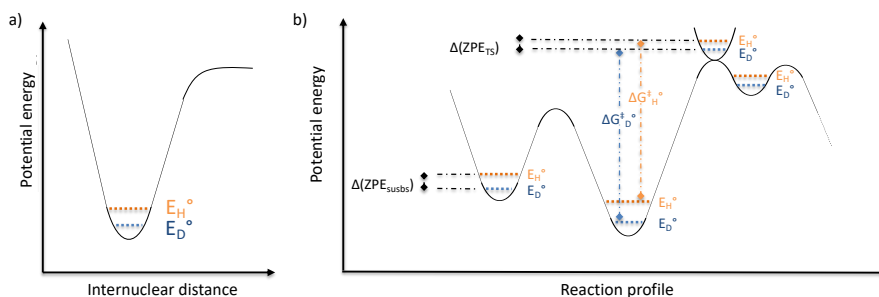
**Figure 9.** a) Gain of electron density in the rate-determining TS and b) Loss of electron density in the rate-determining TS.

In some cases, there exist deviations from linearity in the Hammett plot, observing a change in the slope that can result in either a concave upwards or downwards trend. These results suggest a change in the mechanism or in the rate-determining step, respectively.<sup>53</sup>

### 1.5.2. Deuterium labelling investigations

At a first sight, deuterium does not seem to present a very different chemical effect compared to hydrogen, since they differ by a single neutron. However, in some cases a slight modification such as the substitution of hydrogen by its isotope deuterium can significantly affect the overall reaction rate. Having in mind that deuterium–carbon bonds are between six to ten times stronger than the corresponding hydrogen–carbon analogues, the rate of the reaction will be affected by a change of C–H to C–D if the cleavage of such bonds is involved in the slowest step, namely the rate-determining step (r.d.s.) of the reaction pathway.<sup>54</sup> The change in reaction rates caused by the presence of different isotopes in the starting material is denominated kinetic isotope effect (KIE),<sup>55</sup> and to get an overview of what this mechanistic tool consists of, the theory behind potential energies at an atomic scale should be discussed.

The formation of a chemical bond is directly related to the distance and type of interaction between two atoms, and as a result of that, the potential energy of a bond varies depending on how far the two atoms to study are from each other. Plotting the potential energy vs the bond distance, results in the so-called Morse potential curve.<sup>56</sup> The lowest potential energy of a molecule does not lie at the bottom of the well, but at the zero-point energy (ZPE) of that specific system due to the Heisenberg uncertainty principle.<sup>57,58</sup> This energy level depends on the atomic weight of the atoms involved (Figure 10,a)).



**Figure 10.** a) Morse potential curve and b) Comparison of hydrogen vs deuterium in a multistep reaction.



From that point, the potential energy rises as the bond distance increases, reaching a maximum at which the bond under study cleaves ( $\Delta G_x^\ddagger$ ). In the following figure, the different energies of a C–H ( $E_H$ ) and C–D ( $E_D$ ) bond in a multistep reaction are shown (Figure 10,b)).

In this regard, the KIE equation is described by the rates between the non-deuterated and the deuterated substrates.<sup>59</sup> The value obtained gives us information about whether this specific C–H or C–D bond is being modified in the rate determining step. If so, the result obtained will be either larger than 1 ( $k_H/k_D > 1$ , kinetic isotope effect) or lower ( $k_H/k_D < 1$ ) if the hybridization is changing from  $sp^2$  to  $sp^3$  (eqn. (2)).<sup>60</sup>

(2)

$$KIE = k_H / k_D$$

## 1.6. Purpose and objectives of this thesis

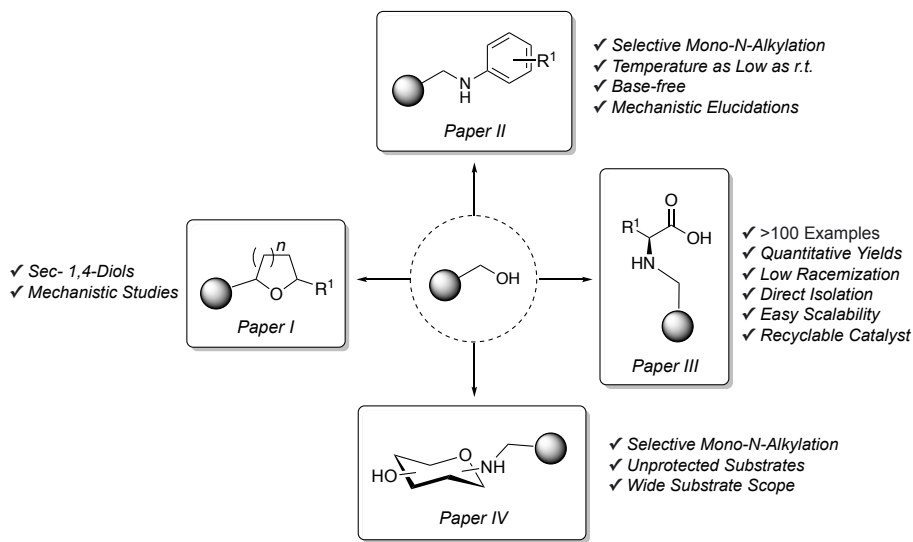
The work presented in this thesis covers investigations in the use of iridium-based complexes as catalyst for C–O and C–N bond formation reactions *via* transfer hydrogenation pathways (Scheme 6). This reactivity is presented as a sustainable approach and with high atom economy, in which alcohol substrates are used as alkylating agents, and water is formed as the only byproduct. The thesis is divided into two distinctive parts that differ in the iridium catalyst employed.

In the first paper, the applicability of an alkoxy-functionalized Ir-NHC catalyst for the synthesis of cyclic ethers from diols is described. Deep mechanistic investigations allow us to propose a hydrogen transfer mechanism for this transformation that up to date has not been explored.

The second part of the thesis covers the following three projects and starts with the design and synthesis of a new amino-functionalized Ir-NHC complex. This new catalyst is aimed to overcome the limitations shown by already existing catalysts. Then, the target is set to develop a general catalyst for the *N*-alkylation of aromatic and aliphatic amines with a broad variety of alcohols at room temperature, and in the absence of base.

Consequently, the novel synthesis of selective mono-*N*-modified  $\alpha$ -amino acids from unprotected substrates is set as a major goal. Access to these valuable compounds opens up new paths for the synthesis of *N*-modified peptides.

Further, the last work aims at developing a catalytic system to afford *N*-modified carbohydrates. The high functionalization level that they present makes them very challenging substrates to work with. In this work, the goal is to expand our methodology to non-protected aminosugars, avoiding tedious protection/deprotection steps, and therefore developing a highly atom-economical synthesis of this important molecules.

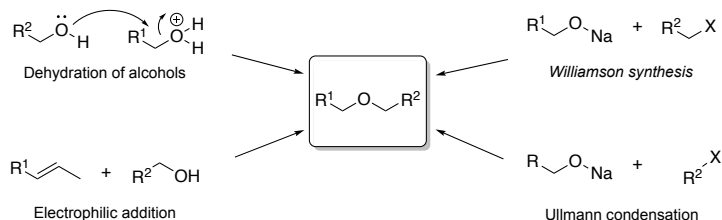


**Scheme 6.** Aim of this thesis.

## 2. C–O Bond Forming Reactions *via* Hydrogen Transfer. Synthesis of Substituted Tetrahydrofuranes and Tetrahydropyrans from Diols (Paper I)

### 2.1. Introduction

An important and widely used family of organic compounds are aliphatic ethers.<sup>61</sup> Due to their high stability towards diluted acids/bases, oxidizing/reducing agents and metals (with the exception of ketals, acetals and epoxides), they are commonly used as solvents. When it comes to the synthesis of those compounds, there are several well-established methodologies in the literature. As shown in Scheme 7, different approaches give access to aliphatic ethers. In this instances, good control of pH, the use of strong bases, or the presence of good leaving groups is required in most cases (Scheme 7).

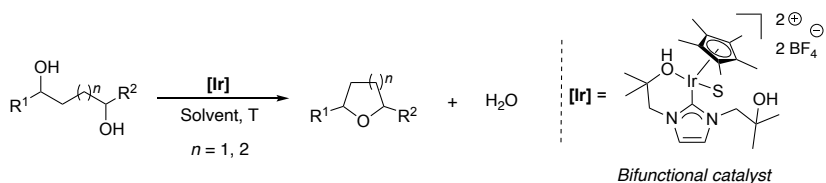


**Scheme 7.** Different approaches for the synthesis of aliphatic ethers.

These traditional methods, however, encounter many difficulties to access cyclic ethers. In this manner, diverse studies have been described using either Lewis<sup>62,63</sup> or Brønsted acids,<sup>64-66</sup> or *via* nucleophilic substitution.<sup>67,68</sup> Surprisingly, the possibility of using a metal as catalyst and the transfer hydrogenation methodology as a greener alternative to afford cyclic ethers from diols have remained unexplored.

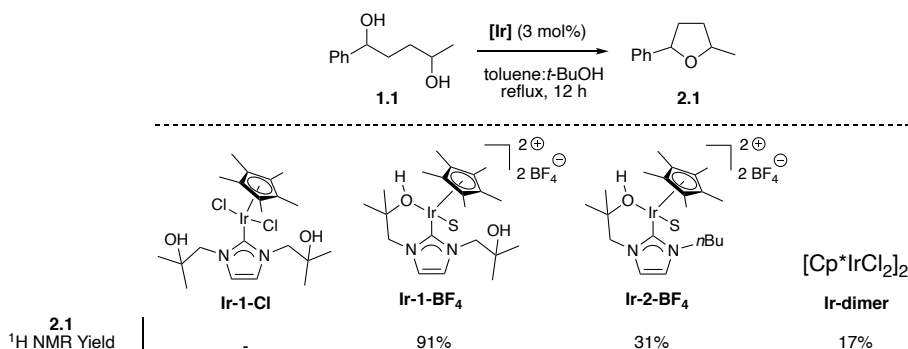
## 2.2. Cyclodehydration of substituted 1,4- and 1,5 diols

In 2018, our group reported an active dihydroxy-functionalized Ir(III) complex (**Ir-1-BF<sub>4</sub>**) towards the acceptorless dehydrogenation of alcohols.<sup>47</sup> Inspired by these results, we investigated the application of that catalytic system on compounds containing two alcohol moieties. It was speculated that the expected oxidation of one alcohol could consequently be followed by nucleophilic attack by the second alcohol, forming the corresponding unsaturated cyclic ether, which is subsequently reduced (Scheme 8).



**Scheme 8.** Cyclodehydration of diols *via* hydrogen transfer. S = solvent.

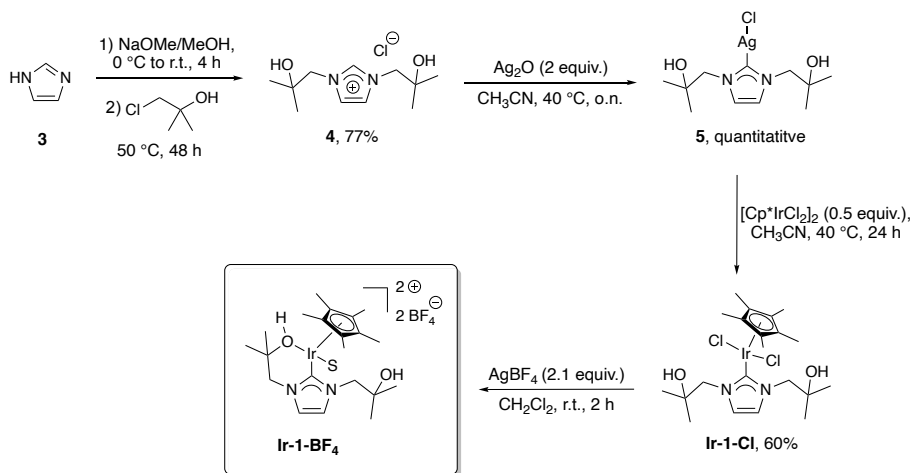
In light of that hypothesis and in the course of our investigations, we first conducted the optimization of the reaction conditions. Results derived from the catalyst screening as well as the optimal reaction conditions are summarized in Figure 11.<sup>69</sup> 1-Phenyl-1,4-pentanediol **1.1** was chosen as model substrate for the initial investigations. The best result was obtained when using biscationic complex **Ir-1-BF<sub>4</sub>** as catalyst in a mixture of toluene and *tert*-butanol as solvent, yielding the desired cyclized product **2.1** in 91% yield (d.r. = 0.45:1), as determined by <sup>1</sup>H NMR spectroscopy. The use of other Ir(III) catalysts, such as **Ir-2-BF<sub>4</sub>** and iridium dimer [Cp\*IrCl<sub>2</sub>]<sub>2</sub>, yielded complex mixtures of oxidized byproducts, while the reaction did not proceed in the absence of a catalyst (Figure 11). Complex **Ir-2-BF<sub>4</sub>** was synthesized following the synthetic procedure previously reported by our group. The synthesis of **Ir-1-BF<sub>4</sub>** is described below.



\*The optimization of the reaction was performed during my master thesis project in the BMM group.

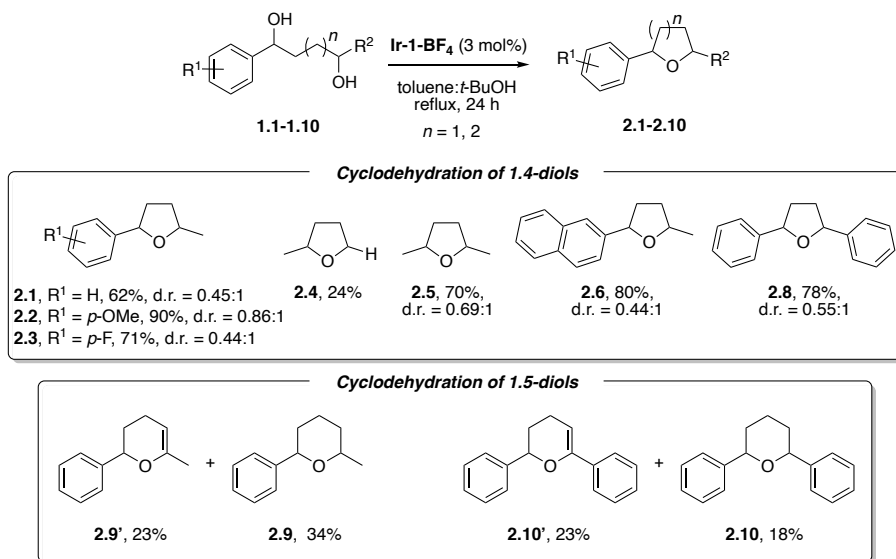
**Figure 11.** Catalyst screening under optimized reaction conditions. S = solvent.

Dihydroxy-functionalized complex **Ir-1-Cl** was synthesized from imidazole in a four-step synthetic route. A double alkylation yielded salt **4** in good yield, and consequent treatment with silver oxide, afforded silver carbene **5**. Upon transmetalation with commercially available iridium dimer  $[\text{Cp}^*\text{IrCl}_2]_2$ , air stable precatalyst **Ir-1-Cl** was obtained as an orange crystalline powder. A last activation of complex **Ir-1-Cl** with silver tetrafluoroborate formed active catalyst species **Ir-1-BF<sub>4</sub>**, which was then used *in situ* for the cyclodehydration of diols (Scheme 9).



**Scheme 9.** Synthetic route to obtain catalyst **Ir-1-BF<sub>4</sub>**. Isolated Yields. S = solvent.

With the catalyst in hand, a variety of 1,4- and 1,5-diols were subjected to the cyclodehydration reaction under the optimal conditions. A selection of the substrate scope is shown in the Scheme 10. The corresponding tetrahydrofuranes resulting from the cyclodehydration of 1,4-diols containing a benzylic alcohol moiety were obtained in very good yields regardless of the electronic nature of the substituents on the aryl group (Scheme 10, **2.1-2.3**). More challenging fully aliphatic substrates pentane-1,4-diol and hexane-2,5-diol were also tolerated and afforded the desired products in moderate to low yield (**2.4** and **2.5**, 24% and 70% isolated yield, respectively). The catalytic system could also be applied to 1,5-diols to yield a mixture of 2,3-dihydropyranes and their corresponding saturated analogs, albeit in lower yields (**2.9'**, **2.9**, **2.10'** and **2.10**).

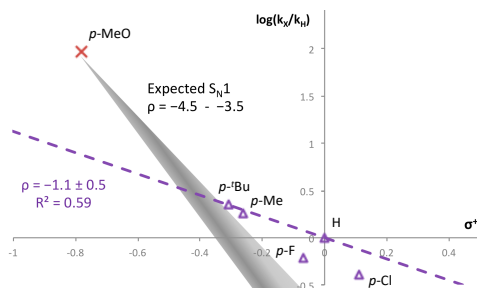


**Scheme 10.** Cyclodehydration of 1,4- and 1,5-diols catalyzed by complex **Ir-1-BF<sub>4</sub>**. Isolated yields. Selected examples.

### 2.3. Mechanistic studies

Motivated by the possibility of this transformation following a non-reported hydrogen transfer pathway, the mechanism was investigated.

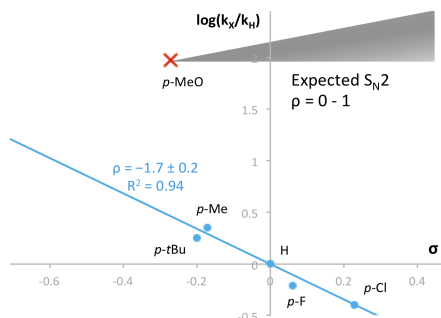
The first subject to study was the effect of the electronic nature of the substrates in the reaction rate. In this regard, Hammett studies were carried out on the cyclodehydration of electron-rich and electron-poor 1,4-*para*-substituted diols. We first tested if the transformation involved formation of carbocation species, which would mean that a S<sub>N</sub>1 pathway is the predominant. This was examined by plotting the log(*k<sub>X</sub>*/*k<sub>H</sub>*) for each specific substrate vs the corresponding ( $\sigma^+$ ) values. Although a fair correlation was



**Figure 12.** Hammet plot for the cyclodehydration of 1,4-diols vs sigma plus.

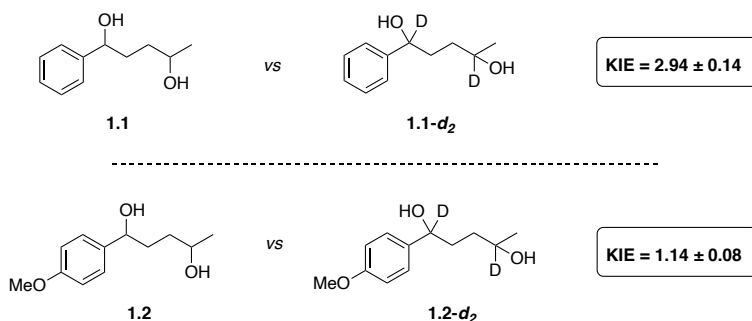
observed between most of the substrates, the very electron-rich *para*-methoxy substituted 1,4-diol presented a significant higher rate than expected. The fact that electron-rich substrates react faster than the rest fits with an S<sub>N</sub>1 mechanism. If that would be the case, the expected  $\rho$  value would be between  $-4.5$  and  $-3.5$ , which is clearly not the case (Figure 12).<sup>70</sup>

Consequently, a neutral pathway for this transformation was considered and investigated. When using the tabulated neutral sigma values for the substrates under study, a nearly perfect correlation was obtained (Figure 13,  $R^2 = 0.94$ ). Once again, the very electron-rich *para*-methoxy substituted substrate showed a completely different behavior, reacting  $10^4$  times faster than expected. These results led us to suggest that except for the very electron-rich substrate **1.2**, a neutral pathway (either  $S_N2$  or hydrogen transfer) is preferred. Had they followed an  $S_N2$  mechanism, the more electron-poor 1,4-diols would react faster, with an expected  $\rho$  value between 0 and 1, which is not in agreement with the experimental results. Indeed, the  $\rho$  value of  $-1.7$  observed is in agreement with the  $\rho$  values reported in the literature for hydrogen transfer reactions of *sec*-benzylic alcohols (Figure 13).<sup>70</sup>



**Figure 13.** Hammett plot for the cyclodehydration of 1,4-diols vs sigma neutral.

Intrigued by this behavior and to further assess the hypothesis that a hydrogen transfer mechanism was operating for all substrates except for the very electron-rich one **1.2**, deuterium labelling studies were carried out. Indeed, kinetic isotope investigations on the non-substituted and *para*-methoxy-substituted substrates gave different outcomes. While in the former case a KIE value of  $2.94 \pm 0.14$  suggested a C–H bond cleavage involved in the rate-determining step (oxidation), the latter resulted in a very low KIE value ( $1.14 \pm 0.08$ ), confirming that the cyclodehydration of substrate **1.2** followed a different pathway (Scheme 11).



**Scheme 11.** Deuterium labelling studies of the cyclization of non-substituted (top) and *para*-methoxy substituted 1,4-diol (bottom).

