THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Valorisation of Renewable Building Blocks via Transition Metal Catalysis

Glycerol- and Amino Acid Derived Compounds in Hydrogen Borrowing and RuAAC Reactions

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Cover: Plant-derived glycerol and amino acids, and compounds that can be synthesised from these compounds and/or via hydrogen transfer catalysis and RuAAC.

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ABSTRACT

To a large extent, organic building blocks are today obtained from petroleum-based products. From an environmental point of view, biomass-derived compounds are more sustainable alternatives to such oil-derived molecules. The 12 principles of g*reen chemistry* describe how chemical processes can be improved in terms of sustainability. With some of these principles as guidelines, this thesis considers the upgrading of renewable glycerol- and amino acid-derived compounds using two different atom economic catalytic reactions: the *hydrogen borrowing reaction*, and the *ruthenium-catalysed azide-alkyne cycloaddition (RuAAC) reaction*.

First, the glycerol derivatives solketal and 1,3-propanediol were investigated as starting materials in organic transformations using hydrogen borrowing methodology. Solketal was aminated with a set of secondary amines as well as sterically hindered primary amines, yielding the corresponding amino glycerol derivatives in good to excellent yields, using $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst. Deprotection of the acetal gave the free amino diol, and this reaction sequence was used to synthesise the antitussive agent dropropizine in two steps from solketal. Furthermore, the iridium-catalysed α-alkylation of acetophenone with 1,3-propanediol was investigated. A mixture of products was obtained in moderate yields when using $[Ir(cod)Cl]_2$ as the catalyst, while the selectivity could be improved by instead utilising an iridium-carbene complex as the catalyst. Hydrogen transfer methodology was also employed in the synthesis of chromanone scaffolds from 2'-hydroxyacetophenone and an alcohol. Brief mechanistic insight was gained considering the two reaction types via deuterium-labelling experiments and computational techniques, respectively.

In addition, chiral triazole δ-amino acids were constructed via a RuAAC reaction for the construction of foldamers. Eight chiral triazoles were synthesized in good yields. Computational conformational studies revealed that the synthesised monomers had several low energy conformations that could be part of a well-defined three-dimensional foldameric structure.

Finally, the RuAAC reaction was used in combination with a hydrogen borrowing cyclisation reaction for the construction of 1,5-fused triazole piperazines from a simple amino acid derived azide. A set of 14 different triazoles were synthesised in moderate to excellent yields, and 7 of these triazoles were successfully cyclised to give the desired 1,5-fused triazoles in two steps.

Keywords: alkylation, amination, amino acid-derived azide, glycerol, hydrogen borrowing, 1,3-propanediol, renewable precursors, RuAAC, solketal, 1,2,3-triazole

LIST OF PUBLICATIONS

This thesis is based on the following publications:

I **Glycerol Upgrading via Hydrogen Borrowing: Direct Ruthenium-Catalyzed Amination of the Glycerol Derivative Solketal**
Anna Said Stålsmeden, José Luis Belmonte Vázquez, Kim van Weerdenburg, Rebecca Rae, Per-Ola Norrby, Nina Kann
ACS Sustainable Chemistry and Engineering **2016**, *4*, 5730-5736

II **Direct Catalytic C-C Bond Formation Using a Renewable Precursor: Iridium-Catalyzed Alkylation of Acetophenone with 1,3-Propanediol**
Anna Said Stålsmeden, August Runemark, Fabio Lorenzini, Andrew C. Marr, Per-Ola Norrby, Nina Kann
Manuscript, submitted to *Synlett*

III **Towards Complex Triazole Amino Acids: Synthesis and Structural Properties of Chiral 1,5-Disubstituted 1,2,3-Triazole Dipeptide Derivatives**
Anna Said Stålsmeden, Johan R. Johansson, Linda Thunberg, Tamás Beke-Somfai, Nina Kann
Manuscript for *Organic and Biomolecular Chemistry*

IV **Synthesis of 1,5-Fused 1,2,3-Triazole Piperazines via a RuAAC – Hydrogen Borrowing Route**
Anna Said Stålsmeden, August Runemark, Johan R. Johansson, Per-Ola Norrby, Nina Kann
Manuscript for *Organic Letters*

CONTRIBUTION REPORT

I Contributed to the formulation of the research problem, performed or supervised the major part of the experimental work, contributed considerably to the interpretation of the results, and wrote parts of the manuscript.

II Contributed to the formulation of the research problem, performed or supervised the major part of the experimental work, contributed considerably to the interpretation of the results, and wrote parts of the manuscript.

III Performed half of the experimental work, contributed to the interpretation of the results and writing of the manuscript.

IV Formulated the research problem, performed or supervised the experimental work, interpreted the results, and wrote the majority of the manuscript.

Related publication, not included in this thesis:

Ruthenium-Catalyzed Azide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications
Johan R. Johansson, Tamás Beke-Somfai, Anna Said Stålsmeden, Nina Kann
Chemical Reviews, **2016**, *116*, 14726-14768

ABBREVIATIONS

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
Boc	*tert*-Butyl carbamate
Cat.	Catalyst
CataCXium® PCy	2-(Dicyclohexylphosphino)-1-phenyl-1*H*-pyrrole
cod	1,5-Cyclooctadiene
Conv.	Conversion
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
CuAAC	Copper-catalysed azide alkyne cycloaddition
p-Cymene	1-Isopropyl-4-methylbenzene
DDGS	Distiller dried grains with solubles
DFT	Density functional theory
DMSO	Dimethyl sulfoxide
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
dppb	1,4-Bis(diphenylphosphino)butane
DMP	Dess-Martin periodinane
DPPBz	1,2-Bis(diphenylphosphino)benzene
dppe	1,2-Bis(diphenylphosphin)ethane
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-Bis(diphenylphosphino)propane
ee	Enantiomeric excess
GC-MS	Gas chromatography mass spectrometry
HPLC	High performance liquid chromatography
Me	Methyl
MP-Carbonate	Macroporous polymer-bound carbonate
MS	Mass spectrometry

μw	Microwave
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Ph	Phenyl
PipPhos	(3,5-Dioxa-4-phosphacyclohepta[2,1-a:3,4-a']dinaphthalen-4-yl)piperidine
rt	Room temperature
RuAAC	Ruthenium-catalysed azide alkyne cycloaddition
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
SEGPHOS	5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
SIRT2	NAD^+-dependent deacetylase sirtuin 2
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
pTsOH	*p*-Toluenesulfonic acid
w/w	weight per weight
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

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1. INTRODUCTION

The past century has seen amazing discoveries and technical advances in areas such as communication, infrastructure, transportation, and materials. The drawback however, is that a large proportion of the increasing need for power and materials has been fulfilled by the oil industry. From a global sustainability perspective, this cannot continue forever.[1] As a consequence, the European Commission recently initiated a circular economy package.[2] Chemistry holds a central role in this shift and is the foundation of for example the pharmaceutical and material industries, which are highly dependent on the use of organic compounds. This includes building blocks, reagents and solvents for the processes and manufacturing of a wide range of products. With diminishing oil reserves, industrial actors have to find alternative raw materials that can provide the community with organic building blocks, reagents and reaction media. Materials from wood and plants are possible alternatives to petroleum-derived building blocks. Such compounds do, however, differ in terms of structure and properties, meaning that chemical modifications of these materials must diverge from traditional methods employed for petroleum derived compounds. Moreover, many chemical transformations suffer from issues such as the use of stoichiometric amounts of reagents and hazardous reactants. The employment of more benign starting materials and efficient catalysts could lower the production costs in industry as well as be beneficial for the environment. These ideas are not new in any way and are all included in the concept of *green chemistry*, discussed in the next section.

1.1 GREEN CHEMISTRY

The idea of green chemistry, in great pioneered by Paul Anastas and John Warner in the 1990s, considers how chemistry can be performed with minimum environmental impact and minimal overall cost.[3] It involves essential principles such as performing chemical transformations with a low degree of waste formation and high atom economy,[4] the use of non-hazardous chemicals and solvents, high energy efficiency, and the utilisation of renewable feedstock. In this work, we have implemented a few of these principles as guidelines to make certain choices. These are the use of catalysis, atom economy, renewable feedstock, and waste prevention.