Encouraged by these studies, carbocation trapping experiments were performed on an analogue of substrate **1.2**, resulting in the formation of the product obtained from the nucleophilic attack of indole (see Supporting Information Paper I for details). To summarize, the different behavior in the Hammett studies, together with the low KIE value and the fact that a carbocation is being formed in one of the intermediates, we conclude that very electron rich tetrahydrofuran **2.2** was afforded predominantly *via* S<sub>N</sub>1 mechanism.

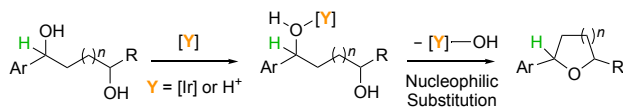
## 2.4. Proposed mechanism

The results obtained from the different mechanistic studies lead to suggest that with the exception of the very electron-rich 1,4-diol, a hydrogen transfer pathway is operating in this catalytic system. In contrast, the *p*-methoxy substituted substrate follows a Lewis acid catalyzed mechanism. The dialkoxy-functionalized iridium complex operates as a bifunctional catalyst assisting in both the oxidation and reduction steps.

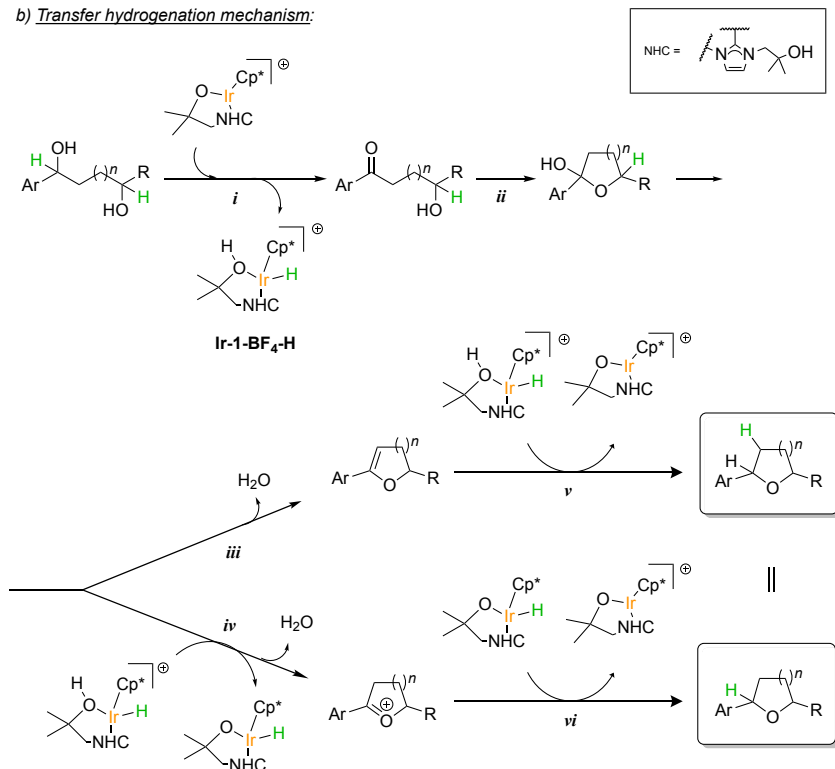
Firstly, the benzylic alcohol is oxidized releasing a metal-hydride species (**Ir-1-BF<sub>4</sub>-H**) (Scheme 12, step i). Consequently, an internal cyclodehydration leads to the formation of the corresponding dihydrofuran and dihydropyran (Scheme 12, steps ii and iii), which are then hydrogenated by the metal-hydride species affording the desired fully saturated cyclic ethers (Scheme 12, steps iv, v).



a) Lewis acid catalysis mechanism:



b) Transfer hydrogenation mechanism:



**Scheme 12.** Proposed mechanism for the cyclodehydration of diols.

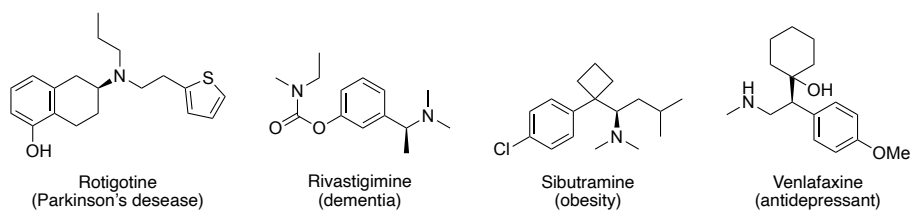
## 2.5. Conclusions

In this work, we have investigated the synthesis of cyclic ethers from diols. For this, a bifunctional Ir-NHC catalyst has been employed and the mechanism has been elucidated by a compilation of results obtained from different mechanistic tools such as Hammett studies and KIE investigations. Strong evidences were obtained suggesting that while very electron-rich substrates may follow an  $S_N1$  pathway, the cyclodehydration of the rest of 1,4- and 1,5- diols to their corresponding cyclic ethers occurs *via* hydrogen transfer methodology.

### 3. C–N Bond Forming Reactions *via* Hydrogen Transfer. *N*-Alkylation with Alcohols Catalyzed by an Iridium(III)-NHC Complex (Papers II, III and IV)

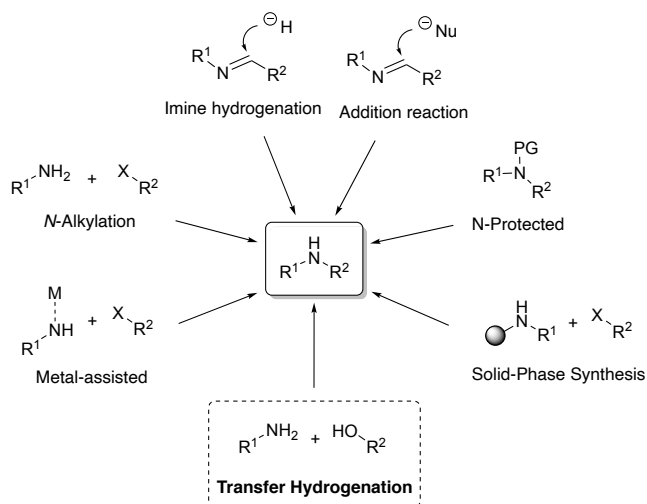
#### 3.1. Introduction

The amine group is an essential moiety that is present in a wide range of bioactive organic compounds, from proteins, enzymes, peptides and hormones to agrochemicals, polymers and pharmaceutical drugs (Figure 14).<sup>71-74</sup>



**Figure 14.** Examples amine-containing compounds.

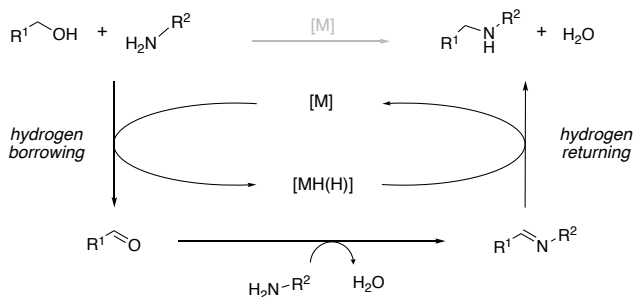
During the last decades, the development of new and more efficient methodologies to access higher order amines has received tremendous attention.<sup>75</sup> Secondary amines are of special interest in pharmacophores since they present important physiological activities.<sup>76</sup> Furthermore, they can be used as key scaffolds to obtain tertiary or quaternary amines with different substitution patterns.<sup>77</sup> However, although there are many methodologies when it comes to C–N bond formation, traditional methods are highly substrate dependent and quite often require harsh reaction conditions to yield the desired products (*vide infra*, Scheme 13).<sup>78</sup> Due to the widespread interest on these highly valuable moieties, it is of importance to develop effective and sustainable methods to construct C–N bonds in a selective manner to complement the existing ones. As an attractive alternative we find the so-called hydrogen autotransfer reactivity. This transformation has risen the interest in the scientific community and it consists of the use of alcohols as alkylating agents. It is an atom-economical approach that reduces the amount of waste considerably, and results in formation of water as the only byproduct (Scheme 13).



**Scheme 13.** Most representative methods to obtain *N*-alkylated compounds.

Since reported for the first time by Grigg<sup>79</sup> and Watanabe<sup>80</sup> in 1981 using homogeneous metal complexes, numerous examples have proven their efficiency using a variety of catalysts. Among the most efficient, we find transition-metal complexes containing manganese,<sup>81</sup> iron,<sup>82</sup> cobalt,<sup>83</sup> copper,<sup>84,85</sup> ruthenium,<sup>86-88</sup> palladium<sup>89,90</sup> and iridium as metal center.<sup>91-94</sup>

In general, the mechanism consists of three main steps. First, oxidation of the alcohol substrate, forming a metal-hydride species (Scheme 14, [MH(H)]), gives the corresponding carbonyl analog. Then, amine condensation results in formation of an imine intermediate. This species is further reduced by the metal-hydride complex previously formed, yielding the final saturated product and regenerating the active catalyst species (Scheme 14).



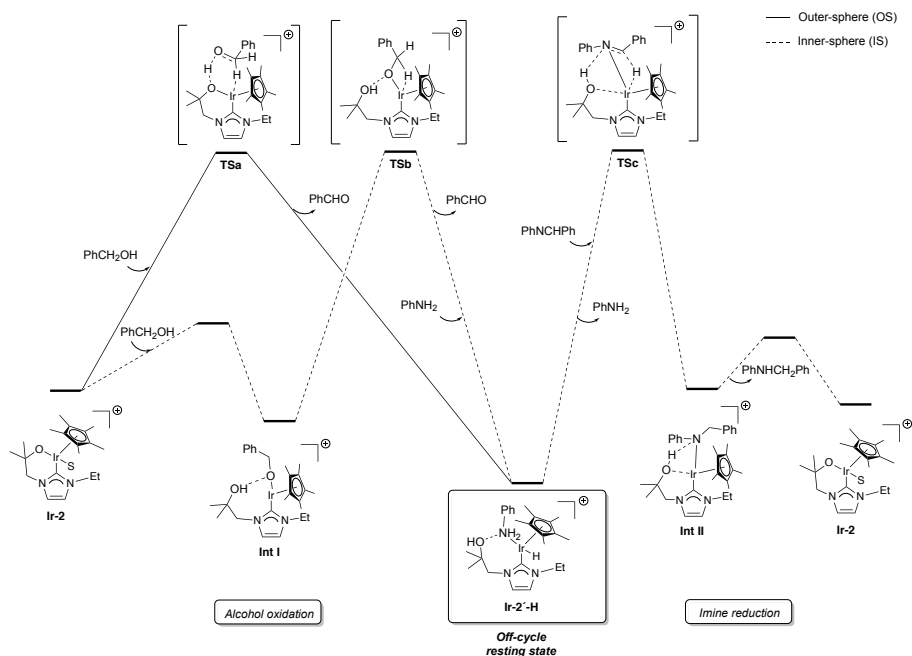
**Scheme 14.** General mechanism for the *N*-alkylation of amines with alcohols *via* hydrogen transfer.

The “green” feature of this reaction, promoted by the low generation of waste and excellent atom economy makes it a very attractive methodology to study and develop. Despite the success already reported, the design of more robust catalytic systems with broad functional group tolerance remains a big challenge, particularly when it comes to aliphatic amine substrates. Further, the application of this method to the late-stage functionalization of organic compounds has not been significantly explored.

### 3.2. Catalyst design: Synthesis of a new Ir(III)-NHC complex

Finding more efficient pathways than the existing ones is a common aim for every chemist. A reasonable approach to achieve this is by acquiring a detailed picture of the mechanism that is operating in a specific transformation. In this regard, understanding the role of each component, and especially that of the catalyst, is key.

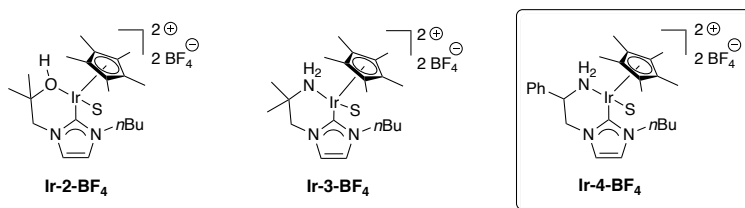
In 2012, the Martín-Matute group reported a bifunctional Ir(III)-NHC catalyst bearing an alkoxy functionality on the *N*-heterocyclic carbene ligand, formed from the corresponding alcohol-functionalized **Ir-2** (which undergoes deprotonation under the reaction conditions) for the *N*-alkylation of anilines with aliphatic and benzylic alcohols.<sup>93</sup> Shortly after, extensive mechanistic studies including theoretical calculations revealed the formation of an off-cycle resting state (Figure 15).<sup>95</sup> This complex was formed after the alcohol oxidation step, which could take place by outer-sphere (**TSa**) or inner-sphere (**TSb**) pathways, and consisted of an iridium hydride species with the aniline substrate coordinated (Figure 15, **Ir-2'-H**). The traceability of such stable complex also provided information about the r.d.s. of the reaction, which consisted of a series of elementary steps involved in the imine reduction through a favored inner sphere mechanism (Figure 15).



**Figure 15.** Simplification of the calculated free-energy profile. Only key transition states shown. Identification of resting state **Ir-2'-H**.<sup>95</sup>

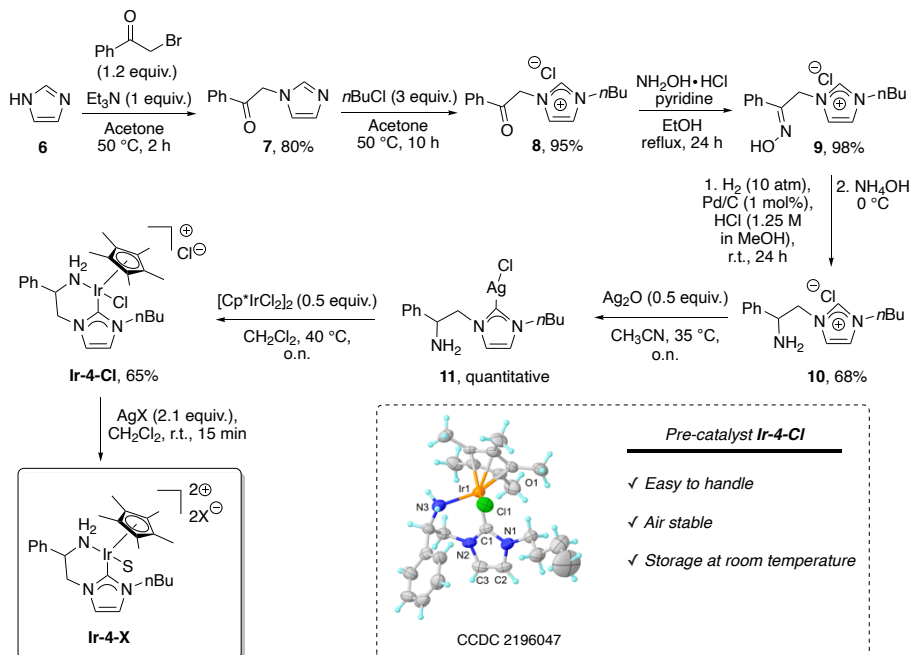
Despite the remarkable activity showed by the reported alkoxy-functionalized Ir(III) complex (**Ir-2**), it was limited to relatively simple alcohols and electron-poor amines. With more electron-rich amines, namely aliphatic amines, the formation of the mentioned resting state hampered the reactivity.<sup>93</sup> Our ambition then turned into the design of a new generation of the catalyst that would diminish, or even completely inhibit, formation of such a resting state, enhancing the reaction rate and offering the potential to broaden the applications.

To address these questions and motivated by the limitations of the previous alkoxy-functionalized catalyst (Figure 16, left), we embarked on the design of a new complex bearing an amine group instead of the alcohol moiety. Our hypothesis was that the stronger  $\sigma$ -donating character of the N vs that of the O would enforce coordination of the nitrogen functionality on the wingtip to the Ir center, consequently inhibiting the formation of the off-cycle species observed with the previous catalyst.<sup>95</sup> We therefore proceeded with the synthesis of two novel amino-functionalized Ir(III) complexes. The former bearing an amino group instead of the hydroxy analog, while the latter contains a benzylic amino substituent (Figure 16).



**Figure 16.** Previous catalyst<sup>93</sup> (**Ir-2**, left); Amino analogue<sup>47</sup> (**Ir-3**, middle); New catalyst (**Ir-4**, right).

The new amino-functionalized Ir(III) catalyst **Ir-4-Cl** is synthesized as shown in Scheme 15. Starting from imidazole (**6**), a double consecutive alkylation, first with 2-bromoacetophenone and then *n*-butyl chloride, affords salt **8** in a high yield over the two steps. After treatment with hydroxylamine hydrochloride, the resulting compound **9** is hydrogenated in the presence of palladium on carbon to yield the final ligand **10**. From there, upon reaction with silver oxide, carbene **11** transmetallates with commercially available iridium dimer [Cp\*IrCl<sub>2</sub>]<sub>2</sub> affording the pre-catalyst **Ir-4-Cl** (characterized by single crystal X-ray diffraction analysis),<sup>47</sup> which remains air stable and can be easily stored. With complex **Ir-4-Cl** in hand, a simple activation with a silver salt provides the active catalytic species **Ir-4-X**, which is used *in situ* for every reaction.

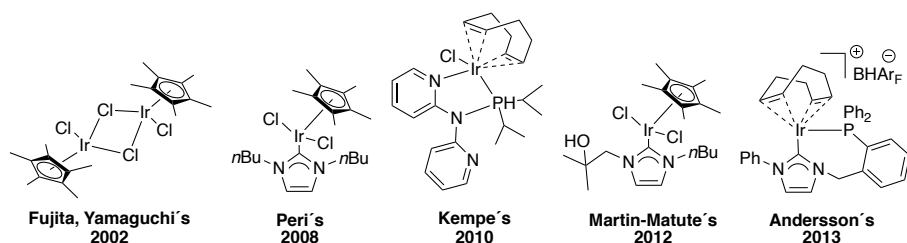


**Scheme 15.** Synthetic route of Ir(III) complex **Ir-4-X**. S = solvent.

### 3.3. A General and “Universal” Catalyst for the Base-Free Selective Mono-*N*-Alkylation of Amines with Alcohols. Insights into the Mechanism (Paper II)

#### 3.3.1. Background and purpose of this work

Focusing on the evolution of iridium-based complexes employed for the *N*-alkylation of amines with alcohols, we find an early example dating from 2002, where Yamaguchi's and Fujita's group showed the potential activity of the commercially available  $[\text{Cp}^*\text{IrCl}_2]_2$ .<sup>96</sup> Since then, a variety of modifications and functionalizations have been made to the ligands increasing the reactivity and capability of the method (Figure 17).

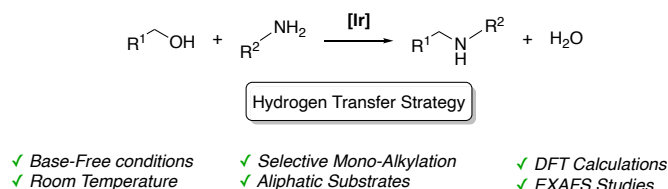


**Figure 17.** Selected Ir(III) catalysts used in *N*-alkylation processes.

Kempe's group, among others, have developed iridium complexes that are able to *N*-alkylate amines with alcohols at temperatures as low as 70 °C.<sup>97</sup> Previously in our group, we reported the *N*-alkylation of amines with alcohols for the first time in the absence of a base at 50 °C, although longer reaction times were needed.<sup>93</sup> In 2013, the Andersson's group reported the *N*-alkylation of aromatic amines for the first time at room temperature, although stoichiometric base was needed.<sup>94</sup>

To the best of our knowledge, these are the mildest reaction conditions reported for this process. In a very recent work, Ke's group demonstrated that this reaction could be performed in an aqueous media, using a different metal-based type catalyst.<sup>98</sup>

In this chapter, the use of an NHC-Ir(III) complex that is able to catalyze the alkylation of amines with alcohols at room temperature and under base-free conditions will be described. The method has remarkable broad substrate scope, and works well with both anilines and even aliphatic amines (Scheme 16).



**Scheme 16.** *N*-Alkylation of amines with alcohols in mild conditions.

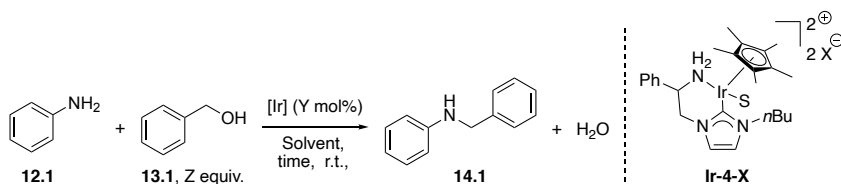
### 3.3.2. Optimization of the reaction conditions and robustness test

The new NHC-Ir(III) complex **Ir-4-BF<sub>4</sub>** was tested on the *N*-alkylation of aniline **12.1** with benzyl alcohol **13.1** in various solvents and temperatures. In Table 1 the results at room temperature are shown. In toluene, the solvent used with the previously reported catalytic system in the Martín-Matute group,<sup>93</sup> only traces of product were observed (Table 1, entry 1). While protic polar solvents like water and isopropanol completely hampered the reactivity, fluorinated solvent 2,2,2-trifluoroethanol (TFE) showed an increase in yield up to 30% (Table 1, entries 2 and 3 vs 4).

Motivated by that result, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was tested under otherwise the same conditions, and to our delight, the desired product **14.1** was obtained quantitatively after 24 h under base-free conditions and at room temperature (Table 1, entry 5). The excellent reactivity was maintained after shortening the reaction time to 15 h, even lowering the equivalents of the alcohol substrate (1 equiv., Table 1, entries 6 and 7). Formation of product dropped when decreasing the catalytic loading, however, a slight improvement was observed at higher concentration (1 M vs 2 M, Table 1, entry 8 vs 9).

Then, a screening of silver salts used in the activation of the catalyst was performed with shorter reaction times. Similar reactivity was observed, with the exception of NTF<sub>2</sub><sup>−</sup> anion, where the yield dropped to 52% (Table 1, entries 12 to 15). A last experiment combining the best conditions found allowed formation of mono-alkylated product **14.1** in quantitative yield after 15 h at room temperature, using the catalyst with the OTf<sup>−</sup> anion, and with 1.5 mol% catalyst loading (Table 1, entry 16).



**Table 1.** Reaction development.<sup>a</sup>

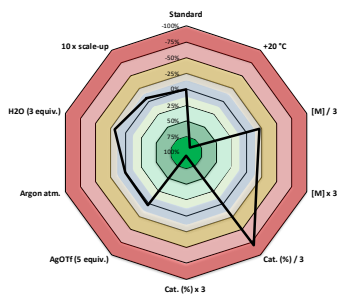
Entry	Solvent	X <sup>-</sup>	Y	Z	Time (h)	Yield (%) <sup>d</sup>
1	Toluene	BF <sub>4</sub> <sup>-</sup>	2.0	2.0	24	5
2	H <sub>2</sub> O	BF <sub>4</sub> <sup>-</sup>	2.0	2.0	24	-
3	<i>i</i> -PrOH	BF <sub>4</sub> <sup>-</sup>	2.0	2.0	24	-
4	TFE	BF <sub>4</sub> <sup>-</sup>	2.0	2.0	24	30
5	HFIP	BF <sub>4</sub> <sup>-</sup>	2.0	2.0	24	>99
6	HFIP	BF <sub>4</sub> <sup>-</sup>	2.0	2.0	15	>99
7	HFIP	BF <sub>4</sub> <sup>-</sup>	2.0	1.0	15	>99
8	HFIP	BF <sub>4</sub> <sup>-</sup>	1.5	1.0	15	82
9 <sup>b</sup>	HFIP	BF <sub>4</sub> <sup>-</sup>	1.5	1.0	15	90
10 <sup>c</sup>	HFIP	BF <sub>4</sub> <sup>-</sup>	1.5	1.0	15	63
11 <sup>b</sup>	HFIP	BF <sub>4</sub> <sup>-</sup>	1.5	1.0	8	63
12 <sup>b</sup>	HFIP	OTs <sup>-</sup>	1.5	1.0	8	-
13 <sup>b</sup>	HFIP	OTf <sup>-</sup>	1.5	1.0	8	77
14 <sup>b</sup>	HFIP	PF <sub>6</sub> <sup>-</sup>	1.5	1.0	8	72
15 <sup>b</sup>	HFIP	NTf <sub>2</sub> <sup>-</sup>	1.5	1.0	8	52
16 <sup>b</sup>	HFIP	OTf <sup>-</sup>	1.5	1.0	15	>99

<sup>a</sup>PhNH<sub>2</sub> (1.0 mmol), solvent (1 mL). <sup>b</sup>Concentration = 2.0 M. <sup>c</sup>Concentration = 4.0 M.

<sup>d</sup>Yield of *N*-benzylbenzylamine determined by <sup>1</sup>H NMR spectroscopic analysis using 2,3,5,6-tetrachloronitrobenzene as an internal standard. S = solvent.

With the optimal conditions in hand, the factors that this transformation is affected by were investigated. A sensitivity assessment was conducted on the model reaction and the results are shown in Figure 18.<sup>99</sup> Although the reaction is conducted under ambient conditions, the same outcome was obtained using inert atmosphere. A large excess of silver salt in the activation step of the catalyst (*vide supra*, Scheme 15) did not affect noticeably the reactivity. As previously observed, the reaction rate is dependent of the concentration of the substrates and catalyst loading. Equimolar amount of H<sub>2</sub>O was tolerated. Lastly, the reaction was proven to be easily scalable, maintaining excellent activity (see radar diagram in Figure 18).

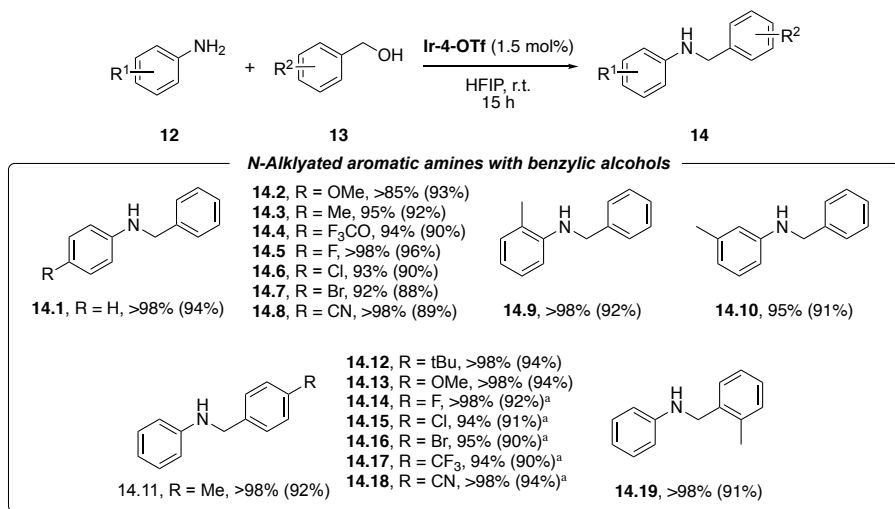
Conditions	% NMR yield	Deviation
Standard	41%	
+20 °C	78%	90%
[M] / 3	53%	-22%
[M] x 3	56%	-18%
Cat. (%) / 3	13%	-81%
Cat. (%) x 3	99%	95%
AgOTf (5 equiv.)	66%	-3%
Argon atm.	67%	-1%
H <sub>2</sub> O (3 equiv.)	55%	-19%
10 x scale-up	64%	-6%



**Figure 18.** Robustness test performed on the *N*-alkylation of aniline with benzyl alcohol catalyzed by **Ir-4-OTf** after 6 h reaction time.

### 3.3.3. Substrate scope and limitations

As for every new catalyst developed in organic synthesis, it is of crucial importance to show its applicability. The optimal reaction conditions were first applied to the *N*-alkylation of a range of different substituted anilines with benzyl alcohol. In all cases excellent yields were obtained regardless of the electronic properties of the amine substrate. The substituents were not limited to be in the *para*-position of the aryl ring and fluoro- substituted anilines were tolerated (Scheme 17, **14.1-14.10**). The electronic nature of the benzylic alcohol substrate was then modified, and again, excellent reactivity was observed. In this case, although the more electron poor alcohols needed longer reaction times (36 h vs 15 h), the desired products were formed without the need of increased temperatures (Scheme 17, **14.11-14.19**).

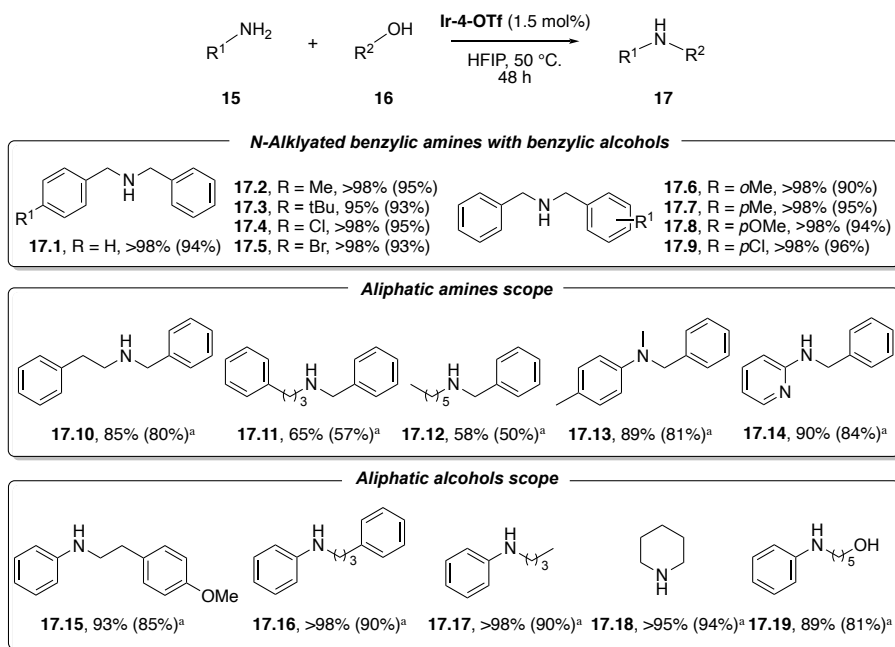


**Scheme 17.** Substrate scope of aromatic amines with benzylic alcohols. Conversion determined by <sup>1</sup>H NMR spectroscopic analysis. Isolated yields are shown in parenthesis. <sup>a</sup>36 h reaction time.

To expand the methodology, the catalytic system was tested on more nucleophilic amine substrates. By increasing the temperature to 50 °C a family of different substituted benzylic amines yielded the desired higher order amines using benzylic alcohols as alkylating agents. As previously observed, the electronic nature or the position of the substituent in any of the substrates did not affect the reactivity significantly, although electron-poor alcohols also required longer times (Scheme 18, **17.1-17.9**). Encouraged by the high activity of the method, a further optimization round towards more challenging substrates was carried out. Gratifyingly, by rising the temperature to 90 °C, we had access to a variety of products with a higher aliphatic character (Scheme 18, **17.10-17.19**).

The substrates used under these conditions are known to be challenging in this transformation due to the high affinity to coordinate to the metal, inhibiting the catalysis. Phenylethyl- and phenylpropylamine afforded the corresponding products in high yields (Scheme 18, **17.10** and **17.11**). By reacting fully aliphatic hexylamine with benzyl alcohol, the corresponding product was obtained in 50% isolated yield (Scheme 18, **17.12**). A secondary amine could also be used yielding the desired tertiary amine **17.13**. Furthermore, heteroatomic compound 2-aminopyridine was efficiently alkylated with benzyl alcohol yielding product **17.14**, which is an important building block in drugs and insecticides.<sup>100,101</sup> Regarding the scope of alcohols, very high yields were obtained using 4-methoxyphenylethanol and phenylpropanol (Scheme 18, **17.15** and **17.16**, respectively). Aliphatic 5-aminopentanol and easily available *n*-butanol could also be used as alkylating agents in this transformation (Scheme 18, **17.17** and **17.18**).

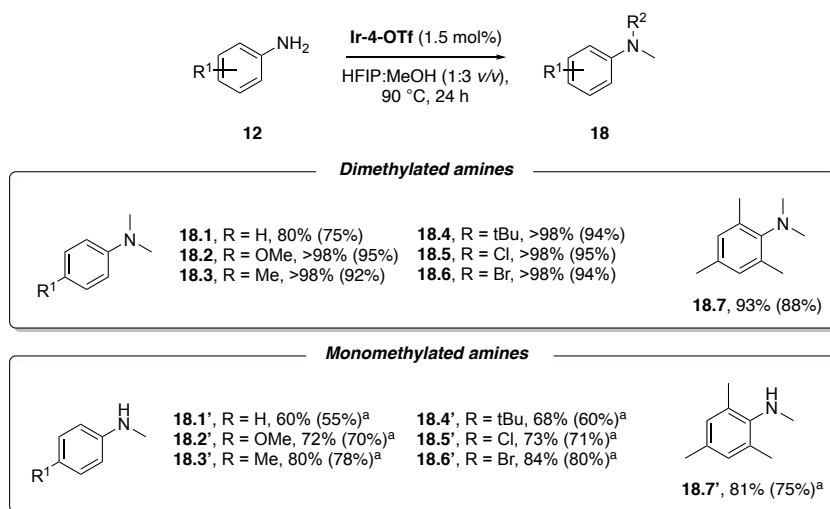
Lastly, the excellent selectivity towards mono-*N*-alkylation of this catalyst is demonstrated using 1,5-pentanediol as substrate. Monoalkylated product **17.19** was obtained in high yield, while formation of the corresponding cyclized analog was not observed in the reaction mixture.



**Scheme 18.** Substrate scope of benzylic- and aliphatic amines with alcohols. Conversion determined by <sup>1</sup>H NMR spectroscopic analysis. Isolated yields are shown in parenthesis. <sup>a</sup>90 °C, 24 h.

Moreover, the use of the simplest alcohol as alkylating agent, methanol, was investigated. Methylation is highly important in medicinal chemistry, due to the magic methyl effect,<sup>102,103</sup> namely the profound effect that a CH<sub>3</sub> group can have on the bioactivity or selectivity of a molecule.<sup>104</sup> Motivated by this challenge, we performed a short optimization of the initial reaction conditions to access methylated anilines. The catalyst showed good reactivity when using methanol as co-solvent, affording bismethylated anilines in good yields (Scheme 19, **18.1-18.7**) at 90 °C.

Interestingly, we noticed formation of traces of mono-methylated products in some reactions. We then discovered that the selectivity between mono- and dimethylation was purely temperature dependent, a factor that could easily be controlled. As a result, by lowering the temperature to 50 °C, monomethylated anilines **18.1'-18.7'** were obtained selectively in synthetically useful yields (Scheme 19).

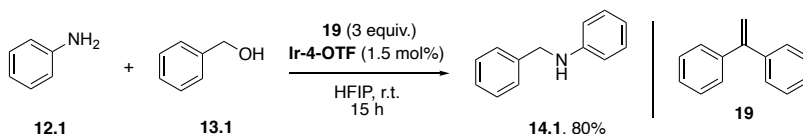


**Scheme 19.** Substrate scope of di- and monomethylated amines. Conversion determined by  $^1\text{H}$  NMR spectroscopic analysis. Isolated yields are shown in parenthesis. <sup>a</sup>50 °C.

Satisfied by the wide applicability of this catalytic system, a series of experiments were designed and carried out to obtain insights into the reaction mechanism.

### 3.3.4. Mechanistic studies

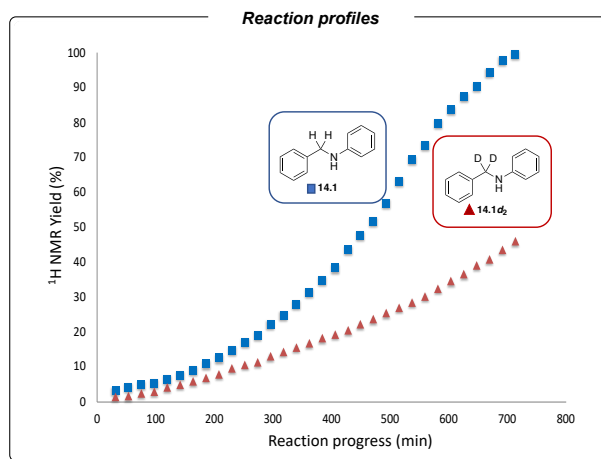
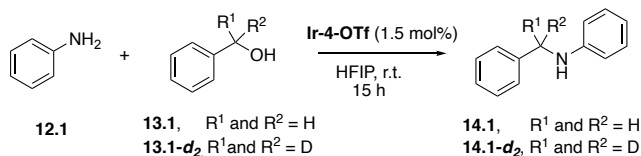
Firstly, experiments were carried out to discard that a radical pathway may be occurring. When 1,1-diphenylethylene (**19**) was used as additive in the *N*-alkylation of aniline (**12.1**) with benzyl alcohol (**13.1**), the desired product *N*-benzylaniline (**14.1**) was obtained in 80%  $^1\text{H}$  NMR yield (Scheme 20). This result rules out a possible radical pathway.



**Scheme 20.** Radical trapping experiment using 1,1-diphenylethylene (**19**) as radical scavenger. Conversion determined by  $^1\text{H}$  NMR spectroscopic analysis using 2,3,5,6-tetrachloronitrobenzene as an internal standard.

Next, the reaction between aniline **12.1** and benzyl alcohol **13.1** was closely monitored by  $^1\text{H}$  NMR spectroscopy until completion. Interestingly, an induction period lasting for 4 h until the yield was ca 15% was observed. Then, the reaction rate increases noticeably until ca 80% yield (Figure 19). When the effect of the deuterated analog **13.1-*d*<sub>2</sub>** as alkylating substrate was

examined under the exact same conditions, a substantial difference in rate was observed (Figure 19). This trend suggests the oxidation of the alcohol might be one of the slow steps in the catalytic cycle.



**Figure 19.** Full reaction profile obtained from  $^1\text{H}$  NMR spectroscopy (acquisitions continuously acquired).

A difference in rates was clearly seen from independent reactions using benzyl alcohol or its corresponding deuterated analog as substrates. By studying the initial rates, a decay of the alcohol concentrations as a function of time was plotted, obtaining a KIE of  $1.9 \pm 0.1$ .<sup>54</sup> The difference in rates increases as the reaction proceeds. This result suggests that the alcohol oxidation step is one of the slowest steps of the overall reaction. Hammett plot studies<sup>48</sup> were also performed. The results from the relative reactivities of *para*-substituted anilines showed that electron poor anilines react faster. This could be explained by the fact that the higher nucleophilicity of electron-rich anilines results in a better coordination to the metal center and thus inhibit its activity. In contrast, investigation on the relative reaction rates of *para*-substituted benzyl alcohols showed that electron poor ones react slower. This result indicates that a partial positive charge builds up in the benzylic carbon during the rate-determining step. Thus, the transition state of such step is stabilized by electron rich benzyl alcohols (see Supporting Information Paper II for details).

### 3.3.4.1. Study of the reaction orders. Variable time normalization analysis

In line with our investigations, we decided to study the reaction orders of the species involved in the reaction. Indeed, the approach reported by Burés *et al.* was applied.<sup>105,106</sup> In their work, they develop a method to calculate the reaction orders of transformations that present an induction period by directly comparing reaction concentration profiles. To achieve this, variable time normalization analysis (VTNA) has to be applied. This technique requires data throughout the whole reaction and not only initial rates. Then, by normalizing the time scale at certain concentration of one of the specific reaction species, the direct comparison of concentration profiles becomes possible and effective (eqn (1)).<sup>105</sup>

(1)

$$\Sigma[A]^{\alpha}[B]^{\beta}[\text{cat}]^{\gamma}\Delta t = \sum_{i=1}^n \left( \frac{[A]_i + [A]_{i-1}}{2} \right)^{\alpha} \left( \frac{[B]_i + [B]_{i-1}}{2} \right)^{\beta} [\text{cat}]^{\gamma} (t_i - t_{i-1})$$

Data treatment revealed a high dependance on the concentration of benzyl alcohol, behaving as 2<sup>nd</sup> order reagent. This result would imply that more than one molecule of benzyl alcohol is involved in the rate determining step. In regards to the aniline substrate, and in contrast with the previous study where we use the alcohol-functionalized Ir(III) complex **Ir-2-BF<sub>4</sub>**,<sup>95</sup> different concentrations of aniline did not affect the reaction process (zero order). The catalyst **Ir-4-OTf** showed a 1<sup>st</sup> order behavior, meaning that one molecule of the catalyst is involved in the rate determining step. In the same regard, the imine intermediate did not seem to lower nor increase the reaction rate (zero order). Interestingly, when studying the reaction order of the benzylated amine product **14.1**, we observed a behavior corresponding to a reaction order between 0 and 1. We attributed this last result to be the cause of the induction period observed in the overall reaction profile (*vide supra*, Figure 19). This could be explained by a potential competition between the aniline substrate and the higher order aniline for coordination to the iridium complex, forming a resting state or an off-cycle intermediate similar to the resting state formed with **Ir-2-BF<sub>4</sub>** (*vide supra*, Figure 15).<sup>95</sup>

These results obtained from the study of the reaction orders applying the VTNA together with the deuterium labelling studies, where we observe a clear difference in rate when deuterated benzyl alcohol **13.1-d<sub>2</sub>** was used, point to the oxidation of the alcohol substrate as one of the slowest steps of the catalytic cycle (see Supporting Information Paper II for details).