There are several possible renewable sources of organic building blocks and reagents. Lignocellulosic biomass from plants is the most abundant renewable material on our

planet.[5] It consists of cellulose, hemicellulose, and lignin. While cellulose and hemicellulose are polymeric materials built up by carbohydrate units, lignin is a randomly cross-linked aromatic amorphous material. Plant oils and extracts are also of interest in this context. Renewable feedstock such as rapeseed oil, soybean oil and palm oil can be used to produce biodiesel as an alternative fuel.[6] Via transesterification, the fatty acids can be isolated as for example methyl esters, and applied as bio-based fuels. Glycerol is a small organic molecule, currently obtained in large volumes as a by-product in this process (Figure 1.1). It is dense in alcohol functionalities that can be chemically transformed. This versatile molecule and derivatives thereof has found a wide use, both in the manufacturing of food and cosmetics,[7] as well as in the chemical industry.[8] We have set out to investigate the use of glycerol as a starting material for organic synthesis. By employing the different alcohol functionalities as "handles" for organic transformations, we envision that glycerol can be used to construct three-carbon fragments of small organic molecules.

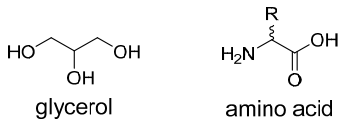


Figure 1.1 Glycerol and the general structure of amino acids. R = H or alkyl.

Living organisms use proteins called enzymes for catalysing chemical reactions.[9] Proteins are constructed of long chains of amino acids (Figure 1.1). Amino acids are versatile renewable building blocks obtainable from many sources including biofuel production waste streams.[10] As they contain an amine functionality, they are suitable for the construction of nitrogen containing molecules. Conversion of the acid functionality of the amino acid into an azide, enables the formation of nitrogen containing heterocyclic compounds that may be of interest for the pharmaceutical industry. We have examined amino acid derivatives as precursors for the formation of organic building blocks.

1.2 CATALYSIS

A catalyst is a compound that increases the rate of a chemical reaction without altering the change in standard Gibbs free energy.[11] At the end of the reaction, the catalyst is returned to its original state. In practice, this means that a catalyst can be used to perform a reaction under milder conditions or using shorter reaction times, thus increasing the efficiency of the process. Furthermore, catalysts can improve the selectivity of a reaction by enhancing the formation of a certain product over other

possible products, leading to higher yields and less waste. Enzymes in our bodies do this all the time to keep us alive. Enzymes can also be applied as catalysts in organic transformations.[12] Another class of catalysts called organocatalysts are organic compounds that can mediate chemical reactions.[13] Transition metal complexes are yet another group of compounds that can serve as catalysts.[14] Such transformations are powerful tools in the modern chemistry toolbox and several Nobel prizes have been awarded for transition metal-catalysed reactions, including palladium-catalysed cross-coupling reactions in 2010 (Richard Heck, Ei-ichi Negishi, and Akira Suzuki), the metathesis reaction in 2005 (Yves Chauvin, Robert Grubbs and Richard Schrock), and asymmetric catalysis in 2001 (William Knowles, Ryōji Noyori, and Barry Sharpless).[15]

Catalysis is an important tool for performing green chemical transformations and we are interested in exploring the construction of small organic molecules by means of atom economic transition metal-catalysed reactions. The *hydrogen borrowing reaction* allows the facile and direct substitution of an alcohol functionality by a nucleophile such as an amine or an enolisable carbonyl compound, forming water as the only by-product, and avoiding the use of stoichiometric reagents associated with traditional pre-activation of the hydroxyl group.[16] In this thesis, hydrogen borrowing is investigated as a method for the modification of glycerol derivatives as well as for the formation of fused heterocyclic compounds. The *ruthenium-catalysed azide alkyne cycloaddition (RuAAC) reaction* permits the selective formation of 1,5-disubstituted 1,2,3-triazoles, with all substrate atoms retained in the product.[17] Such structural motifs are interesting from a synthetic point of view, and are present in several biologically active molecules such as antibacterial, antiviral, antifungal, anticancer, and anti-inflammatory agents.[18] Moreover, triazoles have received attention in the field of synthetic peptide-like structures known as peptidomimetics.[19] In this thesis, amino acid derivatives are investigated as substrates in the RuAAC reaction, with the purpose of forming triazole monomers for the construction of foldamers. Foldamers are oligomeric compounds that can form well-defined three-dimensional structures resembling natural peptides.[20] Furthermore, the RuAAC reaction is applied in combination with the hydrogen borrowing reaction, yielding polycyclic triazole-containing compounds from amino acid derived azides.

2. AIMS

The overall aim of this thesis has been to:

- Develop chemistry that is adapted for the utilisation of renewable organic building blocks in organic synthesis.
- Investigate more sustainable and atom economic catalytic methods for these transformations.
- To apply these chemical reactions towards the atom economic construction of polycyclic nitrogen containing compounds, of possible interest for the pharmaceutical industry.

In order to do so, we have explored several different routes.

In the first part of the thesis, glycerol derivatives were studied as renewable starting materials for organic transformations. Here, we wanted to investigate if amines and enolisable carbonyl compounds could be alkylated using different glycerol derivatives. This work is described in chapters 4 and 5.

In the second part, amino acid derived azides were employed to form 1,5-disubstituted 1,2,3-triazole monomers via a RuAAC reaction, for the construction of foldameric structures. In this project, we were interested in exploring how the chirality of amino acid derivatives would affect the structural properties of the formed triazole monomers. Moreover, we wanted to learn how such monomers would behave in foldamers, with a possible end use in peptidomimetics. This work is discussed in chapter 6.

In the final part of the thesis, the chemistry from the two previous parts was combined in order to form polycyclic structures that may find applications in medicinal chemistry. In this chapter, we were interested in investigating if it was possible to construct 1,5-fused 1,2,3-triazole piperazines from amino acid derived azides via a RuAAC reaction, followed by an intramolecular hydrogen borrowing reaction. These results are discussed in chapter 7.

3. BACKGROUND

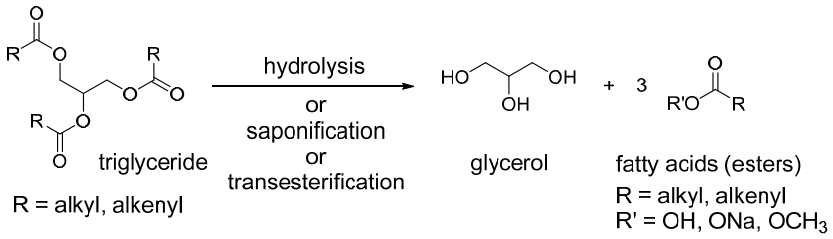
3.1 BIOMASS-DERIVED BUILDING BLOCKS

One of the objectives of this thesis has been to investigate the use of renewable starting materials in organic synthetic transformations. This chapter gives an introduction to biomass-derived glycerol and amino acids.

During the past decades, efforts to improve the efficiency of chemical transformations and minimise their impact on the environment have increased. Renewable feedstocks will in the future be essential assets for preparing materials and small functional molecules.[21] In addition, more sustainable catalysts, reagents and solvents will be important in the manufacturing process of these molecules and materials. Organic building blocks and reagents are to a large extent obtained from the petroleum industry. For example, in 2010 only around 3-4% of globally produced chemicals were bio-based.[21] Biomass or renewable feedstock are generic terms for materials produced by currently or recently living organisms (such as wood that may have a lifetime over hundreds of years), yielding "short-cycle carbon system" production chains and thus not adding notably to the amount of carbon dioxide in the atmosphere.[21] Depending on the source, a wide range of substances are accessible. In this thesis, two kinds of building blocks from renewable sources have been used: glycerol derivatives obtained from vegetable oils,[7a] and compounds originating from amino acids, available from for instance plant production waste streams.[10b]

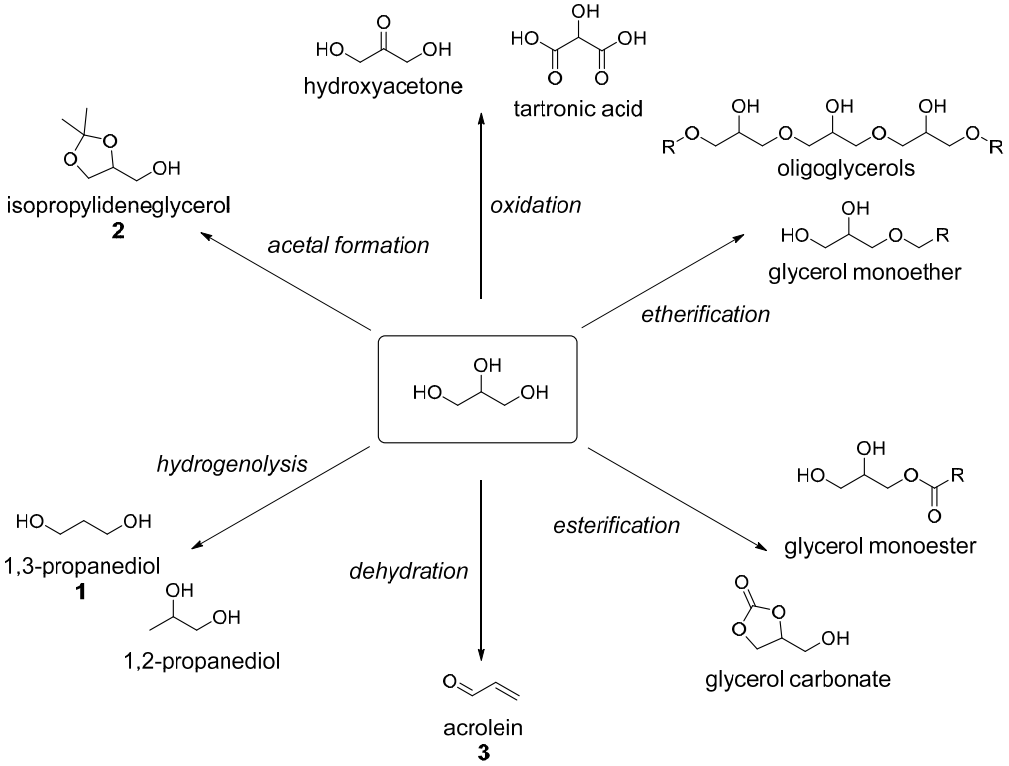
3.1.1 Glycerol and glycerol derivatives

Glycerol (1,2,3-propanetriol or glycerine) is a three carbon compound with one alcohol functionality on each carbon, present in our bodies and in nature as the "backbone" of fats and oils in the form of triglycerides (Scheme 3.1).[7a] In its free form, it is a colourless, hygroscopic, sweet tasting, syrupy liquid that has more than 1500 known end uses. This versatile molecule has no known toxic effects to humans or to the environment. Glycerol was chemically identified by Carl Wilhelm Scheele in the 18th century.[22] Today, glycerol is obtained from fats and oils via hydrolysis, saponification or most commonly transesterification (Scheme 3.1).[7a, 8] The fatty acid esters can be used to manufacture diesel fuel, i.e. biodiesel, and the major by-product formed is glycerol (around 10 % w/w).



Scheme 3.1 Formation of glycerol and fatty acids or fatty acid esters from triglycerides.[8]

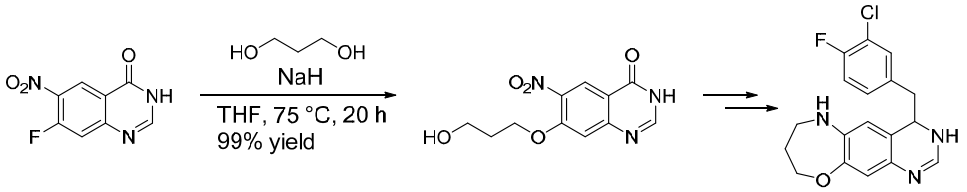
Early practical use of glycerol on a large scale can be exemplified by the importance of nitroglycerine in the form of dynamite, discovered by Alfred Nobel in the 19th century.[7a] Glycerol itself has for example been employed as an additive in foods, cosmetics, pharmaceuticals, and other consumer products, benefiting from its viscous texture, sweet taste, hygroscopic, and preserving properties. In addition, glycerol has been applied in a wide range of industrial processes to afford chemicals that can be used as fuel additives, ingredients in cosmetics, antifreeze agents, in polymer- and surfactant production and many other applications.[7] Various chemical modifications have been used to valorise glycerol, for example oxidation,[23] etherification,[24] esterification,[8, 25] hydrogenolysis,[26] as well as acetal formation.[27] Examples of transformations involving glycerol are shown in Scheme 3.2.



Scheme 3.2 Glycerol can be converted into a large number of useful chemicals.[8, 23-27]

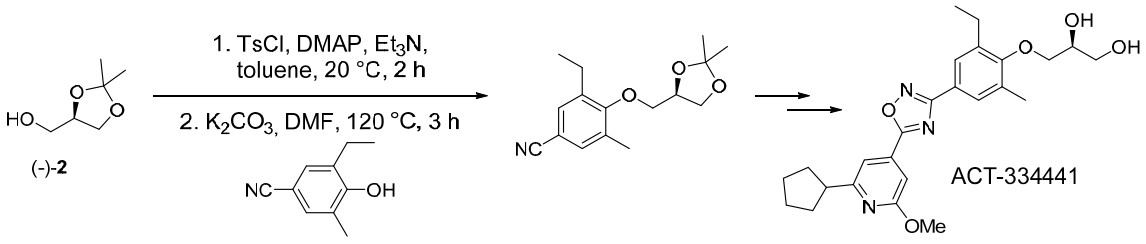
In this thesis, the glycerol derivatives 1,3-propanediol (**1**) and isopropylideneglycerol (**2**) have been utilised (Scheme 3.2). The former is obtained from glycerol via hydrogenolysis (dehydration followed by hydrogenation). Such processes are employed to produce both 1,2-propanediol and 1,3-propanediol.[26] 1,2-Propanediol is used as an additive in for example nutrition products and paint, but also directly as a de-icing agent, while 1,3-propanediol is applied mainly in polymer production. 1,3-Propanediol can also be formed from glycerol via fermentation.[28]

1,3-Propanediol can be used as a three carbon fragment in the construction of organic compounds. A recent example is the synthesis of fused oxazepine gefitinib derivatives as potential cancer therapeutics (Scheme 3.3).[29] Following an aromatic nucleophilic substitution employing one alcohol moiety, the second alcohol was transformed into a chloride allowing for formation of the third ring.



Scheme 3.3 1,3-Propanediol in the synthesis of fused oxazepine gefitinib analogues.[29]

Glycerol acetals are a class of compounds that have found industrial applications, for example as fuel additives,[27] surfactants and odorants.[8] Isopropylideneglycerol, also called solketal (**2**, Scheme 3.2 and 3.4), can be synthesised from glycerol and acetone using acid or metal catalysis.[27] It is a suitable substrate for selective reactions at one of the primary alcohols of glycerol. In the synthesis of sphingosine 1-phosphate 1 receptor ($S1PR_1$) agonist ACT-334441, developed for the treatment of autoimmune disease, (–)-isopropylideneglycerol was used as starting material to obtain the chiral side chain (Scheme 3.4).[30] The free alcohol could after tosylation be used to alkylate a phenol. Four additional reaction steps were needed to complete the synthesis.



Scheme 3.4 Synthesis of a $S1PR_1$ agonist from (–)-solketal (**2**).[30]

3.1.2 Amino acids

Amino acids are the building elements of enzymes and proteins in all living organisms (Figure 3.1).[10b, 12] Amino acids are viable as food for humans and animals, but with increasing production of for example biofuels, the plant protein waste production increases.[31] It can be estimated that if 10% of exploited fossil transportation fuel in the mid-2000s was substituted by biomass-derived alternatives, up to 100 million tonnes of protein waste could be produced annually. Such an increase in manufacture would lead to a decreasing market value of waste protein and would further motivate alternative uses such as the production of bulk chemicals. Examples of promising sources of protein waste are distiller dried grains with solubles, commonly called DDGS, from biofuel production such as bioethanol and biodiesel, obtained from various crops, including wheat, corn, rape, and maize.[10a, 31]

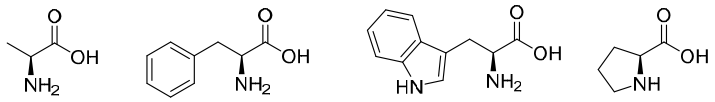
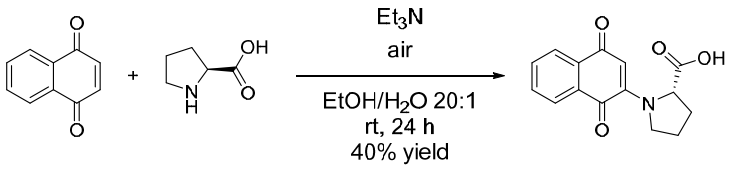


Figure 3.1 Four of the twenty common amino acids found in proteins.[12]

However, protein waste valorisation is not completely straightforward, and several approaches have been undertaken in order to achieve selective isolation and value upgrading.[10b] Initially, the proteins need to be hydrolysed into the individual amino acids, which can then be further isolated and finally modified. The hydrolysis step can be carried out using for example chemical or enzymatic approaches, or via fermentation. Separation of the individual amino acids can be accomplished by chromatography, sometimes in combination with chemical or enzymatic modification. These procedures are still expensive however, and a lot of work remains for these methods to become economically competitive. Nonetheless, amino acids are promising starting materials for nitrogen containing chemicals, and when a viable isolation process has been developed, there will be clear environmental benefits of using waste protein material. As an example, the amino acid proline (Figure 3.1) can be selectively de-carboxylated to give the cyclic amine pyrrolidine.[32] Moreover, there are numerous examples of the use of amino acids and derivatives thereof in organic synthesis, often related to medicinal chemistry. One example is the work of Masłyk and co-workers concerning 2-aminonaphthoquinones as potential antibacterial agents (Scheme 3.5).[33] By allowing naphthoquinone to react

with different amino acids in the presence of triethylamine, a set of 2-aminonaphthoquinones could be obtained and their antibacterial activity was tested.