#### 3.3.4.2. Density functional theory (DFT)

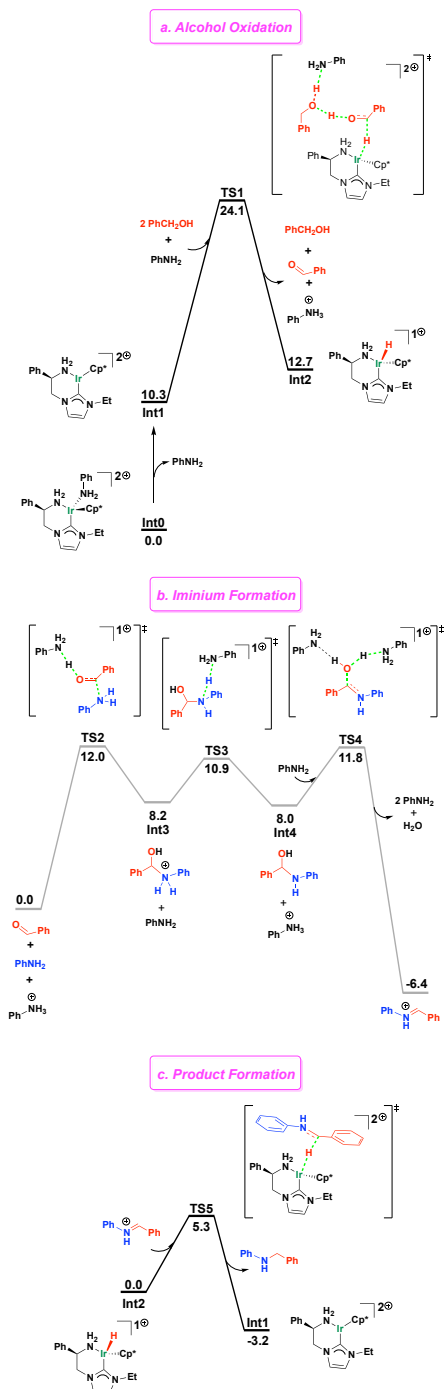
To shed light into the mechanism, theoretical calculations were performed. The calculations were conducted by co-worker Dr. Man Li, who studied the *N*-alkylation of aniline (**12.1**) with benzyl alcohol (**13.1**). For simplicity, the *n*-butyl chain in the NHC ligand was replaced by an ethyl group. With the same purpose, the methyl groups in the Cp\* ring were also removed. For clarification, the mechanism will be discussed based on three main steps, starting with the oxidation of the alcohol substrate, followed by formation of the iminium intermediate and its reduction, ending with the product formation and regeneration of the active catalyst species.

The calculations show the formation of a stable complex upon coordination of a molecule of aniline to the simplified iridium complex **Ir-4-OTf**<sup>+</sup> (Figure 20, **Int0**). This complex resulted to be the resting state of the catalytic cycle. With an energy cost of 24.1 kcal/mol, the transition state corresponding to the oxidation of benzyl alcohol is achieved (**TS1**), *via* decoordination of aniline (**Int1**). Such oxidation takes place in an outer-sphere manner. It consists of a concerted transfer of the  $\alpha$ -hydrogen and the proton from the alcohol to the Ir-center and to a molecule of aniline, respectively. This leads to the release of benzaldehyde and anilinium cation, while forming Ir-hydride intermediate **Int2** (Figure 20). Interestingly, the transition state with the lowest energy found for this step involves a second molecule of benzyl alcohol as proton shuttle. The Gibbs free energies for the formation of the complex between the anilinium and the counterion OTf<sup>-</sup>, or between the anilinium and the solvent HFIP are calculated to be endergonic. Hence the anilinium is treated as a free ion in the present study.

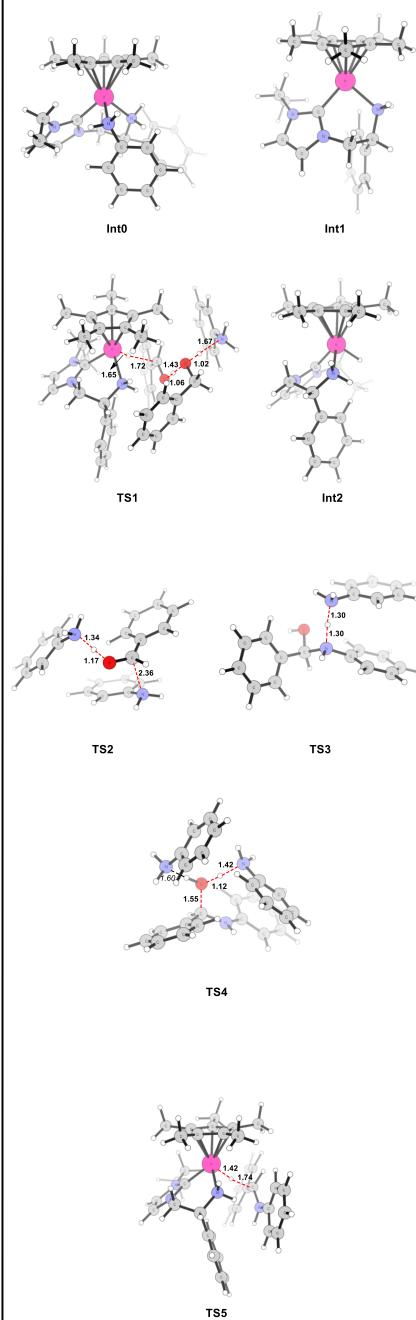
In the middle part of the cycle, we encounter the condensation between the aldehyde and the amine substrates, which under the slightly acidic conditions of the media, yields the iminium intermediate. This reaction occurs assisted by a second molecule of aniline in an off-cycle manner, involving three similar energy demanding consecutive steps (Figure 20, **TS2**, **TS3** and **TS4**). The highest energy barrier was found to be 12.0 kcal/mol, and the overall process is exergonic by 6.4 kcal/mol.

In a last step of the catalytic cycle, the reduction of the iminium ion intermediate takes place in an outer-sphere pathway by the metal-hydride species **Int2**. This step requires only 5.3 kcal/mol and it proceeds *via* biscationic complex **TS5**. Such low energy was expected, as reduction of the electrophilic iminium ions is facile. Consequently, the final product **14.1** as well as the catalytic active species **Int1** are released. In Figure 21, the key structures are shown including some important bond distances.





**Figure 20.** DFT calculations. Calculated Gibbs free energy profile (kcal/mol).



**Figure 21.** Selected structures. Label: pink, red, gray and white represent Ir, O, C and H, respectively.

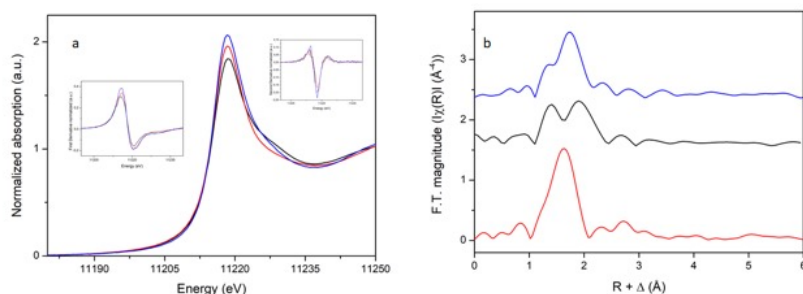
### 3.3.4.3. Structural studies: X-ray absorption spectroscopy

In parallel, X-ray spectroscopic (XAS) experiments were performed to gain further knowledge about the structural transformations that were occurring during the catalyst activation step. The experiments were performed in the DESY synchrotron facility, located in Hamburg, Germany, and the interpretation of the results was performed together with my co-worker Dr. Aditya Dharanipragada.

To investigate the catalyst activation, we focused our attention on the variations in the white line (WL) intensity in the X-ray absorption near edge spectroscopy (XANES) region. Indeed, by examining the Ir-L<sub>III</sub> edge in the XANES region, some effects produced by the electron nature of the ligands on the iridium metal center may be noticeable. A decrease in intensity might mean that the d-orbitals of the iridium atom might be occupied, either partially or fully. On the contrary, a higher number of vacant d-orbitals results in an increase of the absorption character of the metal (higher intensity).

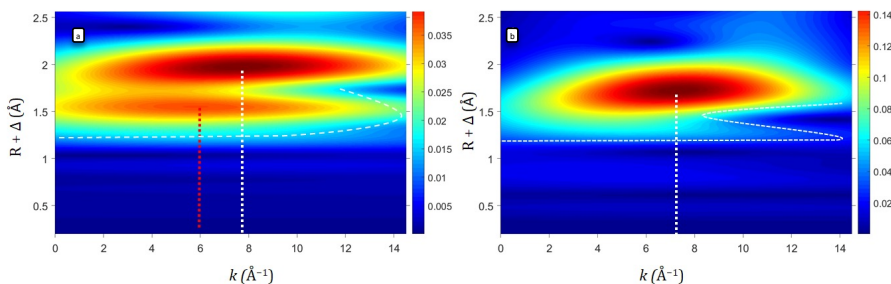
For this first series of experiments, iridium complex [Cp\*Ir(H<sub>2</sub>O)<sub>3</sub>SO<sub>4</sub>] was used as reference. In Figure 22 a), it is shown the difference in absorption between the reference complex (bottom), the non-active catalyst **Ir-4-Cl** (middle) and the active catalyst species **Ir-4-OTf** (top). As a matter of fact, this increase in absorption can be attributed to the removal of the chloride atom from the complex in the activation step by addition of the corresponding silver salt (*vide supra*, Scheme 15).<sup>107</sup> This hypothesis was supported by the results obtained from the Fourier transformation (FT) of the EXAFS (extended X-ray absorption fine structure) spectra (Figure 22, b). As expected, the shape of the FT spectra of the reference complex [Cp\*Ir(H<sub>2</sub>O)<sub>3</sub>SO<sub>4</sub>] shows a single peak, that illustrates the contribution of the carbon atoms on the Cp\* ring and the O atoms bonded to the iridium.

When comparing the non-active (**Ir-4-Cl**) and the active catalyst (**Ir-4-OTf**) species, we observed that the former presents two well-defined peaks (for Ir–O/C and for Ir–Cl distances), while the latter exhibits a major peak (attributed to Ir–O/C distances) with an asymmetric shoulder. This is an indication that the chloride has been displaced from the iridium center (Figure 22, b).



**Figure 22.** a) XANES of  $[\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3\text{SO}_4]$ , inactive and active catalyst species. b) Fourier transformed  $k^3$ -weighted EXAFS spectra Ir-L<sub>III</sub> edge. (—) reference  $[\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3\text{SO}_4]$ ; (—) **Ir-4-Cl**; (—) **Ir-4-OTf**.

The decooordination of the chloride atom from the iridium center upon activation was also observed comparing the continuous Cauchy wavelet transform (CCWT) of the inactive catalyst species (Figure 23, a) with that of the activated analog (Figure 23, b). The wavelet transform of the inactive species **Ir-4-Cl** shows two different lobes (one centered at  $k \sim 6 \text{ \AA}^{-1}$ , and one centered at  $k \sim 8 \text{ \AA}^{-1}$ ), agreeing with the presence of heavy atoms such as chloride. In contrast, the active species **Ir-4-OTf** showed only one major lobe centered at  $k \sim 7\text{--}8 \text{ \AA}^{-1}$  (Figure 23). The absence of a distinct second peak in the FT and in the CCWT analysis confirm the activation of catalyst by removal of the chloride atom.



**Figure 23.** CCWT spectra of the a) inactive catalyst **Ir-4-Cl**, and b) active analog **Ir-4-OTf**.

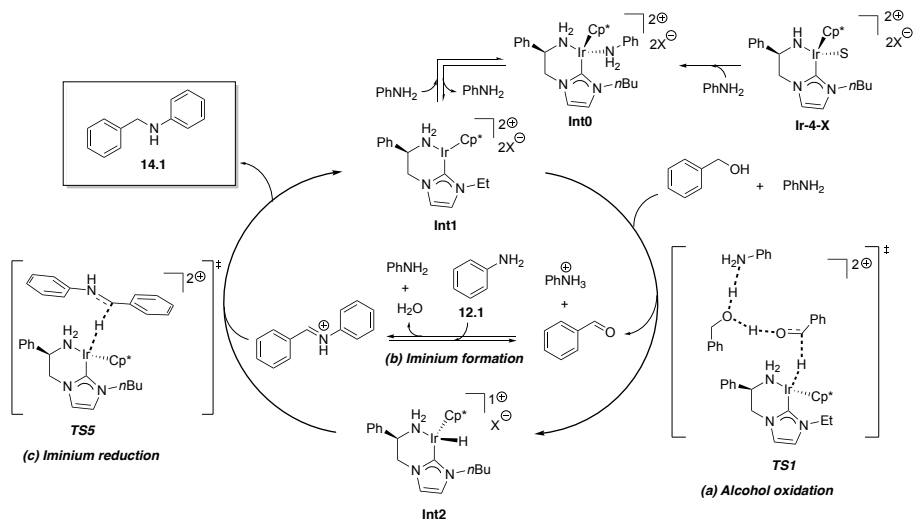
### 3.3.5. Summary of the mechanistic studies and proposed catalytic cycle

The implementation of different mechanistic tools provided us a good insight into the pathway of this transformation. An accurate acquisition of the reaction profile allowed us to identify the existence of an induction period, that was attributed to competition between the aniline substrate and higher-order aniline product to the iridium atom in the catalyst. The determination of the reaction orders of the different species present in this reaction also indicated

the presence of more than one molecule of benzyl alcohol involved in the rate determining step, which was supported by DFT calculations (see Paper II).

Indeed, deuterium labelling studies showed that the oxidation of the alcohol moiety is one of the slow steps of the reaction. The activation of the catalyst by a silver salt was monitored by X-ray spectroscopy, revealing a decoordination of the chloride substituent from the metal center. Finally, theoretical investigations provided a detailed description of all the steps taking place, with the energy barriers from the formation of the resting state, to the final releasing of the desired product and regeneration of the catalyst.

In a general picture, the reaction starts with a first activation of the precatalysts **Ir-4-Cl** by reacting with a silver salt, affording the active catalyst species **Ir-4-X**. A molecule of solvent coordinated to the iridium metal center is then displaced by aniline, forming complex **Int0**. This complex is the intermediate with the lowest energy in the whole reaction profile, and therefore the resting state. The dissociation of the aniline releases an empty site on the iridium center, setting the conditions for the hydride acceptance. After the hydride transfer step *via* **TS1**, benzaldehyde is released. In an off-cycle reaction, condensation of the aldehyde and aniline yields the corresponding iminium compound. The iminium reduction step takes place in an outer-sphere fashion upon interaction with the iridium-hydride species **Int2**, through **TS5**, and it provides us with the desired saturated amine product **14.1** and the active catalyst species **Int1**. Formation of the iminium compound could not be identified by  $^1\text{H}$  NMR, suggesting that the hydrogenation step occurs fast, which is in accordance to the calculations.



**Scheme 21.** Catalytic cycle for the *N*-alkylation of amines with benzylic alcohols catalyzed by Ir(III) complex **Ir-4-X**. S = solvent.

### 3.3.6. Conclusions

The excellent activity of a new Ir-NHC designed and synthesized with the aim of overcoming the limitation of the ones previously reported in the group has been shown. The substitution of the alcohol moiety on the wing-tip of the NHC by an amino group was shown to raise the energy of the resting state, increasing the chances of finding a lower energy barrier for the C-N bond formation method. This fact allows us to achieve the selective *N*-alkylation of amines with alcohols in base-free conditions at room temperature for a very broad substrate scope of alcohols with anilines. Further, by increasing the temperature to 90 °C even the challenging aliphatic amines can be alkylated by alcohols. During this transformation, the only byproduct generated is H<sub>2</sub>O, highlighting the high atom-economy and environmentally friendly character of this method. To the best of our knowledge, such mild conditions for this reaction are yet to be reported. A variety of mechanistic studies were performed, providing us with a good understanding of the reaction mechanism.

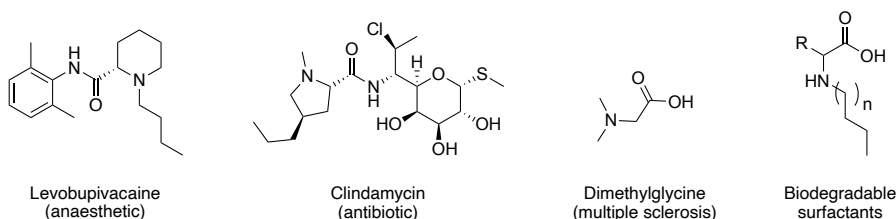
### 3.4. Selective and Quantitative Functionalization of Unprotected Amino Acids Using a Recyclable Homogeneous Catalyst (Paper III)

#### 3.4.1. Background and purpose of this work

$\alpha$ -Amino acids are the building blocks for the construction of peptides and proteins, which are vital for all living organisms. The structural and physical properties of these building units have a direct impact on the folding and function of peptides and proteins.<sup>104,108</sup> These supramolecular compounds are widely used as antibiotic drugs, treatment of cancer, and development of vaccines.<sup>109</sup>

In this regard, peptides containing substituents in the nitrogen atom may provide new functionalities such as higher proteolytic stability,<sup>110</sup> enhanced membrane permeability<sup>111</sup> and longer peptide half-lives,<sup>112</sup> which are important factors for peptide-based drugs (*i.e.* peptidomimetics) formed from non-natural amino acids.<sup>110,113-115</sup>

Simpler alkylated amino acids are found in small-molecule pharmaceuticals as well. Examples of such pharmaceuticals are Ropivacaine and Levobupivacaine, used as local anesthetics. Furthermore, modified amino acids present a wide variety of applications nowadays, from organocatalysts or additives in catalytic reactions, to biodegradable surfactants (Figure 24).<sup>116-121</sup>



**Figure 24.** Selected drugs containing *N*-alkylated amino acids.

Up to date, the synthesis of *N*-alkylated  $\alpha$ -amino acids remains a challenge. This is mainly due to the fact that  $\alpha$ -amino acids exist in their zwitterionic form under neutral conditions, which translates to a very poor solubility in organic solvents. This fact makes them a family of substrates which are difficult to work with.<sup>122,111</sup> In addition to that, due to the high polarity of these compounds, derivatization steps are required to isolate them from the starting materials. The need of such extra steps makes the overall process laborious and poorly sustainable. The development of a robust method to access *N*-alkylated  $\alpha$ -amino acids that does not require derivatizations or tedious

purifications would overcome this limitation. Moreover, it would as well contribute to a high atom- and synthetic step-economy.<sup>2</sup>

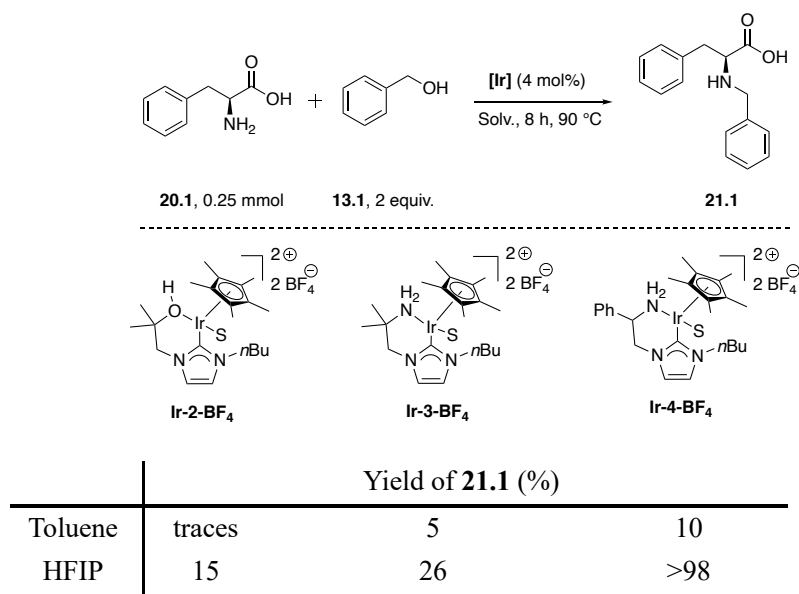
In the context of this thesis, the different existing pathways to access higher order amines have been discussed (*vide supra*, Scheme 13). Although they are efficient methods, they can hardly be applied for the *N*-alkylation of  $\alpha$ -amino acids, mainly because of their poor solubility in organic solvents. In addition, the difficulties associated to the presence of a carboxylic acid group in the molecule contribute to difficult purifications.

Being able to implement a hydrogen transfer approach to access *N*-alkylated  $\alpha$ -amino acids would overcome most of the abovementioned limitations. In the literature, there is only one report by Barta and Feringa in 2017 where this method is applied using Shvo's ruthenium complex as the catalyst.<sup>88</sup> In this work, they achieved the *N*-alkylation of a variety of unprotected amino acids with alcohols for the first time and with excellent levels of retention of the configuration. Unfortunately, the substitution pattern could not be controlled, resulting in double alkylations in some cases. Additionally, the products obtained needed to be derivatized to their corresponding esters before isolation, increasing the number of steps and lowering the atom economy of the process. This method, however, marked a very important milestone in this field of research to obtain highly valuable building blocks.

In this work, the use of amino-functionalized Ir-NHC complex **Ir-4** (*vide supra*, Scheme 15) as catalyst to synthesize mono-*N*-alkylated unprotected  $\alpha$ -amino acids using alcohols as alkylating agents is reported.