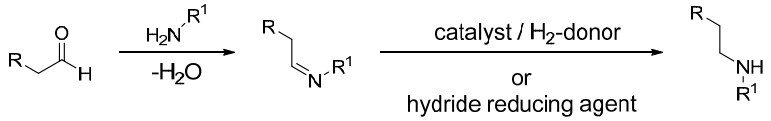


Scheme 3.5 Synthesis of 2-aminonaphthoquinones from the amino acid proline.[33]

3.2 THE HYDROGEN BORROWING REACTION

Glycerol has three alcohol functionalities. In order to efficiently upgrade glycerol derivatives, we have investigated hydrogen borrowing as a direct and green approach towards the construction of small functional molecules. Moreover, we have employed the hydrogen borrowing reaction in the synthesis of fused polycyclic triazole derivatives. This section deals with the scope and mechanism of the hydrogen borrowing reaction.

In traditional transformations of alcohols, the nucleophilic oxygen can be used to form new bonds, yielding compounds such as ethers and esters.[34] Alternatively, the alcohol can be converted into a more reactive species such as a halogen, tosylate, or carbonyl functionality. Halogens and tosylates are good leaving groups that allow for substitution on the adjacent carbon atom by a nucleophile. Carbonyl groups have an electrophilic carbon atom that can be subjected to nucleophilic addition. Amines are common nucleophiles that give imines upon nucleophilic addition. The addition of an amine to a carbonyl functionality in combination with reduction, i.e. reductive amination, is a common way to form new carbon-nitrogen bonds (Scheme 3.6). [35]

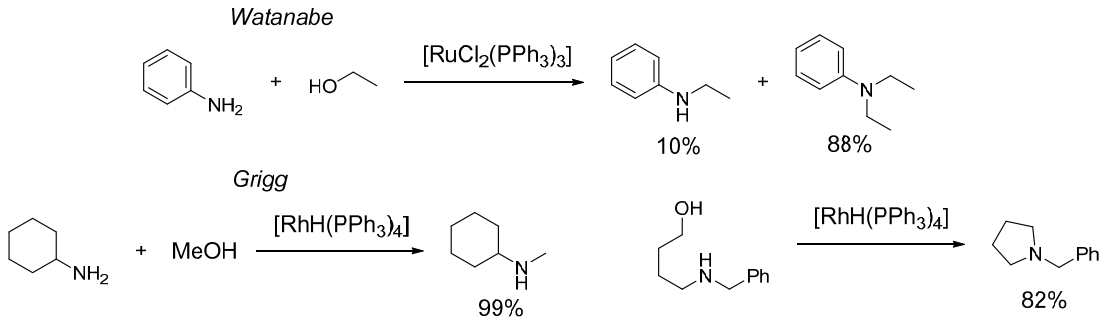


Scheme 3.6 Reductive amination reaction.[35a]

From an environmental point of view, there are some drawbacks with the methods mentioned above. The approaches that result in a new bond to the carbon atom all include activation of the alcohol functionality prior to the bond forming reaction, resulting in additional reaction steps as well as work-up, and purification. In addition, stoichiometric amounts of sometimes hazardous waste in the form of inorganic salts is often generated in the activation step and/or in the bond forming reaction. To

avoid these issues, we decided to exploit a process that enables the direct use of alcohols in carbon–carbon and carbon–nitrogen bond forming reactions.

In the early 1980s, Grigg[36] and Watanabe[37] independently reported the first examples of the homogenously catalysed hydrogen borrowing or hydrogen autotransfer reaction, involving the direct coupling of alcohols with amines (Scheme 3.7). Watanabe used a ruthenium catalyst at 180 ºC, employing the alcohol itself as the solvent and aniline as the nucleophile, resulting in alkylated aniline. Grigg instead used a rhodium or iridium complex in refluxing alcohol and an aliphatic amine as the nucleophilic species, and further demonstrated that cyclic amines could be formed from amino alcohols.



Scheme 3.7 Early examples of the hydrogen borrowing reaction. [36-37]

Since then, these reactions have been extensively investigated and reviewed.[16, 38] Examples of nucleophiles that have been used in the hydrogen borrowing reaction are amines, enolisable carbonyl compounds, nitroalkanes, nitriles, phosphonium ylides, dienes, enynes and indoles (Figure 3.2).[38a] A large number of catalytic systems have proven efficient in catalysing these reactions, most commonly homogenous transition metal complexes based on iridium and ruthenium.[39] There are also many examples of heterogeneous catalysts that can mediate this kind of transformation,[40] although this is not discussed further in this thesis.

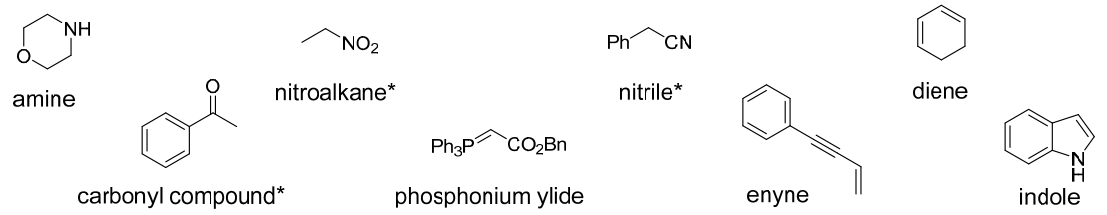
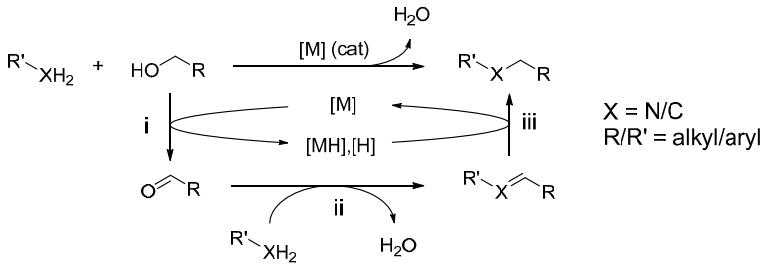


Figure 3.2 Examples of nucleophiles employed in the hydrogen borrowing reaction.[38a] (*Compounds shown in their neutral form, the corresponding anion is the nucleophile.)

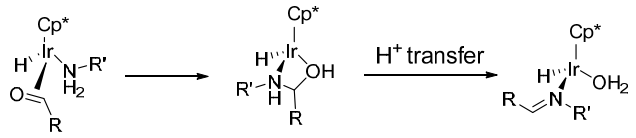
3.2.1 General mechanism of the hydrogen borrowing reaction

The hydrogen borrowing reaction involves the use of a catalyst, usually transition metal-based, that can activate an alcohol *in situ* via hydrogen transfer (hydrides/protons) to give a carbonyl compound that can react further with a nucleophile.[38f, 38h] Both primary and secondary alcohols can be used in the reaction. In this work, two types of nucleophiles have been utilised, i.e. enolisable carbonyl compounds and amines, resulting in α-alkylated ketones and alkylated amines, respectively. The detailed mechanism of the reaction depends on the nature of the substrates, the catalytic system used, and the reaction conditions.[41] However, the overall mechanism is the same in all cases: the first reaction step is the dehydrogenation (oxidation) of the alcohol by the catalyst, resulting in the corresponding carbonyl compound (step i, Scheme 3.8). In the second step, the aldehyde (or ketone) is subject to a nucleophilic attack by the amine or enolate and dehydration takes place (step ii). Finally, the catalyst returns hydrogen to the unsaturated intermediate to give the saturated product (step iii).



Scheme 3.8 General mechanism for the hydrogen borrowing reaction.[38f, 38h]

The dehydrogenation/hydrogenation process is closely related to the catalytic transfer hydrogenation reaction that involves hydrogen transfer from an alcohol to a carbonyl compound or *vice versa*.[42] The dehydrogenation step can result in either a monohydride metal intermediate[41a, 41b] (Scheme 3.9) or a dihydride metal complex[41c, 41d] that is then further involved in the hydrogenation of the unsaturated intermediate. After dehydrogenation, the formed carbonyl compound may stay within the coordination sphere of the catalyst,[41b] allowing for condensation to occur within this sphere (Scheme 3.9), or it can dissociate.[41d] In the latter case, recomplexation occurs prior to reduction of the unsaturated intermediate.



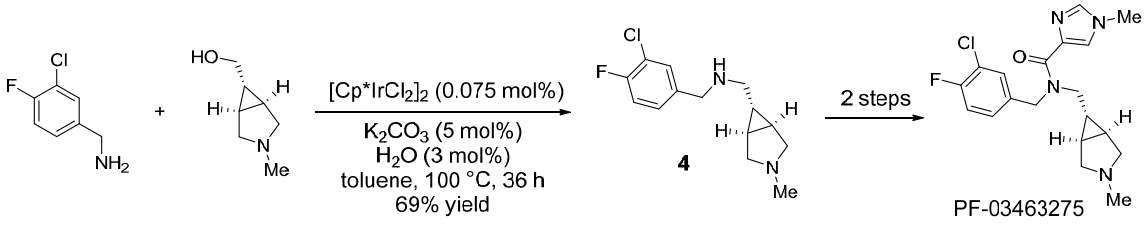
Scheme 3.9 A monohydride complex, condensation occurs with the substrates coordinated to the metal.[41a]

3.2.2 Alkylation of amines via hydrogen borrowing

A number of different catalytic systems have proven successful in mediating the alkylation of amines via a hydrogen borrowing reaction. In this section, representative examples will be highlighted.

Generally, iridium- and ruthenium-based complexes are the most commonly used catalysts in the alkylation of amines, although other metals have been employed.[38f] In most cases, the reaction is carried out under an inert atmosphere at temperatures ranging from 100 to 130 °C. Different solvents such as toluene, dioxane, and *tert*-amyl alcohol are often used, as well as solventless conditions. Both primary and secondary amines can be used as nucleophiles in the hydrogen borrowing reaction. For primary amines, an imine is formed in the condensation step (step ii, Scheme 3.8) yielding a secondary amine as the final product. Secondary amines form an iminium intermediate upon nucleophilic addition to the aldehyde (step ii), which is further reduced to a tertiary amine (step iii).

One efficient and commonly used iridium-based catalyst is $[Cp^*IrCl_2]_2$.[38b, 38f] This catalyst has been utilised by Fujita and Yamaguchi to form nitrogen heterocycles from diols,[43] and later by Cumpstey and Martín-Matute to prepare aminosugars.[44] Furthermore, chemists at Pfizer have shown that the synthetic route to secondary amine intermediate **4** in the synthesis of GlyT1 inhibitor PF-03463275, could be improved using this catalyst (Scheme 3.10).[45] An earlier approach using a two-step oxidation-reductive amination pathway gave 30-45% overall yield of compound **4**. With this improved route, a yield of 69% – 4.5 kg – of compound **4** was obtained in a single step.



Scheme 3.10 Improved synthesis of a GlyT1 inhibitor via hydrogen borrowing.[45]

In most cases these reactions are performed at relatively high temperatures (>100 °C) but there are some exceptions. For example, catalysts developed by groups of Martín-Matute[46] and Kempe[47] operate at temperatures around 70 °C, while a bidentate iridium NHC-phosphine complex, developed by Andersson and co-workers has proven to alkylate anilines in high yields at room temperature (Figure 3.3).[48] In order to enable the execution of these kinds of transformations in aqueous reaction media, water-soluble catalysts such as $[Cp^*Ir(NH_3)_3]I_2$ have also been developed.[49]

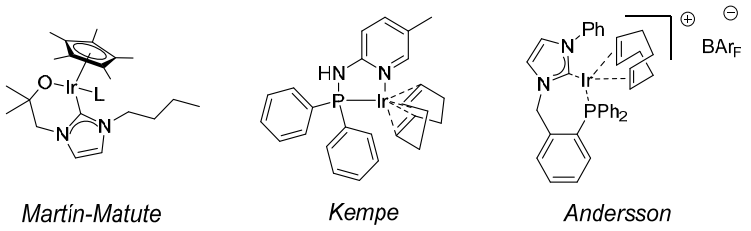
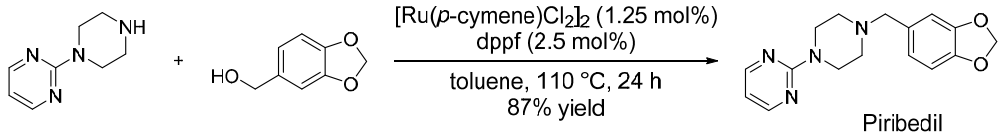


Figure 3.3 Catalysts operating below 100 °C.[46-48]

Moreover, several ruthenium-based catalysts show excellent results in this reaction. $[Ru_3(CO)_{12}]$ has been used by Beller and co-workers,[50] as well as Vogt,[51] and gives good yields for a wide variety of substrates, in some cases in conjuction with CataCXium® PCy as the ligand. The preferred solvent is generally *tert*-amyl alcohol at 130 °C. Williams and co-workers have instead used $[Ru(p\text{-cymene})Cl_2]_2$ with dppf or DPEphos as the ligand (Scheme 3.11).[52] The reaction gives high yields, for example in the synthesis of dopamine agonist Piribedil, used in the treatment of Parkinson's disease. Sulfonamides can also be alkylated using this catalytic system.



Scheme 3.11 Synthesis of Piribedil using a ruthenium catalyst.[52]

The hydrogen borrowing reaction using ruthenium and iridium catalysts has proven to be valuable tools for more efficient and environmentally benign alkylation reactions. The drawback, however, is that both ruthenium and iridium have very low abundance in the Earth's crust.[53] In contrast, iron (situated in the same group as ruthenium in the periodic table) is the fourth most abundant element[53] and has lately received increasing attention as a potential catalyst in organic synthesis.[54]

The capacity of iron catalysts in the context of amination via hydrogen borrowing has been demonstrated for several structurally similar iron cyclopentadienone complexes, as reported by Feringa and Barta,[55] as well as Zhao,[56] and Wills[57] (Figure 3.4). The reactivity of the iron cyclopentadienone complexes was initially discovered by Knölker,[58] revealing their potential as a redox catalysts. This capacity has since then been employed in other hydrogen transfer reactions such as hydrogenations and dehydrogenations, including asymmetric versions,[59] and carbon–carbon bond forming reactions that will be discussed in the following chapter. Furthermore, a pincer complex based on manganese, recently reported by Beller, has also proved to efficiently catalyse this type of transformation (Figure 3.4).[60] Although we have not employed any of these catalysts in the current work, these reports are of great interest for our future investigations towards green transformations of renewable building blocks.

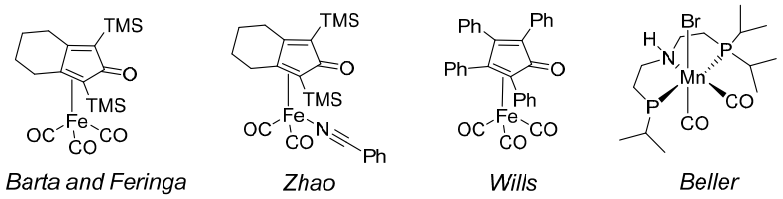


Figure 3.4 Iron and manganese complexes used for the amination of alcohols.[55-57, 60]

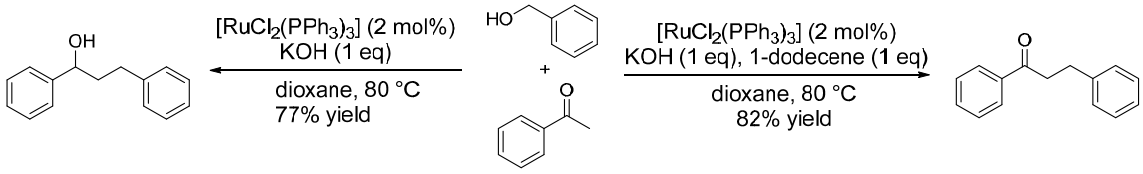
3.2.3 α-Alkylation of ketones via hydrogen borrowing

The borrowing hydrogen reaction is a suitable alternative to several of the traditional carbon–carbon bond forming reactions that employ electrophiles such as aldehydes, tosylates, and alkyl halides. Enolates, generated from carbonyl compounds via removal of acidic α-protons, are nucleophiles that can be efficiently alkylated using this methodology. In the following section some examples demonstrating such transformations will be emphasised.