### 3.4.2. Optimization of the reaction conditions and robustness test

First, and due to the novelty of the transformation, iridium-NHC complexes **Ir-2-BF<sub>4</sub>**, **Ir-3-BF<sub>4</sub>** and **Ir-4-BF<sub>4</sub>** were tested for the *N*-alkylation of L-phenylalanine (**20.1**) with benzyl alcohol (**13.1**). The reaction was initially run using the solvents that were previously proven to be suitable for complexes **Ir-2-BF<sub>4</sub>**<sup>93</sup> and **Ir-4-BF<sub>4</sub>** for the *N*-alkylation of amines with alcohols (toluene and HFIP, respectively) (Figure 25). Very low yields were obtained using toluene as the solvent, regardless of the iridium complex used as catalyst. However, when fluorinated solvent HFIP was used, the yields improved in all cases, particularly when using amino-functionalized **Ir-4-BF<sub>4</sub>** as the catalyst, where complete conversion into the desired mono-alkylated product **21.1** was accomplished. This can be due to the high polarity of the amino acid substrate, which showed a better solubility in the more polar solvent HFIP (Figure 25).



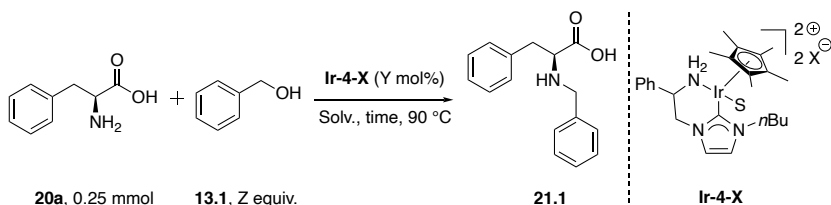
**Figure 25.** Screening of catalysts. Solvent = 1 mL. Yield of *N*-benzyl-L-phenylalanine determined by  $^1\text{H}$  NMR spectroscopic analysis using 2,3,5,6-tetrachloronitrobenzene as an internal standard. S = solvent.

Delighted by the high affinity of complex **Ir-4-BF<sub>4</sub>** for the selective mono-*N*-alkylation of phenylalanine **20.1** with benzyl alcohol **13.1**, the use of other solvents was explored. Although almost no reactivity was observed in  $\text{CH}_2\text{Cl}_2$ , the desired product was achieved in up to 30% yield in an aqueous media (Table 2, entries 3 and 4, respectively). Surprisingly for us, even though a good catalytic activity was also observed in TFE as the solvent (the product was obtained in a quantitative yield), a better retention of the configuration was obtained in comparison with the results in HFIP (Table 2, entry 5 vs 2). From that point onwards, a series of experiments led us to lower catalyst loadings, as well as the number of equivalents of the alcohol substrate, affording the product in quantitative yield and with high retention of configuration after 20 h (Table 2, entry 6). Neither decreasing the concentration of the substrates nor slow addition of the alcohol substrate improved the outcome of the reaction (Table 2, entries 7 and 8, respectively). Then, the effect of the counter anion was investigated. A considerably lower yield was obtained when silver *p*-toluene sulfonate was used for the activation of the catalyst ( $\text{AgOTf}$ ), however, silver trifluoromethanesulfonate ( $\text{AgOTf}$ ) and silver hexafluorophosphate ( $\text{AgPF}_6$ ) formed product **21.1** in high yields and high enantiomeric excess (Table 2, entries 9, 10 and 11, respectively). Gratifyingly, the use of silver bis(trifluoromethanesulfonyl)imide ( $\text{AgNTf}_2$ ) to form the catalytic active species **Ir-4-NTf<sub>2</sub>** resulted in an excellent catalytic



performance, obtaining the desired product **21.1** in quantitative yield, with almost complete retention of the configuration (Table 2, entry 12).

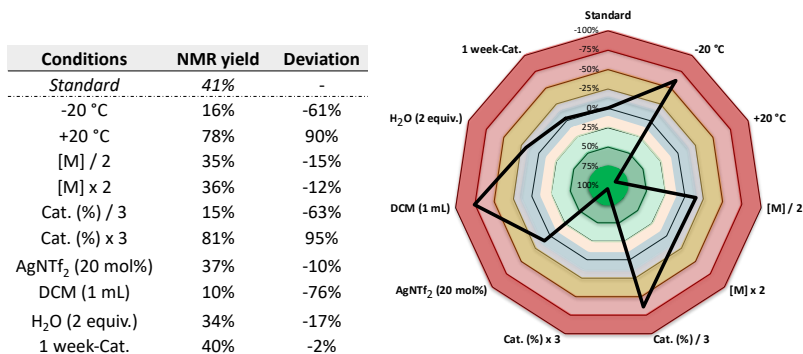
**Table 2.** Reaction development.<sup>a</sup>



Entry	Solvent	X <sup>-</sup>	Y	Z	Time (h)	Yield (%) <sup>d</sup>	ee (%) <sup>e</sup>
1	Toluene	BF <sub>4</sub> <sup>-</sup>	4	2.0	8	10	n.d.
2	HFIP	BF <sub>4</sub> <sup>-</sup>	4	2.0	8	>99	60
3	CH <sub>2</sub> Cl <sub>2</sub>	BF <sub>4</sub> <sup>-</sup>	4	2.0	8	<5	n.d.
4	H <sub>2</sub> O	BF <sub>4</sub> <sup>-</sup>	4	2.0	8	30	n.d.
5	TFE	BF <sub>4</sub> <sup>-</sup>	2	2.0	8	>99	82
6	TFE	BF <sub>4</sub> <sup>-</sup>	2	1.5	20	>99	82
7 <sup>b</sup>	TFE	BF <sub>4</sub> <sup>-</sup>	2	1.5	20	72	n.d.
8 <sup>c</sup>	TFE	BF <sub>4</sub> <sup>-</sup>	2	1.5	20	40	n.d.
9	TFE	OTs <sup>-</sup>	2	1.5	20	45	n.d.
10	TFE	OTf <sup>-</sup>	2	1.5	20	91	90
11	TFE	PF <sub>6</sub> <sup>-</sup>	2	1.5	20	89	78
12	TFE	NTf <sub>2</sub> <sup>-</sup>	2	1.5	20	>99	98

<sup>a</sup>Solvent = 1 mL. <sup>b</sup>TFE = 2 mL. <sup>c</sup>Slow addition of **13.1**. <sup>d</sup>Yield of *N*-benzylaniline determined by <sup>1</sup>H NMR spectroscopic analysis using 2,3,5,6-tetrachloronitrobenzene as an internal standard. <sup>e</sup>Enantiomeric excess (*ee*) measured after esterification. S = solvent.

Several experiments were carried out with the aim to identify what factors this transformation is more affected by. In Figure 26, it is shown how the yield is highly dependent on the catalyst loading, as well as on the reaction temperature. Interestingly, the presence of water or significant excess of the silver salt did not affect noticeably the outcome of the reaction, while the removal of CH<sub>2</sub>Cl<sub>2</sub> upon catalyst activation showed to be of high importance for the reaction to proceed. Furthermore, the stability of **Ir-4-NTf<sub>2</sub>** was proven by running the reaction with a catalyst sample that had been activated one week before, and was stored in the fridge, showing the same catalytic performance (Figure 26).



**Figure 26.** Sensitivity assessment for the *N*-alkylation of phenylalanine with benzyl alcohol.

### 3.4.3. Substrate scope and limitations

The efficiency of the method was further demonstrated by the easy isolation of the product. After the reaction was complete using the optimal conditions (*vide supra*, Table 2, entry 12), and the solvent was removed under vacuum, the mixture was washed with diethyl ether to remove the excess of the alcohol substrate. This simple isolation method afforded the *N*-alkylated  $\alpha$ -amino acid product. In this section of the work, a large variety of compounds are proven to be suitable substrates for this transformation (more than 100 examples), showing the outstanding scope, and the good functional group tolerance of the catalytic system. All products shown were obtained in quantitative yields under the optimal conditions (unless otherwise specified) without the need of derivatization or further purification techniques.

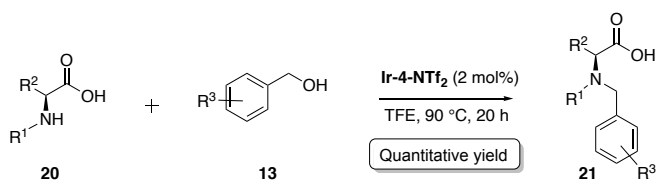
#### 3.4.3.1. Direct synthesis of non-natural amino acids

A number of amino acids **20** were reacted with different benzylic alcohols (**13**) as alkylating agents (Scheme 22). The alkylation of phenylalanine and proline took place in excellent yields, regardless the electronic nature of the benzylic alcohols (Scheme 22, **21.1-21.13**). High retention of the configuration was confirmed for most of the products. When using 2-methylbenzyl alcohol, a slight racemization of the product was observed (Scheme 22, **21.10**). Aliphatic amino acids such as glycine, alanine, leucine and valine afforded the desired mono-alkylated product (Scheme 22, **21.14-21.17**) upon reaction with benzyl alcohol. The presence of heteroatoms in the amino acid substrate was perfectly tolerated. Nitrogen-containing amino acids such as tryptophan and histidine yielded the corresponding alkylated products **21.18-21.23** using different substituted benzylic alcohols. Moreover, examples of  $\alpha$ -amino acids bearing a hydroxy functionality gave selectively the desired products (Scheme 22, **21.24-21.26**). Sulfur-containing substrates such as methionine and ethyl

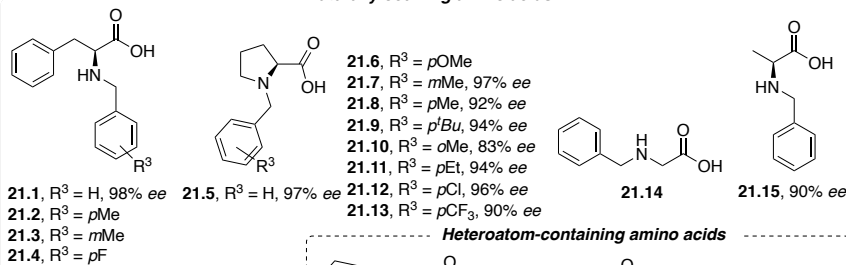
cysteine were alkylated to their corresponding *N*-alkylated derivatives **21.27-21.29** in excellent purities. This approach was also applied to  $\beta$ -amino acids. To our delight,  $\beta$ -alanine and homoalanine formed the desired products also in quantitative yields (Scheme 22, **21.30** and **21.31**, respectively). Along the study of the substrate scope, we also encountered some limitations. Cysteine (Cys), containing a thiol group, as well as basic amino acids lysine (Lys) and arginine (Arg) could not be tolerated and a mixture of products, or no reactivity at all, was observed.

In an attempt to further explore the functional group tolerance of this system, the methodology was extended to non-proteinogenic amino acids. Functionalized phenylalanine derivatives were used as substrates, yielding the aimed alkylated products (Scheme 22, **21.32-21.36**). Outstandingly, a high sterically hindered *tert*-leucine, an ether-containing substrate, and an amino acid presenting a thiophene group were alkylated to give products **21.37**, **21.38** and **21.39**, respectively, in excellent yields. L-Pipecolic acid, a precursor of Ropivacaine<sup>123</sup> and Levobupivacaine<sup>114</sup> was transformed into an *N*-alkyl pipecoloxylidine derivative **21.40**. Lastly, a more peculiar amino acid lacking alpha protons was tested, successfully forming the corresponding product (Scheme 22, **21.41**).

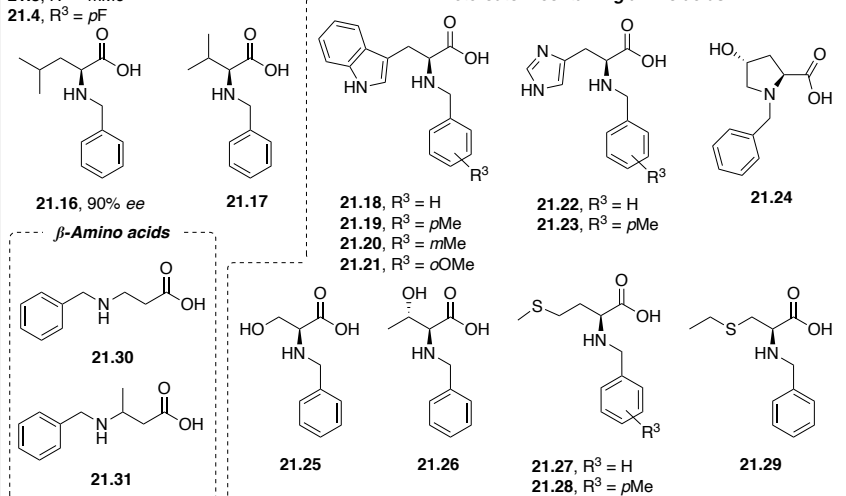
Next the use of a range of alcohols as alkylating agents was investigated. The reaction of various amino acids, including heteroatom-containing examples, with aliphatic cyclopropanemethanol and 3-phenylpropanol, gave products **22.1-22.6** efficiently. The high group tolerance of the method was again confirmed by the use of two functionalized heterocyclic alcohols (Scheme 23, **22.7** and **22.8**). The excellent selectivity of this transformation is shown when using 1,5-pentadiol as alkylating agent. Mono-*N*-alkylated **22.9**, **22.10** and **22.11** were obtained in quantitative yields, not observing the byproduct that would be formed upon intramolecular overalkylation/cyclization (Scheme 23, **22.9-22.11**). Satisfyingly, linear aliphatic alcohol *n*-butanol could also be used as alkylating agent for various amino acids (**22.12-22.14**). Among them, we find mono-*N*-butylated  $\beta$ -alanine (**22.12**), a compound of interest for medical purposes.<sup>74</sup> Next, by using the cheap and easily accessible ethanol as co-solvent in this catalytic system, alkylated proline **22.15** was formed. This approach could be extended to dipeptides. As an example, monoethylated dipeptide **22.16** was obtained from glycylglycine. A limitation of the methodology was encountered using secondary alcohols as alkylating agents (Scheme 23).



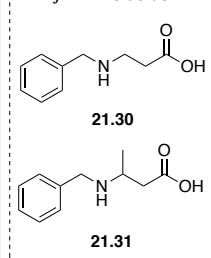
**Naturally-occurring amino acids**



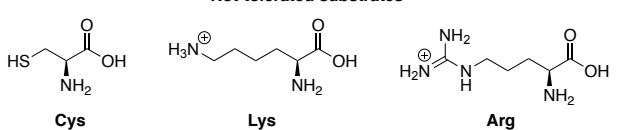
**Heteroatom-containing amino acids**



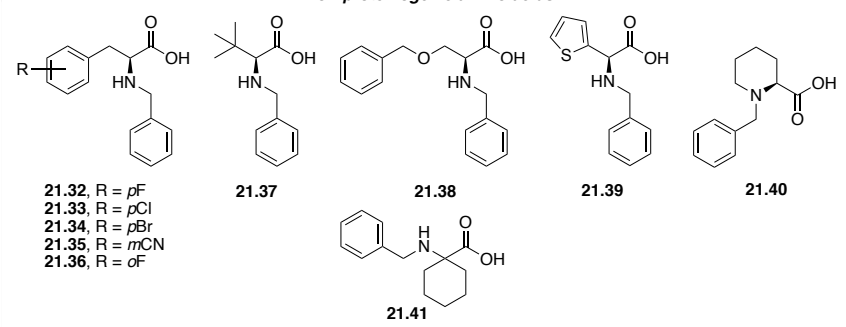
***β*-Amino acids**



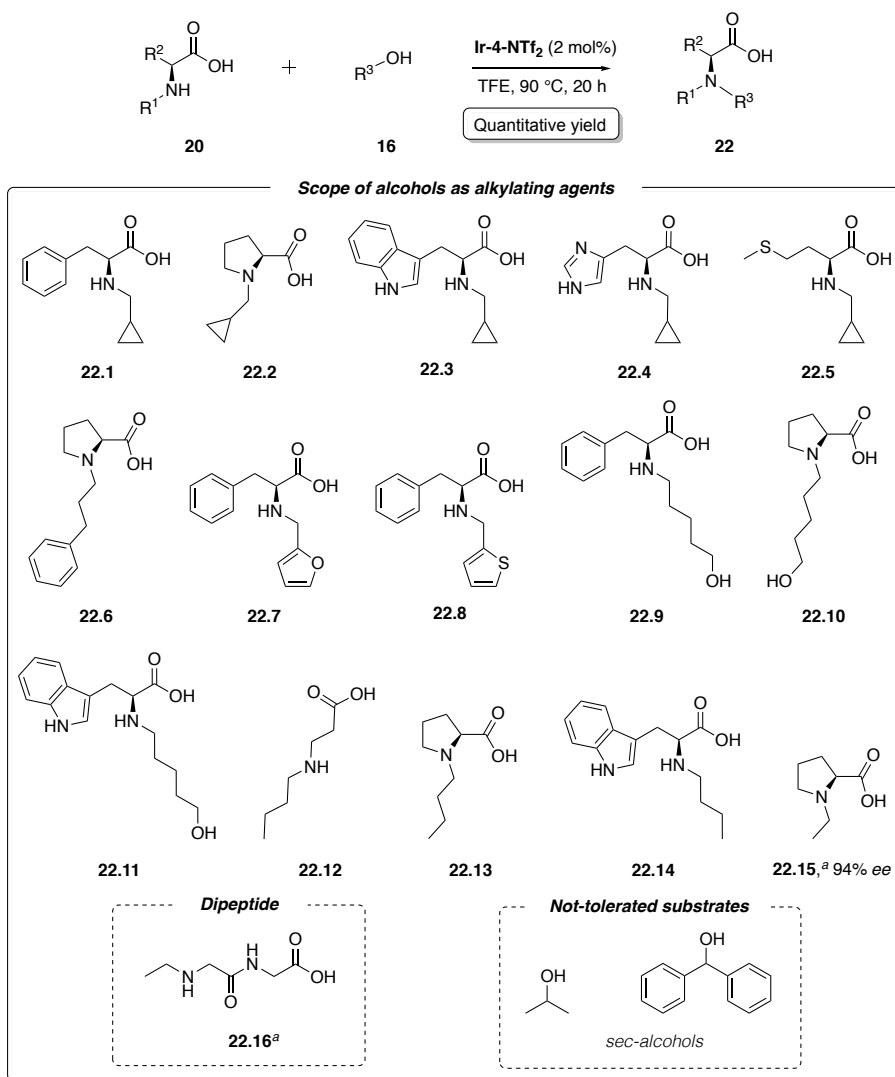
**Not-tolerated substrates**



**Non-proteinogenic amino acids**



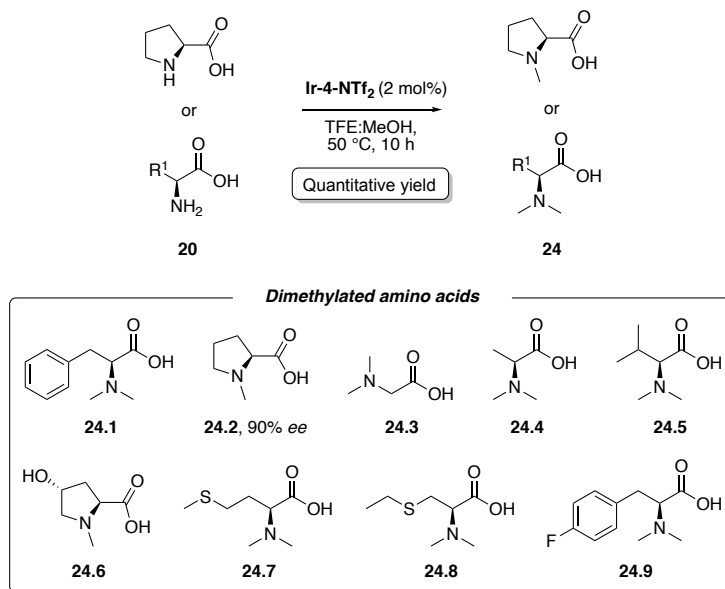
**Scheme 22.** Substrate scope of amino acids and limitations.



**Scheme 23.** Substrate scope of alcohols and limitations. <sup>a</sup>Ethanol (0.1 mL)

Noteworthy, and inspired by the good outcome obtained from using ethanol as substrate, the use of the simplest alcohol MeOH as C<sub>1</sub> source was further attempted. The presence of a methyl group in a molecule is of importance, since such a small modification in a compound affects notably its functional properties.<sup>124</sup> Therefore, methylation is of high importance in medicinal chemistry.<sup>103</sup> Nowadays, more than 66% of all drugs contain at least one methyl moiety in their structure.<sup>125</sup> More specifically, in industry, the synthesis of *N*-methylamines is achieved either by reductive amination processes or by nucleophilic substitution reactions. To accomplish that, large amounts of formaldehyde (proven to be human carcinogen) or toxic

methylation reagents need to be used. In this respect, the use of methanol as alkylating agent presents itself as a greener and more sustainable alternative. As a continuation of our investigations, slight changes to the optimal conditions allowed us to afford a variety of *N*-methylated amino acids. In all cases, complete methylation of the nitrogen atom was obtained, yielding the products in quantitative yields after 10 h at temperatures as low as 50 °C (Scheme 24). The presence of other functional groups in the molecule, including an alcohol moiety in the case of hydroxyproline, were tolerated (Scheme 24, **24.1-24.9**).