As with the amine nucleophiles discussed in the previous section, ruthenium and iridium complexes are most frequently used to catalyse the hydrogen borrowing reaction involving enolate nucleophiles.[38h] Reactions are commonly performed under inert conditions, in solvents such as dioxane or toluene and at temperatures ranging from 80-110 °C. In addition to the catalyst, a base is needed for the deprotonation of an acidic α-proton so that the enolate nucleophile is formed and aldol condensation can take place (step ii, Scheme 3.8). Typically, 20-100 mol% of the base is added. An α,β-unsaturated ketone is formed that is further hydrogenated by the catalyst in the final reaction step to give the α-alkylated ketone (step iii). Moreover,

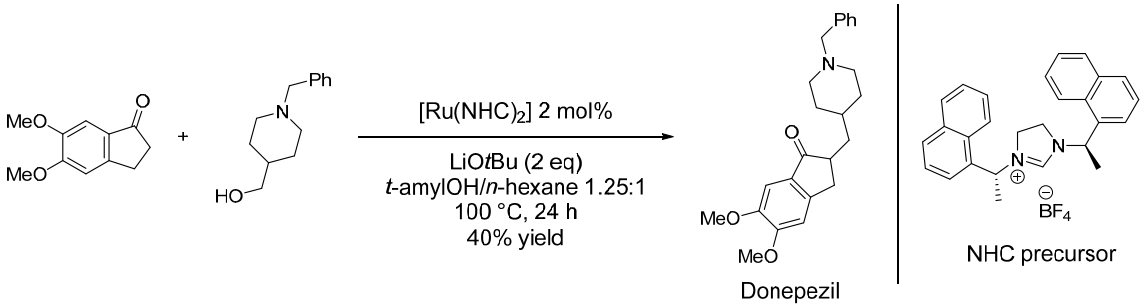
in some cases, a scavenger in the form of an alkene is added in order to suppress competing transfer hydrogenation/overreduction of the carbonyl group of the starting material and the product. A range of carbonyl compounds, with enolisable α-protons can be utilised. Under certain conditions, the carbonyl precursor can have an alkyl group attached to the α-carbon.[61]

Some of the first examples of using enolate nucleophiles were presented by Cho and Shim in the early 2000s. They showed that $[RuCl_2(PPh_3)_3]$ is an efficient catalyst for the α-alkylation of ketones (see Scheme 3.12 for one example).[62] The reaction is regioselective for the least hindered α-carbon and requires equimolar amounts of KOH for enolisation. However, this method required one equivalent of sacrificial alkene (1-dodecene) to prevent overreduction of the product to its corresponding alcohol. In an earlier study by the same group, the corresponding alcohol was obtained in moderate to good yields in the absence of the sacrificial alkene.[63]



Scheme 3.12 α-Alkylation of acetophenone with benzyl alcohol.[62-63]

Furthermore, an iridium based catalytic system was introduced by Ishii and co-worker.[64] They showed that $[Ir(cod)Cl]_2$ with PPh_3 as the ligand can mediate the α-alkylation of ketones under solventless conditions, with only 20 mol% of base (KOH), albeit with a slightly higher reaction temperature (100 °C). It has later been shown that the same catalyst in combination with a different ligand, DPPBz, allows for the formation of branched α-alkylation products.[61] Glorius and co-workers instead utilised a ruthenium-NHC catalyst for the formation of branched α-alkylated ketones.[65] This catalyst has for example proven useful in the formation of Donepezil[66] (used for the treatment of Alzheimer's disease, Scheme 3.13).

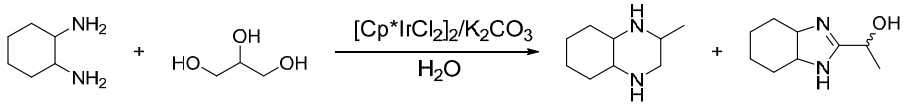


Scheme 3.13 Ru-NHC catalyst for the synthesis of branched alkylated compounds.[65]

As with the amine alkylation, focus in the development of α-alkylation reactions has lately turned to the utilisation of more abundant metal catalysts. For example, an osmium complex developed by Esteruelas and Yus, effectively catalyses the alkylation of acetophenone as well as arylacetonitriles giving high yields of alkylated products.[67] Sortais and Darcel instead employed an iron cyclopentadienone complex in the α-alkylation of various acetophenones,[68] a catalyst previously used by Feringa and Barta in the alkylation of amines (Figure 3.4), while Zhang[69] and Kempe[70] utilised cobalt complexes for the alkylation of ketones and secondary alcohols, respectively.

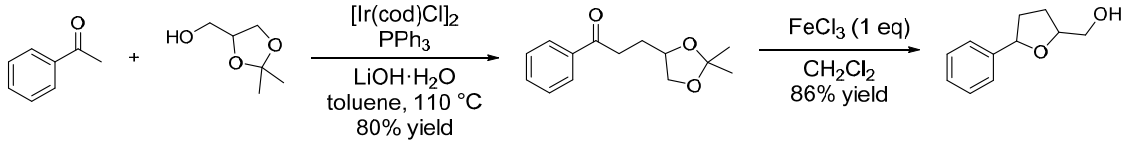
3.2.4 Modification of glycerol derivatives via hydrogen borrowing

Glycerol and glycerol derivatives have been used as substrates in several types of organic transformations. However, when it comes to the application of these substances in the hydrogen borrowing reaction, the examples are scarce. Crotti and co-workers have shown that glycerol can be directly used in an iridium-mediated amination reaction with 1,2-diaminocyclohexane to give a mixture of diaminated products (Scheme 3.14).[71]



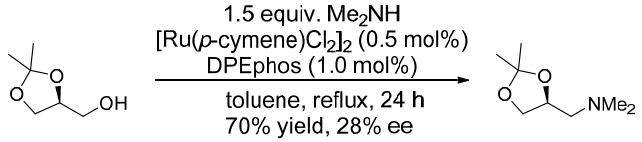
Scheme 3.14 Iridium-mediated coupling of glycerol with 1,2-diaminocyclohexane.[71]

The 1,2-protected glycerol acetonide, isopropylideneglycerol or solketal, was used by Rueping and co-workers in an iridium-catalysed aldol condensation type reaction with various acetophenone derivatives as enolate precursors (Scheme 3.15).[72] Subsequent reduction of the ketone and deprotection of the acetal allowed for cyclisation to 2,5-disubstituted tetrahydrofurans.



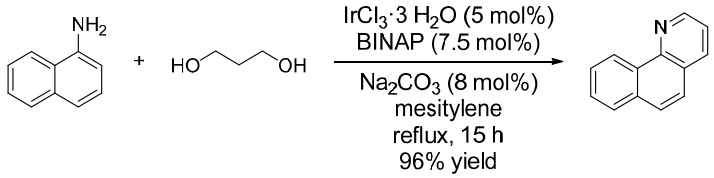
Scheme 3.15 Synthesis of 2,5-disubstituted tetrahydrofurans.[72]

Moreover, Williams and co-workers have shown that isopropylideneglycerol can be aminated using their ruthenium-based catalytic system (Scheme 3.16).[52] The enantiomerically pure alcohol was used, and it was speculated that racemisation of the intermediate aldehyde or imine led to the loss of enantiopurity.



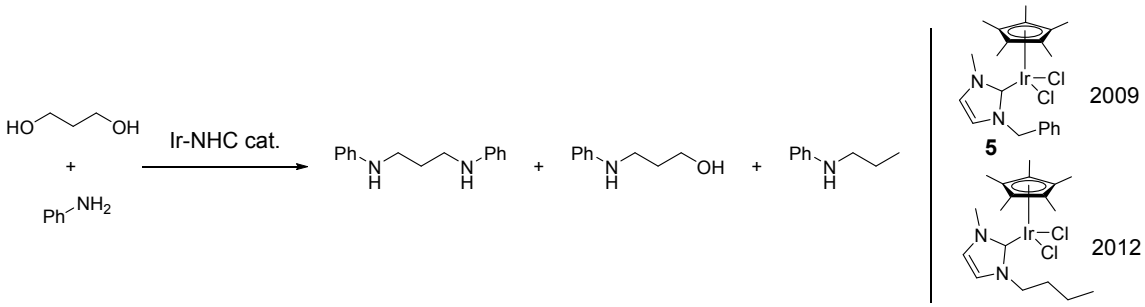
Scheme 3.16 Amination of isopropylideneglycerol.[52]

1,3-Propanediol is one of the most widely used glycerol derivative in these types of reactions. Ishii and co-workers have employed hydrogen borrowing methodology in the synthesis of benzo[*h*]quinolones via reaction of naphthylamines with 1,3-propanediol (Scheme 3.17).[73] These reactions are closely related to the pioneering work of Watanabe in the 1980s where anilines were reacted with 1,3-propanediol[74] and ethylene glycol,[75] using ruthenium catalysis, to give quinolones and indoles, respectively. Later, similar transformations have been performed by Achard and co-workers.[76]



Scheme 3.17 Preparation of benzo[*h*]quinolones.[73]

Stephens and Marr have shown that 1,3-propanediol directly derived from crude glycerol via biocatalysis can be aminated with aniline using Ir-NHC catalyst **5** (Scheme 3.18).[77] Three different products could be obtained in various ratios depending on the solvent, reaction temperature and reaction time. Later, the selectivity was further enhanced via catalyst improvement[78] and the group has continued studying the behaviour of 1,3-propanediol under the influence of their Ir-NHC catalyst and in the absence of the aniline component.[79]



Scheme 3.18 Amination of 1,3-propanediol can be mediated by an iridium-NHC catalyst.[77-78]

This thesis focuses on the utilisation of hydrogen borrowing methodology for the valorisation of glycerol derivatives. Moreover, we have also explored the use of hydrogen transfer chemistry as a route to more complex molecular structures. This type of chemistry was used in the amination of solketal (chapter 4), in the investigation of 1,3-propanediol as alkylating agent (section 5.1), in the synthesis of chroman-4-ones (section 5.2), and in the construction of 1,5-fused 1,2,3-triazol piperazines (chapter 7).