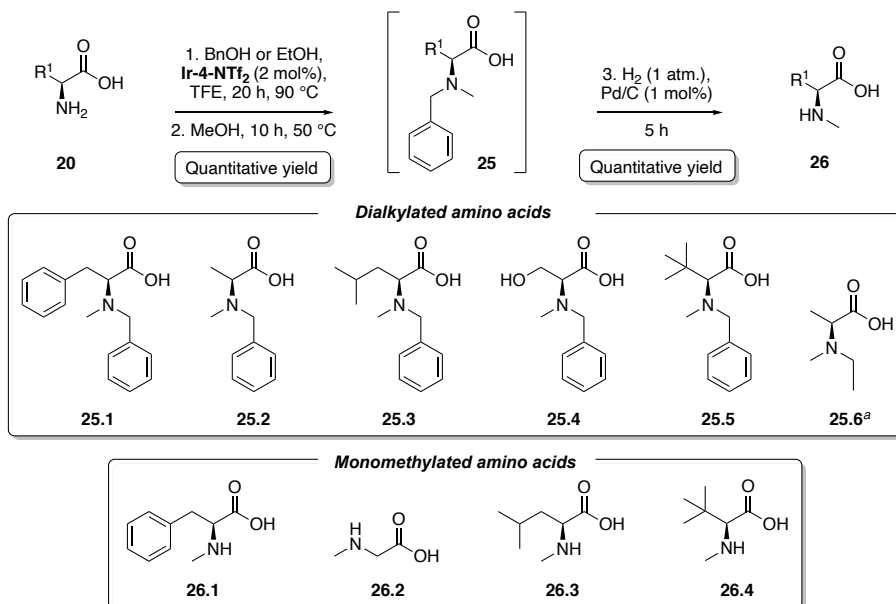
**Scheme 24.** Synthesis of methylated amino acids. MeOH (0.1 mL).

Despite the remarkable affinity showed by this catalytic system to the use of methanol as substrate, the fact that only fully methylated products were obtained intrigued us. The formation of mono-*N*-methylated  $\alpha$ -amino acids remained a challenge.

### 3.4.3.2. Facile access to mono-methylated amino acids

The observation that a double alkylation occurred when using MeOH as alkylating agent led us to take advantage of the excellent performance of this catalytic system to develop a three-steps, one-pot procedure that would allow access to the desired mono-*N*-methylated amino acid products (Scheme 25). This approach consists of a first alkylation using benzyl alcohol, which under the optimized reaction conditions occurs quantitatively, followed by addition of methanol, leading to dialkylated intermediates **25**. Lastly, hydrogenolysis

using palladium on carbon yields the aimed mono-*N*-methylated amino acids (Scheme 25, **26**). As an application of interest in medicinal chemistry, this method could be applied to the synthesis of *N*-methylglycine (Scheme 25, **26.2**), a drug used for treatment of schizophrenia.<sup>126</sup>



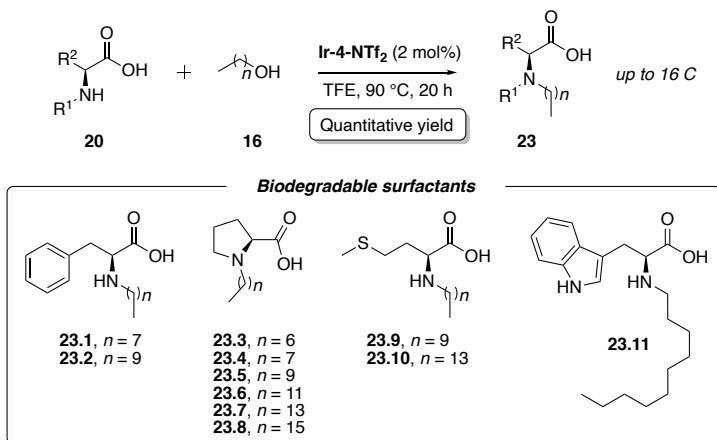
**Scheme 25.** Synthesis of monomethylated amino acids. MeOH (0.1 mL). <sup>a</sup>Ethanol (0.1 mL)

### 3.4.3.3. Synthesis of biodegradable surfactants

Satisfied by the wide substrate scope of the reaction, the use of long-chain aliphatic alcohols (fatty alcohols) was then investigated. This kind of substrates would generate a peculiar family of products that can behave as biodegradable surfactants, due to the presence of a highly polar region (amino acid) and a long aliphatic non-polar tail. There are a few well-established methodologies that are used in industry to access them. However, lack of high atom economy and generation of a considerable amount of waste are presented as major concerns.<sup>127,128</sup> In the pioneering report previously highlighted, published by Feringa and Barta, they employed the well-known Shvo catalyst to successfully afford a series of surfactants *via* hydrogen transfer. These compounds were isolated after derivatization in low to moderate yields.<sup>88</sup>

We then investigated whether the catalytic activity could be expanded to the synthesis of biodegradable surfactants by applying the optimal conditions to a variety of  $\alpha$ -amino acids in the presence of fatty alcohols with different carbon chain lengths. In Scheme 26, surfactants obtained from unprotected amino

acids and aliphatic alcohols consisting of up to sixteen-carbon chains are shown. All compounds were obtained in quantitative yields (Scheme 26, **23.1-23.11**).



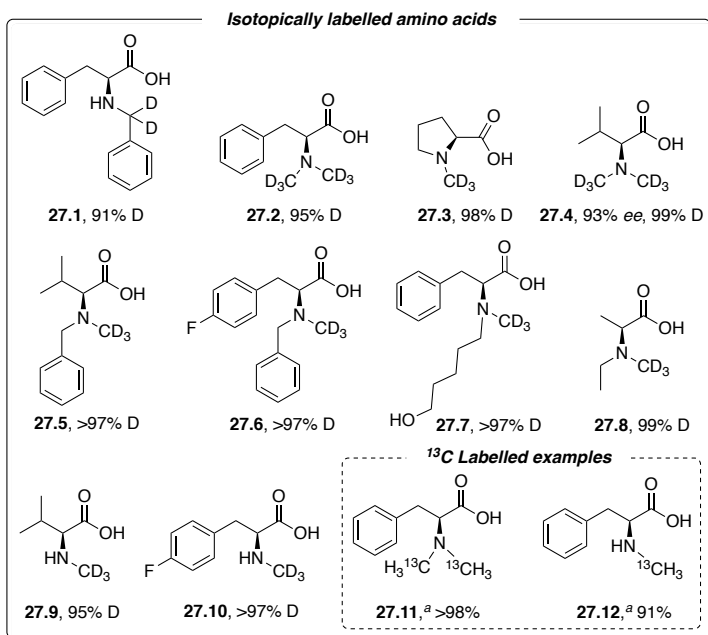
**Scheme 26.** Synthesis of surfactants.

#### 3.4.3.4. Synthesis of isotopically labelled *N*-alkylated amino acids

The exchange of hydrogen for deuterium atoms in clinical agents is at the forefront of medicinal chemistry, since deuterated drugs can have favorable pharmacokinetic properties compared to the hydrogen parent. Further, being able to employ methanol as alkylating agent for this transformation, could give access to atomic-labelled compounds rather simply. In Figure 27, examples of molecules synthesized by the different procedures previously discussed in this chapter using isotopically labelled reagents are shown. Phenylalanine was successfully monoalkylated by deuterated benzyl alcohol **13.1-*d*<sub>2</sub>** with 91% deuterium incorporation (Figure 27, **27.1**). The use of deuterated methanol as co-solvent in the reaction afforded fully methylated amino acids **27.2-27.4** with excellent levels of deuterium incorporation. Interestingly, various deuterium-labelled dialkylated amino acids were successfully obtained using different alcohols with almost no loss of deuterium content (Figure 27, **27.5-27.8**). Remarkably, this method could be applied to the synthesis of deuterium-labelled monomethylated amino acids. Products **27.9** and **27.10** were obtained by following the three-steps, one-pot procedure previously described.

Next, the use of <sup>13</sup>C labelled methanol as alkylating agent was investigated. Isotopically labelled dimethylated phenylalanine **27.11**, as well as monomethylated phenylalanine **27.12** were obtained in quantitative yields and with complete, or very high, <sup>13</sup>C incorporation (Figure 27).





**Figure 27.** Isotopically labelled amino acids. Quantitative isolated yields. <sup>a</sup>NMR yield.

#### 3.4.4. Synthesis of modified peptides

The use of peptides as drugs has noticeably increased in recent years. Several studies speculate that the market for peptide-based active pharmaceutical ingredients (APIs) will grow twice as much as for any other family of compounds.<sup>129</sup> However, most of the peptides that consist of naturally occurring amino acids do not comply with Lipinski's rules,<sup>130</sup> which evaluates the drug likeliness of a compound and its suitability towards oral intake in humans. This is mainly due to the presence of a high number of hydrogen donors and acceptors in the molecule, as well as their high molecular weight. Furthermore, peptides are known to be rapidly cleared from the body, frequently by being freely filtered by the kidneys.<sup>131</sup> To have an overall picture, nowadays there are more than 700 peptide-based drugs that are either in the market or in clinical phases,<sup>129</sup> and part of the scientific community claims the need of a reassessment of the Lipinski rules, developed back in 1997.<sup>132</sup>

To overcome these limitations, the interest in the synthesis of chemically-modified peptides that could offer an improved bioavailability has increased in the last years, adopting the name of peptidomimetics.<sup>133,108</sup> Easier said than done, a simple replacement of an amino acid with its corresponding *N*-

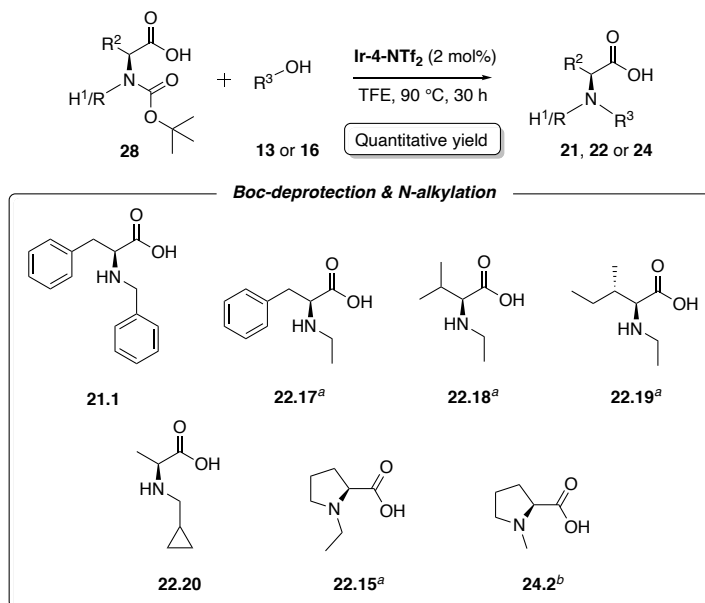
alkylated analog affects the number of possible hydrogen bonds, as well as the folding of the peptide, having in some cases great impact on the final structure and selectivity of the peptide.<sup>134</sup> In Table 3, some examples of the effect that a modified peptide may have compared to the parent analog are shown.<sup>135</sup>

**Table 3.** Selected examples of the effect of chemically-modified peptides in drugs.

Peptide	Pharmacological properties
Somatostatin analogs <sup>135</sup>	
c-(-Pro-Phe-Trp-Lys-Thr-Phe-)	Low apparent permeability ( $P_{app}$ )
	$P_{app}$ increased x 4
c-(-Pro- <i>N</i> <sup>Me</sup> Phe- <i>N</i> <sup>Me</sup> Trp- <i>N</i> <sup>Me</sup> Lys-Thr-Phe-)	Increased lipophilicity
	Oral bioavailability: 9.9% in rats
Ligands of integrin $\alpha_{IIb}\beta_3$ <sup>136</sup>	
c-(-Arg-Gly-Asp-Phe-Leu-Gly-)	Moderate selectivity
	$(IC_{50}[\alpha_V\beta_3]/IC_{50}[\alpha_{IIb}\beta_3]) = \mathbf{0.5}$
c-(- <i>N</i> <sup>Me</sup> Arg-Gly-Asp-Phe-Leu-Gly-)	Increased selectivity
	$(IC_{50}[\alpha_V\beta_3]/IC_{50}[\alpha_{IIb}\beta_3]) = \mathbf{64}$
c-(- <i>N</i> <sup>Me</sup> Arg-Gly-Asp-Phe- <i>N</i> <sup>Me</sup> Leu-Gly-)	Increased selectivity
	$(IC_{50}[\alpha_V\beta_3]/IC_{50}[\alpha_{IIb}\beta_3]) = \mathbf{86}$
c-(- <i>N</i> <sup>Me</sup> Arg-Gly-Asp- <i>N</i> <sup>Me</sup> Phe- <i>N</i> <sup>Me</sup> Leu-Gly-)	Exceptional selectivity
	$(IC_{50}[\alpha_V\beta_3]/IC_{50}[\alpha_{IIb}\beta_3]) = \mathbf{406}$

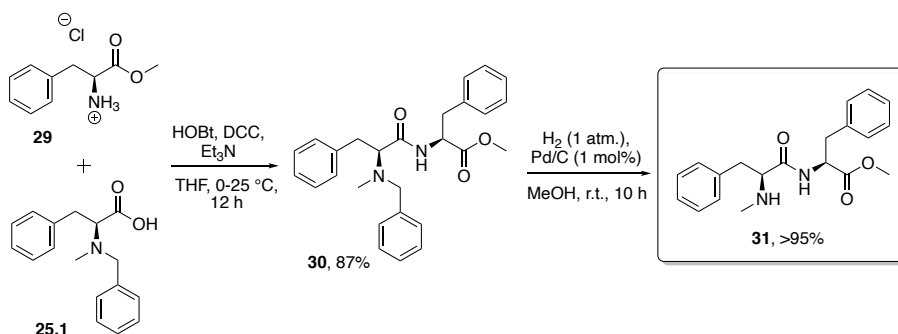
With the aim of widening the applicability of the method, we went on to investigate the synthesis of chemically modified peptides by using the *N*-alkylated  $\alpha$ -amino acids, as prepared in the previous chapter, as building blocks. Commonly, there are two main well-established procedures for the synthesis of peptides, the so-called solid-phase peptide synthesis (SPPS)<sup>138</sup> and liquid-phase peptide synthesis (LPPS).<sup>108</sup> Both approaches consist of a coupling between a Boc-protected  $\alpha$ -amino acid and an amino ester substrate. We first applied the optimal reaction conditions to the commercially available Boc-protected phenylalanine **28.1** (Scheme 27). To our surprise, the corresponding Boc-deprotected and mono-*N*-alkylated product **21.1** was obtained in quantitative yields. We hypothesized that due to the slightly acidic conditions in the media, deprotection of the NH-Boc group, followed by monoalkylation took place. The approach could be applied to other substrates and using different alcohols as alkylating agents yielding the corresponding products in quantitative yields (Scheme 27). This reactivity shows a new and very convenient application due to the easy access to commercially available

Boc-protected  $\alpha$ -amino acids, while providing access to mono-*N*-alkylated  $\alpha$ -amino acid products avoiding the extra deprotection step.



**Scheme 27.** Consecutive Boc-deprotection/*N*-alkylation of  $\alpha$ -amino acids. <sup>a</sup>Ethanol (0.1 mL). <sup>b</sup>Methanol (0.1 mL).

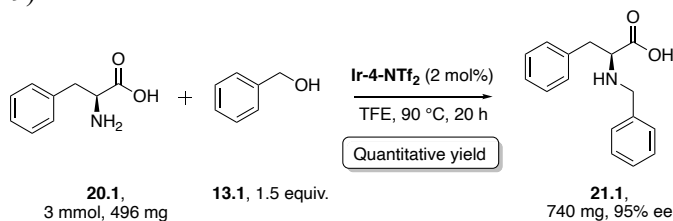
Encouraged by the good results and in line with our work, we investigated the potential application of this method for the synthesis of *N*-modified peptides. Satisfyingly, a direct coupling between dialkylated phenylalanine substrate **25.1** and phenylalanine methyl ester **29** gave the desired modified dipeptide **30** (Scheme 28). Further, and supported by the studies previously performed in this work, hydrogenolysis of **30** gave access to monomethylated dipeptide **31** in excellent yield over two steps (Scheme 28). This approach introduces itself as an alternative method to synthesize modified peptides with a wide range of possible structural shapes and chemical properties.



**Scheme 28.** Synthesis of chemically modified dipeptide. Proof of concept.

### 3.4.5. Scalability of the reaction

Certainly, the design of a highly efficient catalytic system may imply an easy scalability. Therefore, the *N*-alkylation of phenylalanine with benzyl alcohol was tested on a larger scale. The reaction was run using 3 mmol of  $\alpha$ -amino acid substrate (496 mg) and product **21.1** was obtained in quantitative yield and excellent enantiomeric excess, employing the original catalyst loading (Scheme 29).



**Scheme 29.** Scaling up of the reaction.

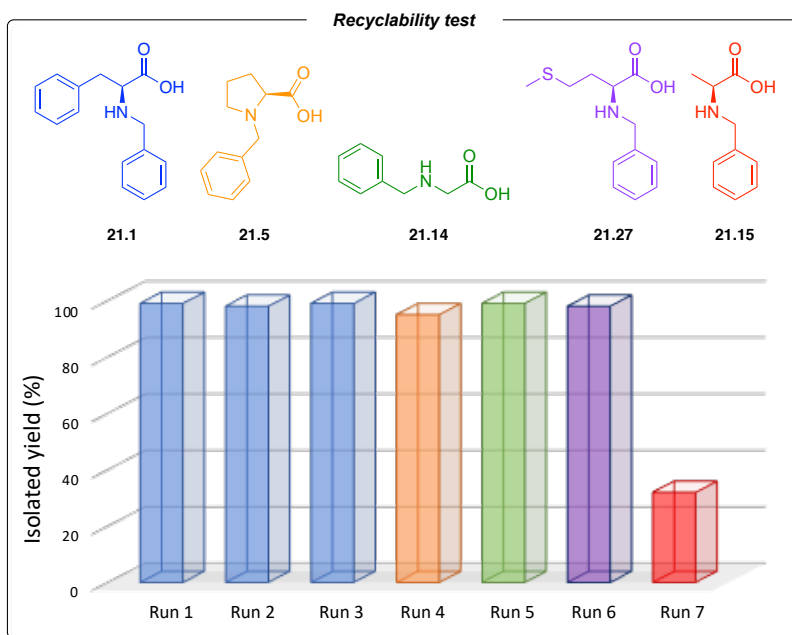
### 3.4.6. Recyclability test

As organic chemists, we have a responsibility to find more efficient and more sustainable pathways to access new, or existing organic compounds. In this regard, special attention should be paid to the search of processes with optimal step-, atom-economy<sup>139</sup> and E-factor.<sup>140</sup> Specifically in the method developed in this chapter, the use of the iridium-NHC catalyst gave full conversions in all instances, what enabled to purify the products without derivatization. This additional derivatization steps do not contribute towards atom-economical synthetic organic methods. To further improve the sustainability, it was tested that the solvent used for the reaction (TFE) could be distilled and used again without any loss of reactivity. This study was performed on the model reaction using L-phenylalanine (**20.1**) and benzyl alcohol (**13.1**) as substrates over 6 consecutive runs, collecting an average of 93% of the TFE used over the 6 runs.

A common and major concern in the field of homogeneous catalysis, is the difficulty to recover, and reuse, the catalyst from the reaction media. Since common purification techniques are just not plausible due to the low concentration in which these species are present, other approaches are to be explored. Some remarkable reports take advantage of the difference in solubility between catalyst and substrates/products in a biphasic media,<sup>141,142</sup> or a dramatic decrease in solubility of the catalyst after the reaction is complete.<sup>143</sup> In our system, the fact that quantitative conversions are achieved in all cases, together with the very poor solubility of the products formed, allows for the separation of the catalyst from the alkylated amino acid products.

Indeed, by filtering-off the dissolved excess of alcohol and the catalyst, followed by removal of solvent, separation of the catalyst from the alkylated amino acid product was possible. The recovered catalyst was used in further catalytic reaction, and the catalytic activity remained up to six runs, yielding the corresponding desired products in quantitative yields. In Figure 28, the results from the recyclability tests are shown. Consecutive additions of phenylalanine afforded product **21.1** in three consecutive runs.

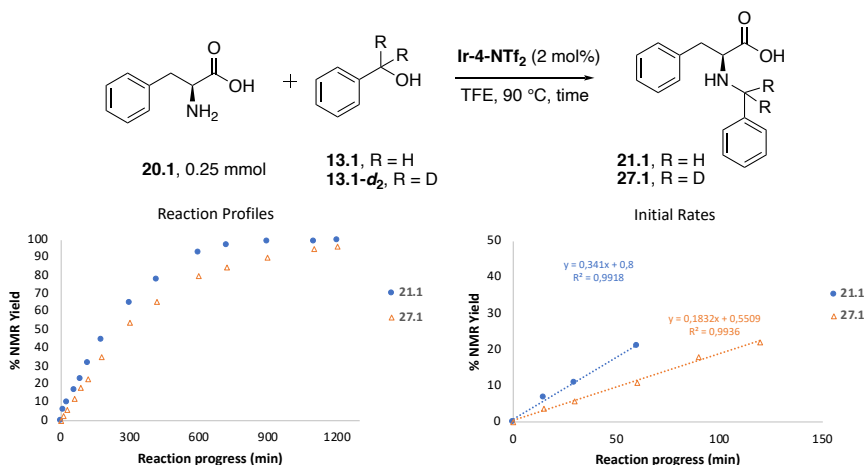
The robustness of the method was again demonstrated by changing the amino acid between runs. Proline, glycine and methionine afforded the corresponding products in quantitative yield (Figure 28, runs 4, 5 and 6; products **21.15**, **21.14** and **21.27**, respectively). A seventh run using alanine resulted in a considerably decrease in yield. This procedure was reproduced several times observing excellent results with up to six runs. The final decrease in yield may be due to either consecutive loss of catalyst between runs or final deactivation of the active species (Figure 28).



**Figure 28.** Recyclability investigations.

### 3.4.7. Mechanistic investigations and proposed mechanism

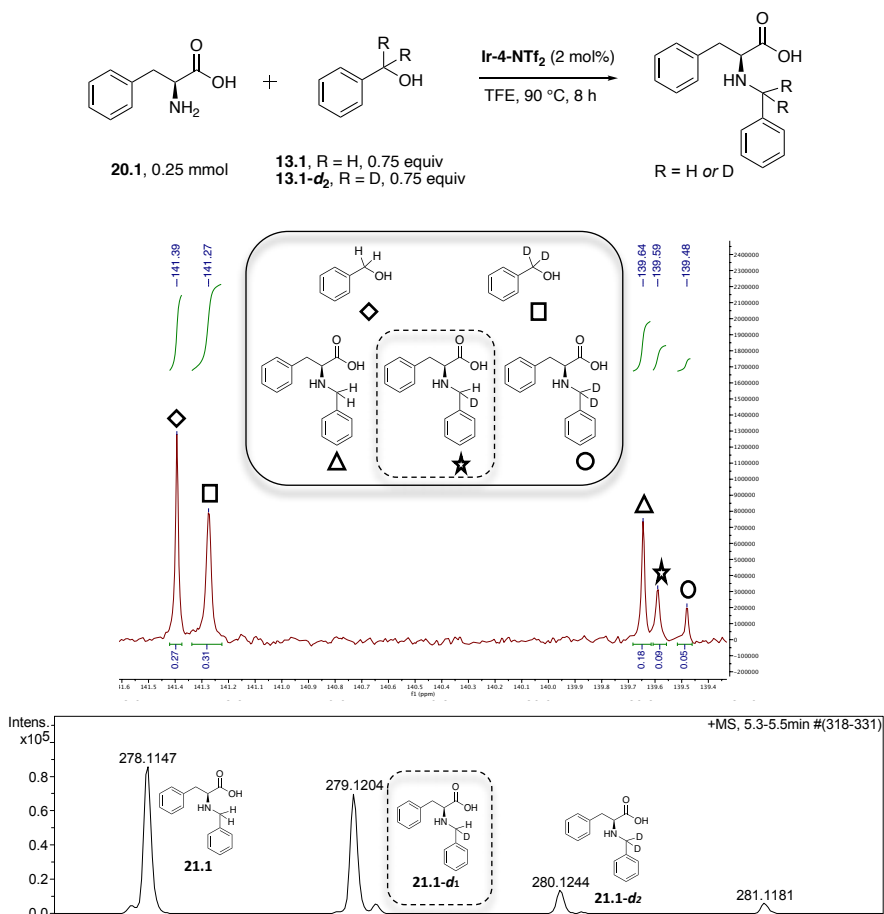
A series of experiments were designed to gain a better insight into the mechanism that this transformation was operating through, aiming to identify the rate-determining step of the reaction (r.d.s.). To achieve that, reaction profiles were obtained from using benzyl alcohol (**13.1**) and its deuterated analog (**13.1-*d*<sub>2</sub>**) as alkylating agents in independent reaction set-ups (Figure 29, left). A clear difference in rates was observed, suggesting that the C–H bond cleavage is involved in the slowest step of the catalytic cycle. This hypothesis was confirmed after the study of the initial reaction rates, obtaining a kinetic isotope effect of  $1.98 \pm 0.18$  (Figure 29, right). In contrast with the previous chapter, an induction period was not observed for this reaction.



**Figure 29.** Reaction profiles (left) and kinetic isotope effect determination (right).

Once determined that the oxidation of the alcohol is one of the highest energy-requiring steps of the cycle, we investigated whether the condensation between the resulting aldehyde and the  $\alpha$ -amino acid substrate, to yield the imine intermediate, would occur in an off-cycle manner. A crossover experiment in the presence of both non-deuterated and deuterated benzyl alcohols in a 1:1 mixture was carried out (Figure 30). Interestingly, monodeuterated product **21.1-*d*<sub>1</sub>** could be identified along the reaction in yields up to 28%. Such a product is formed by oxidation of a specific alcohol substrate, which then condenses with an  $\alpha$ -amino acid (forming the corresponding imine intermediate) and consecutive hydrogenation of the imine by an iridium-hydride species that contains a different isotope of hydrogen. It can be then concluded that the aldehyde intermediate decoordinates from the iridium metal center, resulting in an off-cycle imine formation reaction.

Furthermore, the fact that formation of monodeuterated benzyl alcohol is not observed during the reaction supports the irreversibility of the alcohol oxidation step (Figure 30).

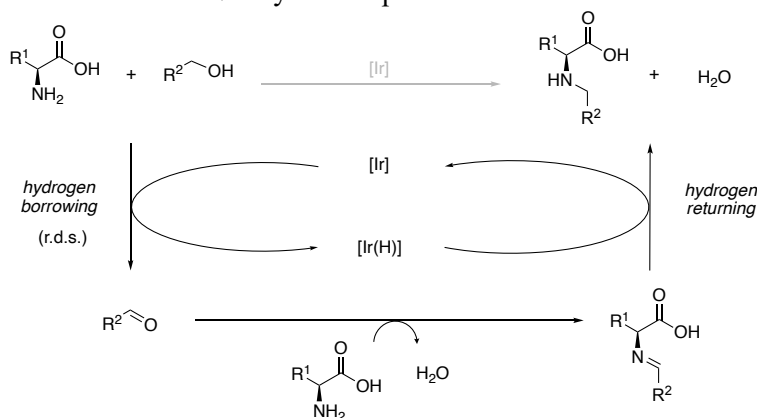


**Figure 30.** Crossover experiment. Identification of product **21.1-*d*<sub>1</sub>** by <sup>13</sup>C NMR spectroscopy (top) and HRMS (bottom).

### 3.4.8. Proposed mechanism

In Scheme 30, supported by the results obtained from the mechanistic studies, a simplification of the mechanistic cycle believed to be operating in this transformation is shown. A first oxidation of the alcohol substrate leads to the corresponding carbonyl derivative, with formation of a metal-hydride species. This step is believed to be the most energy-demanding step of the cycle (r.d.s). Then, condensation of the aldehyde with the α-amino acid substrate results in

an imine intermediate, which is finally reduced by the metal-hydride complex to yield the final mono-*N*-alkylated unprotected amino acid.

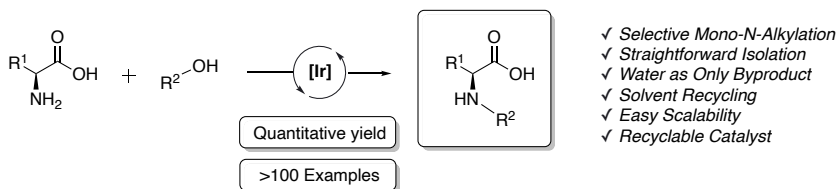


**Scheme 30.** Simplified mechanistic cycle.

### 3.4.9. Conclusions

Herein, a new method to access mono-*N*-alkylated  $\alpha$ -amino acids using alcohols as alkylating agents has been described using an Ir(III)-NHC catalyst. This catalyst allows the use of unprotected  $\alpha$ -amino acids, and affords the alkylated products in quantitative yields, and under base-free conditions. The applicability has been demonstrated by synthesizing more than one hundred non-natural  $\alpha$ -amino acids with high retention of the stereochemistry. In addition, due to the high efficiency of the method, derivatization and purification processes are not needed.

The transformation reported in this work constitutes a robust method to access highly valuable building blocks, including monomethylated amino acids, and surfactants, that can further be used for the construction of more complex molecules. As proof of concept, a modified peptide has been synthesized, proving the applicability of the method. Furthermore, the reaction can be scaled-up easily, and the catalyst can be recycled and re-used for a number of runs (Scheme 31).



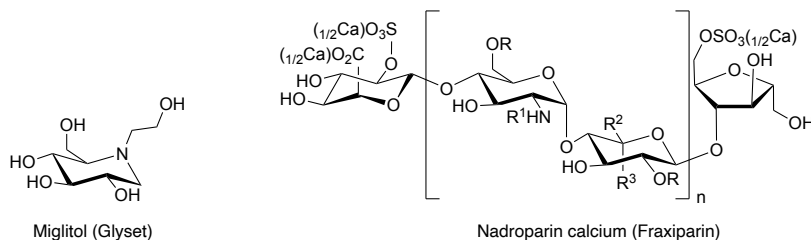
**Scheme 31.** Selective mono-*N*-alkylation of unprotected amino acids with alcohols *via* hydrogen transfer with a recyclable bifunctional Ir(III) catalyst.



## 3.5. Direct *N*-Alkylation of Unprotected Amino Sugars with Alcohols. Fast Access to Highly Functionalized Building Blocks and Biodegradable Surfactants (Paper IV)

### 3.5.1. Background

As it has been previously stated, various core methods have been developed to obtain substituted amines (*vide supra*, Scheme 13). However, there are only a handful of methods that can be applied to highly functionalized substrates, such as *N*-modified carbohydrates. This family of compounds are characterized by their high oxygen content. They play an important role in biological processes and are of special interest due to the wide biological properties that they offer.<sup>144-146</sup> They can be found as small molecules such as Miglitol, used for the treatment of diabetes, or of higher complexity such as heparin derivatives, high efficient anticoagulants<sup>147</sup> (Figure 31).

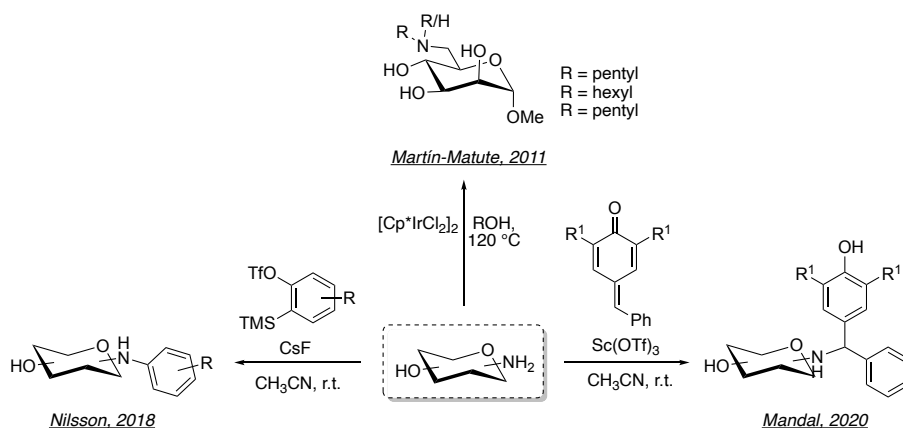


**Figure 31.** Representative examples of *N*-modified carbohydrates containing drugs (trade name in brackets).

Notwithstanding the high importance of these kind of molecules, their high functionalization and extremely polar nature, is translated into poor solubility in organic solvents. They are, therefore, very challenging substrates to work with, commonly needing extra protection/deprotection steps.<sup>146</sup> More specifically, when it comes to the *N*-alkylation of amino sugar derivatives, a limited number of reports are available in the literature. An early example is the one reported by Zhao's group in 2012, where they describe a method to access *N*-arylated D-glucosamines at carbon C2 by copper catalysis. This reaction required protection of the hydroxy moieties of the amino sugar starting material.<sup>148</sup> An alternative approach to obtain the same *N*-arylated products from protected substrates was developed by Liu and co-workers using arylboronic acids as coupling partners.<sup>149</sup> A more recent work reported by Fukase's research group describes the application of Buchwald-Hartwig type conditions on partially protected substrates for the *N*-arylation of

glucosamine intermediates.<sup>150</sup> Further, modifications in C1 have also been developed. In this regard, Chida's<sup>151</sup> and Messaoudi's<sup>152-155</sup> groups have reported different metal-catalyzed approaches to obtain *N*-arylated glycosylamine from protected starting materials.

Nevertheless, when it comes to *N*-modifications on carbohydrates bearing the amino group in different positions of the ring, very few methodologies are known to be successful. In 2018, Nilsson's group reported the use of 2-(trimethylsilyl)phenyl triflates as activated substrates for the synthesis of unprotected *N*-arylated carbohydrates (Scheme 32).<sup>156</sup> In a very recent publication, Mandal's research group describes the access to  $\alpha, \alpha'$ -*N*-diarylmethylated from unprotected starting materials (Scheme 32).<sup>157</sup> However, there is only one report where the hydrogen transfer methodology was investigated for the *N*-modification of carbohydrate amines. It was developed by the Martín-Matute's group in 2011 who used the commercially available iridium dimer complex  $[\text{Cp}^*\text{IrCl}_2]_2$  as the catalyst for the coupling between protected amino sugars and protected carbohydrates, in the presence of base. When the method was applied to other alcohols as alkylating agents, neat conditions were needed, namely the use of the alcohol as the solvent, and no control of overalkylation could be achieved (Scheme 32).<sup>158</sup>

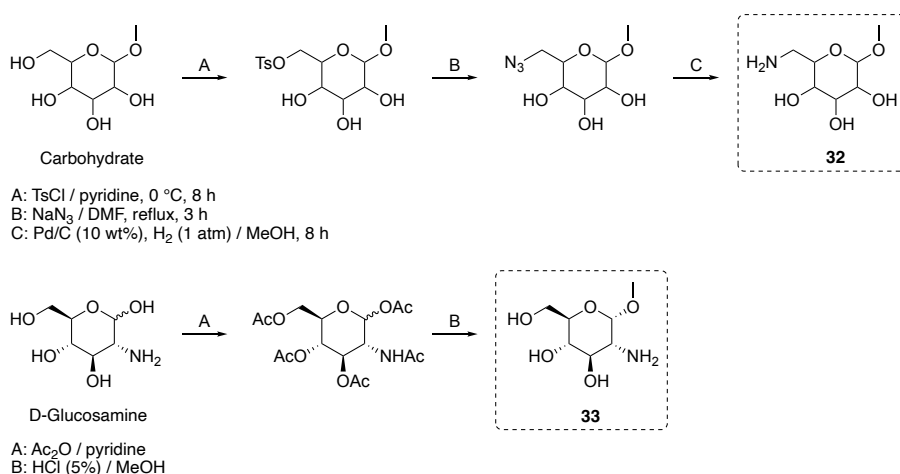


**Scheme 32.** Selected pathways to access *N*-modified carbohydrate amines.

In light of these reports and in the course of our investigations, we embarked on exploring the application of the NHC-Ir(III) catalysts developed in this thesis for the alkylation of unprotected carbohydrate amines with alcohols. This new strategy would allow access to a wide variety of mono-*N*-alkylated carbohydrate amines *via* hydrogen transfer mechanism, without the need of protection/deprotection steps and generating water as the only byproduct.

### 3.5.2. Synthesis of the starting materials

As a starting point in the project, we focused on the synthesis of the amino sugar starting materials. Slight modifications of reported procedures gave access to 6-amino-6-deoxy-carbohydrates<sup>159,160</sup> and 2-amino-2-deoxy- $\alpha$ -D-glucopyranoside.<sup>161</sup> The former were synthesized in a three-step procedure consisting of a first tosylation of the primary alcohol of the corresponding carbohydrate, followed by azide formation. A last hydrogenation assisted by palladium on carbon using a hydrogen balloon afforded the desired products **32** (Scheme 33, top). The latter starting material was accessed from commercially available D-glucosamine. Peracetylation and consequent methyl glycosylation yielded 2-amino-2-deoxy- $\alpha$ -D-glucopyranoside **33** (Scheme 33, bottom).



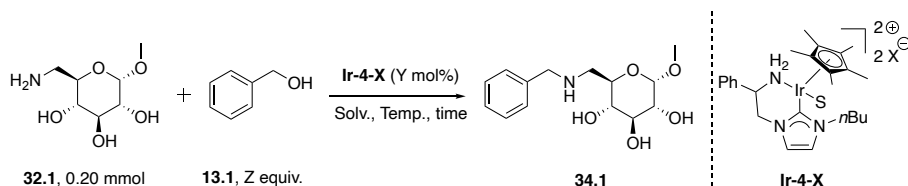
**Scheme 33.** Synthetic routes to access 6-amino-6-deoxy-carbohydrates (top) and 2-amino-2-deoxy- $\alpha$ -D-glucopyranoside (bottom).

### 3.5.3. Optimization of the reaction conditions

With the starting materials in hand, initial tests on the *N*-alkylation of 6-amino-6-deoxy- $\alpha$ -D-glucopyranoside (**32.1**) with benzyl alcohol **13.1** were performed. The complexity of this kind of substrates resulted in a very challenging analysis of the reaction mixtures. Luckily for us and after a large screening of deuterated solvents, it was found that a slightly acidified deuterated methanol as solvent allowed for an optimal identification of isolated signals of the desired product (**34.1**). This result made it possible to monitor the formation of product, facilitating the optimization of the reaction conditions (Table 4). Substrate **32.1** was decided as model substrate for this reaction, and the catalyst performance was first tested using **Ir-4-BF<sub>4</sub>** in different solvents (Table 4, entries 1-5). After 24 h reaction time, no product

was observed using non-protic solvents toluene and tetrahydrofuran. Mono-*N*-alkylated product **34.1** was identified in 24% yield under the same conditions using water as solvent. Then, fluorinated solvents TFE and HFIP, which showed a good affinity to this catalytic system (*vide supra*, Paper II and Paper III), were used. To our delight, the formation of the desired product dramatically increased to 65% and 71%, respectively (Table 4, entries 4 and 5). Changes in molarity, either by dilution or concentration, did not improve the reaction performance (Table 4, entries 6 vs 7). While equimolar ratio of the amino sugar and alcohol substrate resulted in a decrease of yield, a big excess of such did not result in a better outcome of the reaction (Table 4, entries 8 vs 9). Although as expected, shorter reaction time gave lower yield of product **34.1**, leaving the mixture to react for longer times did not considerably increase the formation of product. Similar results were obtained varying the temperature (Table 4, entries 10 vs 11, and entries 11 vs 12, respectively). The reaction performance was clearly sensitive to the catalyst loading. Lowering the amount of catalyst loading to 1 mol% gave product **34.1** in up to 66% yield (Table 4, entry 14). With a catalyst loading of 5 mol% an increase from 71% to 81% yield was obtained (Table 4, entries 5 vs 15, respectively). Lastly, different silver salts used for the activation of the catalyst were tested, which did not improve the catalytic performance (Table 4, entry 15 vs 16 and 17).

**Table 4.** Reaction development.<sup>a</sup>



Entry	Solvent	X <sup>-</sup>	Y	Z	Time (h)	Yield (%) <sup>f</sup>
1	Toluene	BF <sub>4</sub> <sup>-</sup>	3	3.0	24	-
2	THF	BF <sub>4</sub> <sup>-</sup>	3	3.0	24	-
3	H <sub>2</sub> O	BF <sub>4</sub> <sup>-</sup>	3	3.0	24	24
4	TFE	BF <sub>4</sub> <sup>-</sup>	3	3.0	24	65
5	HFIP	BF <sub>4</sub> <sup>-</sup>	3	3.0	24	71
6 <sup>b</sup>	HFIP	BF <sub>4</sub> <sup>-</sup>	3	3.0	24	70
7 <sup>c</sup>	HFIP	BF <sub>4</sub> <sup>-</sup>	3	3.0	24	60
8	HFIP	BF <sub>4</sub> <sup>-</sup>	3	1.0	24	56
9	HFIP	BF <sub>4</sub> <sup>-</sup>	3	5.0	24	77

10	HFIP	BF <sub>4</sub> <sup>-</sup>	3	3.0	15	67
11	HFIP	BF <sub>4</sub> <sup>-</sup>	3	3.0	36	85
12 <sup>d</sup>	HFIP	BF <sub>4</sub> <sup>-</sup>	3	3.0	24	62
13 <sup>e</sup>	HFIP	BF <sub>4</sub> <sup>-</sup>	3	3.0	24	83
14	HFIP	BF <sub>4</sub> <sup>-</sup>	1	3.0	24	66
15	HFIP	BF <sub>4</sub> <sup>-</sup>	5	3.0	24	81
16	HFIP	OTf <sup>-</sup>	5	3.0	24	56
17	HFIP	NTf <sub>2</sub> <sup>-</sup>	5	3.0	24	64

<sup>a</sup>Amino sugar **32.1** (0.2 mmol), solvent (1 mL). <sup>b</sup>Concentration = 0.1 M. <sup>c</sup>Concentration = 1 M. <sup>d</sup>80 °C. <sup>e</sup>120 °C. <sup>f</sup>Yield of *N*-benzyl- $\alpha$ -D-glucopyranoside **34.1** determined by <sup>1</sup>H NMR spectroscopic analysis using 1,2,4,5-tetramethylbenzene as an internal standard.