3.3 THE RUTHENIUM-CATALYSED AZIDE ALKYNE CYLOADDITION REACTION

Nitrogen heterocycles such as triazoles are interesting targets for organic and medicinal chemists. We have used the ruthenium-catalysed azide alkyne cycloaddition (RuAAC) reaction as a route towards new triazole containing molecules. In this section the mechanism and scope of the RuAAC reaction will be discussed.

A vast number of natural products[80] and eight of the twenty best selling drugs in the world in 2015 contain at least one nitrogen heterocycle.[81] In other words, it is of great value for organic chemists to be able to construct nitrogen containing cyclic compounds. There is a large number of different nitrogen-containing heterocycles in terms of structure, ring size and bond types.[82] Triazoles are five-membered rings that contain three nitrogens and two double bonds. The nitrogens can be situated either in the 1-, 2-, and 3- or the 1-, 2-, and 4-positions of the ring, which gives the names to the two different regioisomers 1,2,3-triazole and 1,2,4-triazole (Figure 3.5). This work considers the formation of 1,2,3-triazoles and focus therefore will be on these compounds hereafter.

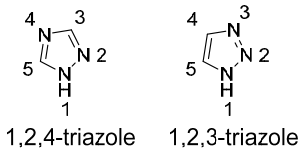
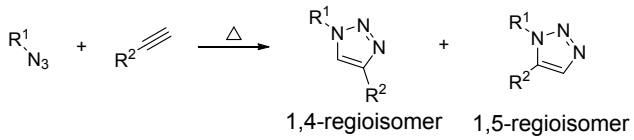


Figure 3.5 The general structure and numbering of triazoles.

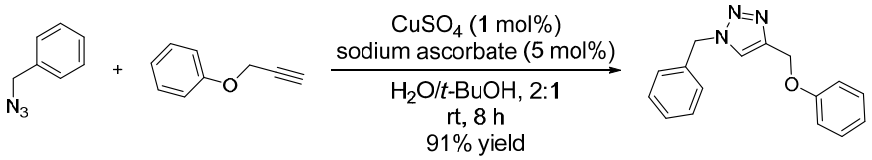
Traditionally, 1,2,3-triazoles are formed via the Huisgen 1,3-dipolar cycloaddition reaction (Scheme 3.19).[83] In this reaction, an alkyl or aryl azide (the 1,3-dipole) is allowed to react with an alkyne (the dipolarophile), formally in a [3+2] cyloaddition reaction, to form a five membered ring. For the original thermal Huisgen reaction, long reaction times at elevated temperatures (around 100 °C) are needed. Furthermore, when the alkyne is not acetylene, a mixture of regioisomers are formed. This lowers the appeal of this kind of transformation as an option for organic chemists interested in forming nitrogen heterocycles.



Scheme 3.19 The thermal Husigen 1,3-dipolar cycloaddition reaction.[83]

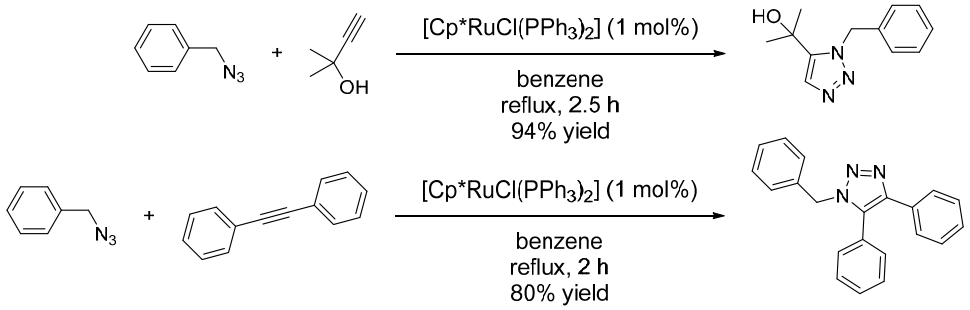
However, in 2002 independent studies by Meldal[84] at the Carlsberg Laboratory, and Fokin and Sharpless[85] at the Scripps Research Institute, were published on the copper-catalysed 1,3-dipolar cycloaddition (CuAAC) reaction of azides with terminal alkynes to form exclusively the 1,4-disubstituted 1,2,3-triazole (Scheme 3.20). In the study by Meldal, the alkyne was attached to a solid support and a Cu(I) salt was used as the catalyst,[84] while Fokin and Sharpless' approach included the use of an aqueous alcoholic solvent and a Cu(II) salt as the added catalyst, with sodium ascorbate as reducing agent to form the active Cu(I) species *in situ*.[85] The mechanism is believed to involve the formation of a copper(I) acetylide, a reaction step that also explains the lack of tolerance for internal alkynes. Later studies indicate that some steps of the mechanism involve the interaction of a second copper center.[85-86] The success of the CuAAC reaction became a fact with its use as a "click" reaction. This concept, coined by Sharpless,[87] describes a set of tools that chemists can use to join or "click" molecules together in a modular and simple way to form a wide scope of new substances. In addition to the modularity, the reaction has to be high yielding, employ readily available starting materials and solvents that are benign, or no solvent at all. Furthermore, the reaction should proceed with the formation of non-hazardous by-

products, and allow for simple product isolation. The CuAAC reaction has found applications in many different areas such as polymer chemistry, dendrimer chemistry, medicinal chemistry, organic synthesis, and bioconjugation.[88]



Scheme 3.20 The CuAAC reaction.[85]

There was, however, also a need to selectively form the other regioisomer, and in 2005 Fokin and Jia reported the first example of the ruthenium-catalysed azide alkyne cycloaddition (RuAAC) reaction, forming selectively the 1,5-disubstituted 1,2,3-triazole (Scheme 3.21).[89] They evaluated a number of ruthenium catalysts in the 1,3-dipolar azide alkyne cycloaddition reaction and found that ruthenium complexes such as [Cp*RuCl(PPh$_3$)$_2$], containing a [Cp*RuCl] structure element, gave excellent regiocontrol for the formation of the 1,5-isomer.

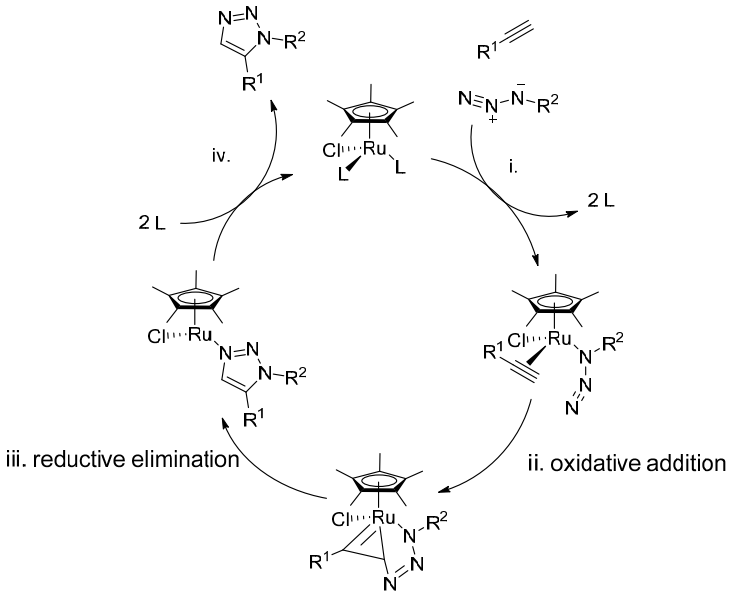


Scheme 3.21 The ruthenium-catalysed azide alkyne cycloaddition reaction.[89]

Remarkably, the internal alkyne diphenylacetylene was also efficiently reacted with benzyl azide and converted into the 1,4,5-trisubstituted-1,2,3-triazole, indicating that a different mechanism must operate for the ruthenium-catalysed version of the reaction as compared to the CuAAC. Additional studies by Lin, Jia, and Fokin shed more light on the impressive scope and functional group tolerance of this reaction and the mechanism was investigated further.[90]

3.3.1 The mechanism of the ruthenium-catalysed azide alkyne 1,3-cycloaddition reaction

In the initial studies of the RuAAC reaction by Jia and Fokin, it was concluded that the mechanism must differ from the one in the CuAAC reaction where a Cu-acetylide is believed to be involved.[89] The reason for this is the acceptance for internal alkynes in the ruthenium-catalysed version of the reaction. In the following paper, Lin, Jia, and Fokin included both experiments and DFT calculations to investigate the mechanism.[90] They proposed that the first step of the RuAAC reaction is the displacement of the spectator ligands by the alkyne that is coordinated side-on to the active catalyst, a neutral [Cp*RuCl] species, while the azide binds to ruthenium with the substituted nitrogen (step i, Scheme 3.22). In a later study, Nolan suggested that coordination of the alkyne to the ruthenium catalyst is part of the catalyst activation and that the active catalyst is a [Cp*RuCl]-alkyne complex.[91] The azide is subsequently coordinated to ruthenium, allowing for nucleophilic attack of the acetylene carbon on the terminal nitrogen of the azide, resulting in an irreversible oxidative addition reaction forming a ruthenacycle (step ii). This step determines the regioselectivity of the final product. Reductive elimination gives the triazole product (step iii) that can be displaced by new substrates or the original ligands (step iv).