### 3.5.4. Substrate Scope and Limitations

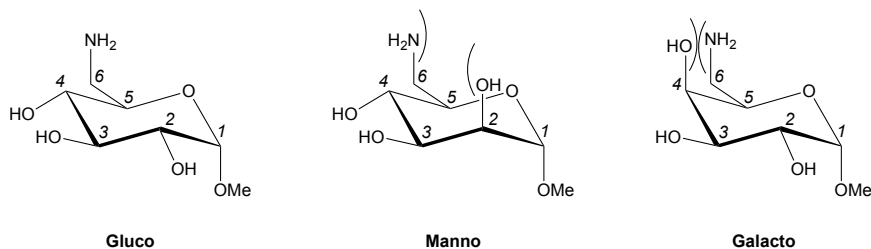
#### 3.5.4.1. Selective *N*-alkylation of unprotected amino sugars with alcohols

The optimized reaction conditions (*vide supra*, Table 4, entry 15) were first applied to 6-amino-6-deoxy- $\alpha$ -D-glucopyranoside (**32.1**) and using a range of different substituted benzylic alcohols. Electron-rich benzylic alcohols formed the desired product in high yields regardless of the position of the substituent on the aryl group (Scheme 34, **34.1-34.5**). The presence of more electron-withdrawing groups in the ring resulted in a loss in yield, fact that could be overcome by increasing the reaction time (Scheme 34, **34.6-34.8**). Next, the applicability of this method to the use of other alcohols than simple benzylic alcohols was explored. Heterocyclic-functionalized alcohols were perfectly tolerated, yielding the aimed products **34.9** and **34.10** in very high yields of 80 and 87%, respectively. Aliphatic alcohol *n*-butanol was also used as substrate successfully forming mono-*N*-alkylated amino sugar **34.11** as major product. The use of ethanol and methanol as co-solvent allowed us to obtain the corresponding fully alkylated products **34.12** and **34.13**, respectively.

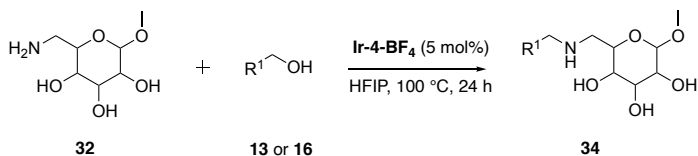
This catalytic system allowed for access to isotopically-labelled compounds. As a matter of fact, using deuterated benzyl alcohol and deuterated methanol gave products **34.1-d** and **34.13-d** in good yields and with almost complete deuterium incorporation for both products. Furthermore, the effect of the stereochemistry on the anomeric carbon was investigated by using 6-amino-6-deoxy- $\beta$ -D-glucopyranoside as substrate. In these cases, similar results to those observed from the  $\alpha$ -analogue were obtained (Scheme 34, **34.14-34.15**).

To expand the methodology, 6-amino-6-deoxy- $\alpha$ -D-mannopyranoside was also tested as substrate. This compound, analogue of methyl- $\alpha$ -D-mannopyranoside, differs from the model amino sugar in the absolute configuration of C2. Interestingly, although the reaction performed well, this structural change in the substrate resulted in lower reactivity. Increasing the reaction time allowed to obtain high yields using again a variety of alcohols as alkylating agents. Different benzylic alcohols regardless the electronic properties and the position in the aryl ring, as well as alcohols containing heteroatom rings were tolerated (Scheme 34, **34.16-34.20**). Good results were also obtained using aliphatic alcohols *n*-butanol and methanol (Scheme 34, **34.21** and **34.22**, respectively).

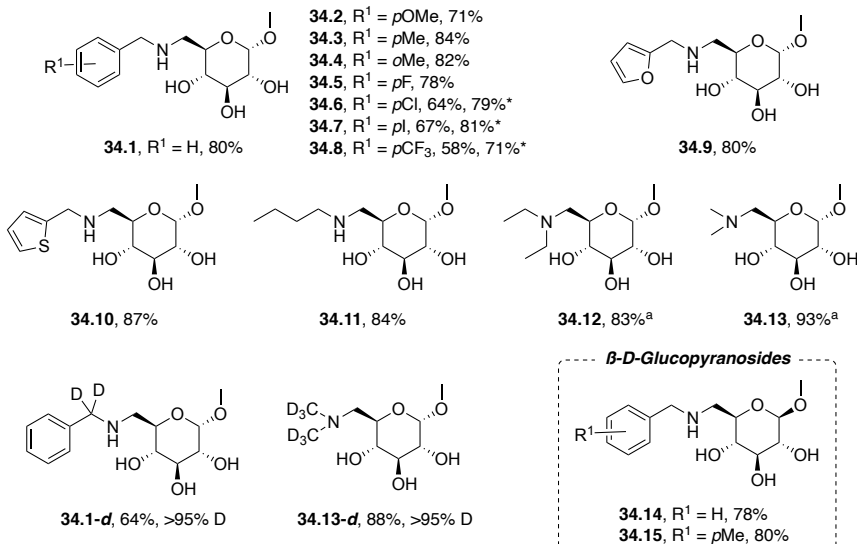
A limitation of this approach was encountered when the system was applied to 6-amino-6-deoxy- $\alpha$ -D-galactopyranoside. Regardless of the configuration on C1, this substrate did not show any reactivity in the presence of any alcohol tested (Scheme 34). A reasonable explanation to this difference in reactivity can be based on the conformation of the carbohydrate substrates. In Figure 32, a 3D conformation of the three amino sugars used in this work is shown. In addition to the potential interactions between the functional groups present in the molecule and the alcohol substrate, the accessibility of the catalyst may be compromised by the steric hindrance observed in C4 of the galactopyranoside analogue (Figure 32, right).



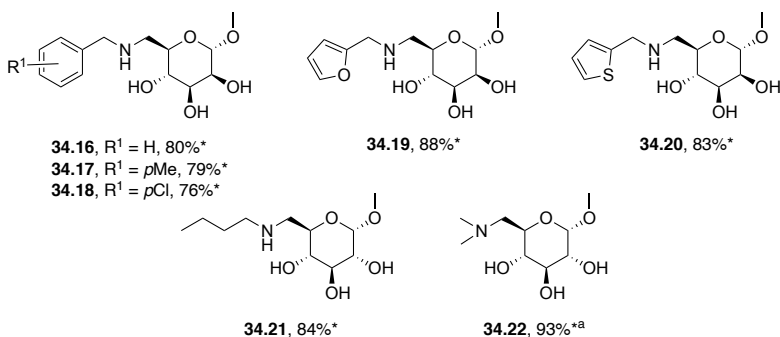
**Figure 32.** 3D conformation of 6-amino-6-deoxy- $\alpha$ -D- glucopyranoside (left), mannopyranoside (middle) and galactopyranoside (right).



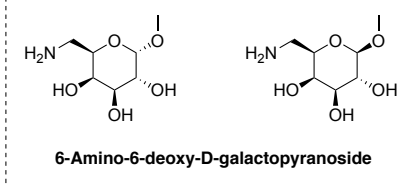
**Alkylated-6-amino-6-deoxy-D-glucopyranosides**



**Alkylated-6-amino-6-deoxy-D-mannopyranosides**

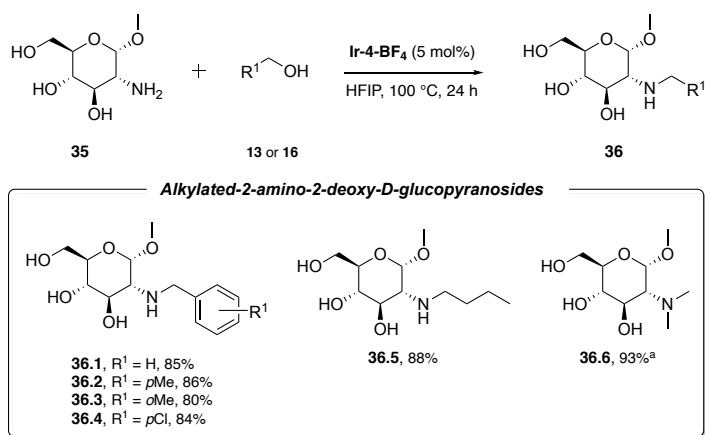


**Not-tolerated substrates**



**Scheme 34.** Scope of the *N*-alkylation of 6-amino-6-deoxypyranosides with alcohols and limitations. Isolated yields. <sup>a</sup>Alcohol as co-solvent. \*48 h.

Motivated by the results obtained using C6-amino sugar derivatives, the possibility of performing this transformation with sugars bearing the amino group at other carbons on the sugar ring was investigated. The reaction was then tested on 2-amino-2-deoxy- $\alpha$ -D-glucopyranoside. Here, the presence of a free primary alcohol (C6), opens up for the possible formation of byproducts (produced by self-condensation), making of it a very challenging substrate for this reaction. Gratifyingly, the reaction performance was not affected and a variety of *N*-alkylated products were obtained in very high isolated yields (Scheme 35, **36.1-36.6**). No self-condensation or formation of any other byproducts was observed in any case.

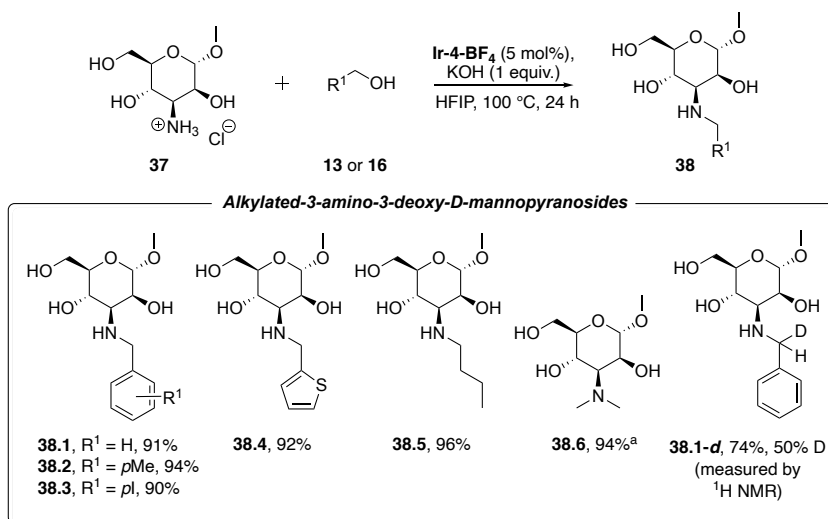


**Scheme 35.** Scope of *N*-alkylated 2-amino-2-deoxy- $\alpha$ -D-glucopyranosides.

<sup>a</sup>Alcohol as co-solvent.

The method was then extended to C3-amino sugars. Commercially available 3-amino-3-deoxy- $\alpha$ -D-mannopyranoside hydrochloride was investigated as substrate. Due to difficulties in the neutralization of the salt (due to its high solubility in aqueous media) prior to the catalytic reaction, new approaches were therefore studied. Indeed, the robustness of the method was shown when addition of 1 equivalent of potassium hydroxide to the reaction mixture allowed access to the desired *N*-alkylated-3-amino-3-deoxy- $\alpha$ -D-mannopyranoside derivatives. Once more, a variety of alcohols including isotope-labelled benzyl alcohol, afforded products **38.1-38.1-d** in moderate to very high yields (Scheme 36).



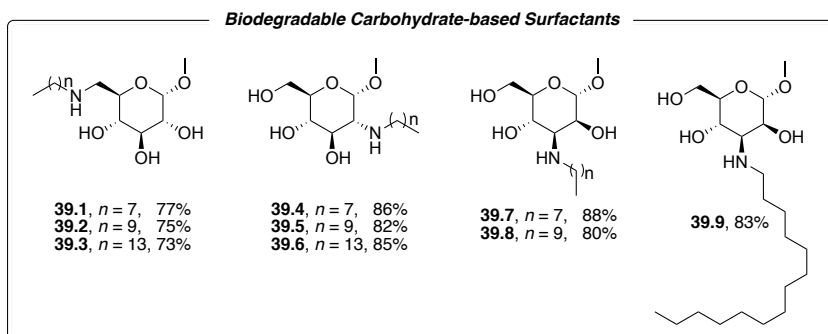


**Scheme 36.** Scope of *N*-alkylated 3-amino-3-deoxy- $\alpha$ -D-mannopyranosides.

<sup>a</sup>Alcohol as co-solvent.

### 3.5.4.2. Synthesis of carbohydrate-based surfactants

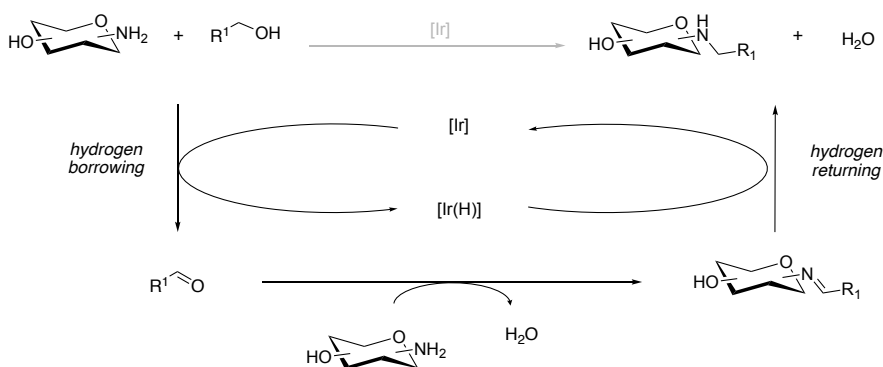
Due to the high hydrophilicity of carbohydrates, they appear ideal building blocks for the synthesis of biodegradable surfactants.<sup>162</sup> Indeed, we explored the use of long-chain aliphatic alcohols as alkylating agents. As a clear advance of our catalytic system, it overcomes the main challenge in the synthesis of this kind of compounds, which consists of the difficulty to accommodate the substrates in same reaction media, in spite of their different polarities. Therefore, a range of fatty alcohols with up to 14 carbons were employed as alkylating agents using a variety of amino sugar substrates (Figure 33). The methodology presented in this work was proven to be optimal for the synthesis of carbohydrate-based surfactants, containing the long aliphatic chain bound to different positions in the amino sugar (Figure 33, 39.1-39.9).



**Figure 33.** Carbohydrate-based Surfactants.

### 3.5.5. Proposed mechanism

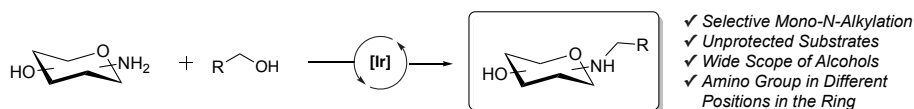
We herein suggest a similar mechanism to the one operating when using aniline as starting material (*vide supra*, Scheme 21). The three-step reaction showed to be sensitive to the stereochemistry of the substituents in the amino sugar substrate. We attribute to the steric clash between the amine and the hydroxyl groups the decrease in rate, or even hampering of reactivity in some cases (*vide supra*, Figure 32). A general mechanism for the synthesis of mono-*N*-alkylated unprotected amino sugars is shown in the following scheme (Scheme 37).



**Scheme 37.** Simplified mechanistic cycle.

### 3.5.6. Conclusions

An efficient approach for the synthesis of *N*-alkylated carbohydrates has been described. This methodology could be applied to different unprotected amino sugar derivatives that contain the amino group at C2, C3 or C6. Unprotected substrates were used, avoiding extra steps and generation of waste, while obtaining very high yields in all the products described. This transformation could be applied to more available hydrochloride starting materials by addition of base, showing the robustness of the catalytic system. As a last application, a series of biodegradable surfactants have been synthesized (Scheme 38). This highly valuable compounds are very challenging to synthesize and the very few reported methods developed up to date require derivatizations steps and harsh reaction conditions.



**Scheme 38.** *N*-Alkylation of carbohydrate amines *via* hydrogen transfer.

## 4. Concluding remarks

To summarize, this thesis has covered the design and application of iridium-based catalyst for C–O and C–N bond forming reactions *via* hydrogen transfer.

In Paper I (Chapter 2), the use of an Ir-NHC complex previously reported by the group for the cyclodehydration of diols was explored. A variety of tetrahydrofuran and tetrahydropyran products were obtained following the new synthetic procedure. Mechanistic investigations on the effect of the electronic properties of the substrates were performed suggesting that with the exception of the very electron-rich substrates, a non-explored hydrogen transfer pathway is operating in this transformation.

In Chapter 3, we ventured into the design of a new catalyst. In a previous report from the Martín-Matute's group, an alkoxy-functionalized Ir-NHC complex was used as catalyst for the *N*-alkylation of amines with alcohols. Interestingly, mechanistic investigations revealed that the resting state species consisted of a molecule of aniline coordinated to the iridium-hydride complex. With the aim of preventing the formation of such stable species, a new amino-functionalized Ir-NHC complex was designed and synthesized during this thesis.

In Paper II, the high efficiency of the new complex in the selective mono-*N*-alkylation reaction of amines with alcohols is demonstrated. A variety of anilines are successfully alkylated in base-free conditions and at room temperature. The method could be extended to aliphatic substrates. Methylated anilines were also synthesized using methanol as cosolvent. In addition, extensive mechanistic studies allowed us to gain a better knowledge of the details of the catalytic cycle.

In line with this thesis, Paper III investigates the use of a new amino-functionalized catalyst for the synthesis of *N*-modified amino acids from unprotected substrates. A new protocol to access mono-alkylated amino acids with exceptional functional group tolerance is described. The excellent activity of this catalytic system formed products in quantitative yields, avoiding the need of extra protection/deprotection steps to isolate the desired products, highlighting the green character of the method. Furthermore, the very poor solubility of the products allowed for catalyst recyclability. This approach constitutes a sustainable path to obtain a large variety of valuable building blocks, very challenging to obtain otherwise.

In the last part of the thesis (Paper IV), a novel approach to access *N*-alkylated carbohydrates is presented. The newly designed catalyst allowed access to a variety of amino sugars from unprotected substrates. The *N*-alkylation reaction could be achieved in different positions of the ring and with very high selectivity towards mono-alkylation. The use of fatty alcohols as substrates gave access to biodegradable surfactants in a straightforward manner.

## 5. Appendix A. Author's contribution list

### *Paper I. Nonclassical Mechanism in the Cyclodehydration of Diols Catalyzed by a Bifunctional Iridium Complex*

Synthesized the catalysts used in the project. Performed the majority of the substrate scope, including isolation and characterization. Carried out the mechanistic studies and analyzed the results. Contributed to the writing of the manuscript and supporting information.

### *Paper II. A General and “Universal” Catalyst for the Base-Free Selective Mono-N-Alkylation of Amines with Alcohols. Insights into the Mechanism*

Optimized the synthetic route of the catalyst. Synthesized the catalyst and performed the full optimization of the reaction conditions. Carried out the investigations of the whole substrate scope and mechanistic studies, with exception of DFT calculations. Wrote the manuscript and the supporting information.

### *Paper III. Selective and Quantitative Functionalization of Unprotected $\alpha$ -Amino Acids Using a Recyclable Homogeneous Catalyst*

Contributed to the optimization of the reaction conditions. Synthesized and characterized the majority of products shown. Performed the mechanistic investigations. Wrote the manuscript and the supporting information.

### *Paper IV. Direct N-Alkylation of Unprotected Amino Sugars with Alcohols. Fast Access to Highly Functionalized Building Blocks and Biodegradable Surfactants*

Performed the complete optimization of the reaction conditions and the majority of the substrate scope. Wrote the manuscript and the supporting information.

## 6. Appendix B. Reprint permissions

Reprint permissions for publications **I–IV** were given by the publishers for each of the following articles:

- I.** González Miera, G.;<sup>#</sup> Bermejo López, A.;<sup>#</sup> Martínez-Castro, E.; Norrby, P. -O. and Martín-Matute, B.\* *Chem. Eur. J.* **2019**, 25, 2631–2636. Copyright © 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Reproduced with permission. *Open access*.

Permissions to reprint parts of figures 5 and 6 were obtained from the respective publishers:

**Figure 5.** Arduengo, A. J. *Accounts of Chemical Research* **1999**, 32, 913-921. Copyright © 1999 American Chemical Society

**Figure 6.** Arduengo, A. J.; Harlow, R. L.; Kline, M. *Journal of the American Chemical Society* **1991**, 113, 361-363. Copyright © 1991 American Chemical Society

## 7. Appendix C. Experimental Data

Full experimental data and supporting information for Paper I can be found at: <https://chemistry-europe.onlinelibrary.wiley.com/doi/full/10.1002/chem.201805460>

The experimental Supporting Information for Paper II can be found at: <https://doi.org/10.5281/zenodo.7013454>

The Raw NMR data for Paper III can be downloaded at: <https://doi.org/10.5281/zenodo.7002830>

The Raw crystallographic data for Chapter 3 can be downloaded at: <https://www.ccdc.cam.ac.uk/structures/>  
The Cambridge Structural Database, CCDC (2196047).

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