Scheme 3.22 Proposed mechanism for the RuAAC reaction (L = ligand).[90]

With unsymmetrical internal alkynes, the regioselectivity is more complex and is dependent on the different groups attached to the alkyne.[17] For example, for alkynes bearing alkyl and/or aryl groups, mixtures of regioisomers are obtained in most cases

(Figure 3.6).[92] Alkynes with amines and alcohols in the propargylic position, on the other hand, form predominantly the regioisomer with the amine/alcohol in the 5-position, most likely due to hydrogen bonding of the NH/OH to the chloride ligand on the metal (Figure 3.6).[90] For alkynes with a halogen directly attached to the triple bond, the halogen will primarily end up in the 5-position (Figure 3.6).[93]

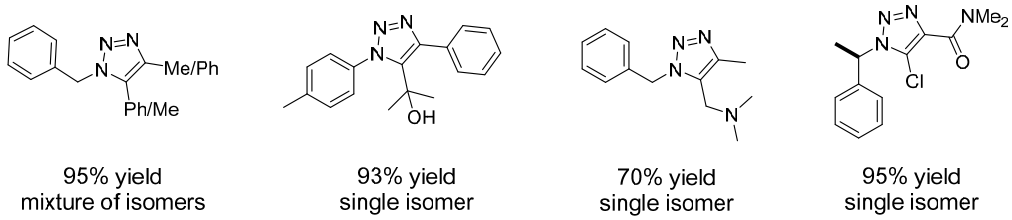


Figure 3.6 Regioselectivity for internal alkynes.[90, 92-93]

There are a number of different catalysts that can mediate the RuAAC reaction to give the 1,5-disubstituted 1,2,3-triazole.[17] The common features of these catalysts is that they all contain the [Cp*RuCl] fragment. The two most commonly used catalysts are [Cp*RuCl(cod)] and [Cp*RuCl(PPh_3)$_2$]. The former is the more active of these two complexes, often allowing for reactions to be performed at room temperature. Other kinds of ruthenium catalysts lacking a Cp* ligand will instead give the 1,4-regioisomer.[89-90]

3.3.2 Synthetic applications of the RuAAC reaction

Already in their first two papers on the subject, Lin, Jia, Fokin and co-workers proved that the RuAAC reaction can be applied towards a wide variety of substrates (Figure 3.7).[90] Although they found that the azide was sensitive to steric hindrance (primary azides being most efficient), the possible complexity of the azide substrates was remarkable. Furthermore, the reaction was tolerant to various functional groups in the alkyne such as alcohols, amines, halogens, ethers, sulfonamides, acetals and nitriles.

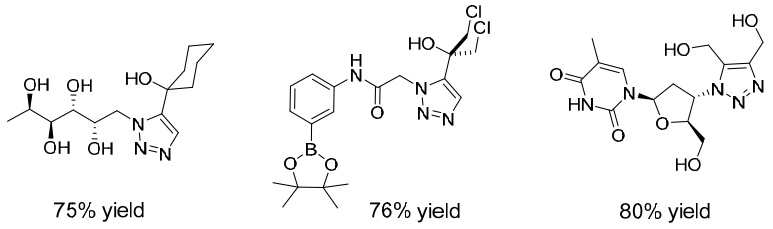
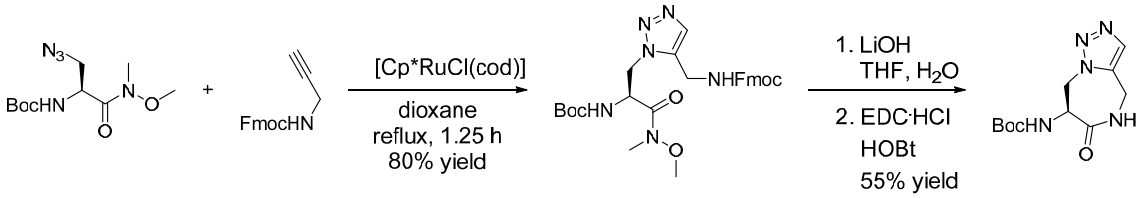


Figure 3.7 Examples of triazoles that can be synthesized via the RuAAC reaction.[90]

Since then, the reaction has found application in areas such as medicinal chemistry, nanochemistry, electronic devices, supramolecular structures, polymer chemistry and organocatalysis.[17] One of the most frequent applications of the RuAAC reaction is in the synthesis of peptidomimetics. For example, constrained amino triazolo diazepines have been synthesised and examined as histidine mimetics.[94] Two different synthetic approaches were used, applying an amino acid-derived azide in RuAAC (see Scheme 3.23) or employing a thermal cycloaddition reaction.



Scheme 3.23 Synthesis of amino triazolo diazepines.[94]

The RuAAC reaction has been investigated in this thesis as a route to triazole amino acids and to fused triazole piperazines, and will be discussed in chapters 6 and 7.

4. AMINATION OF SOLKETAL (PAPER I)

Nitrogen-containing compounds are vastly represented among small functional organic molecules, and can for example be constructed through the formation of new carbon–nitrogen bonds. One of the major objectives of this thesis has been to utilise glycerol, obtainable as a by-product in the production of biodiesel,[7a] as a renewable starting material for organic synthesis. When planning this work, we envisioned that the glycerol hydroxyl groups could be used as handles in the formation of new bonds so that glycerol would constitute a three-carbon fragment in a new molecule. Furthermore, we set out to find a method that permitted such bond formation to be carried out in an atom economic manner. With this in mind, we decided to investigate the utilisation of hydrogen borrowing catalysis, described in chapter 3.2, for the formation of new amino glycerol derivatives. This type of chemistry allows for the direct coupling of an alcohol functionality with a nucleophile such as an amine, without the need for prior activation of the alcohol moiety. Moreover, water is formed as the only by-product in the reaction.

Based on these ideas, we set out to selectively aminate glycerol on one of the alcohol functionalities to form an amino glycerol derivative for further use as an organic building block or for direct use in for example biological applications. Such structural features can be seen in drugs such as the β-blocker propranolol, the antiviral agent indinavir, and the antitussive agent dropropizine (Figure 4.1).

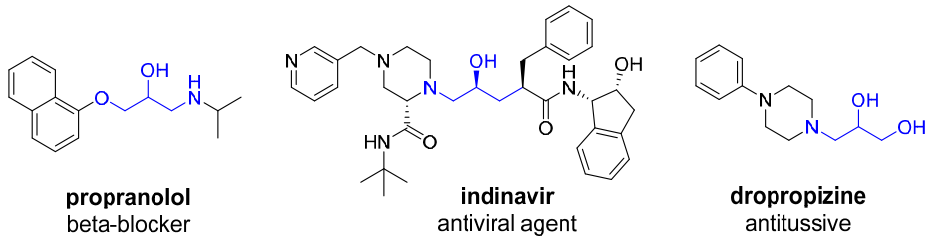
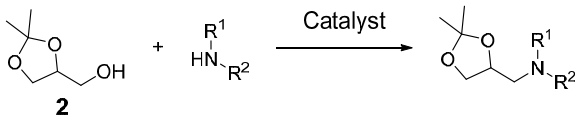


Figure 4.1 Biologically active compounds with amino glycerol moieties.

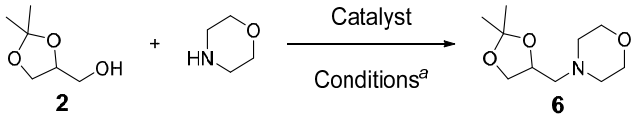
However, as shown by Crotti and co-workers in their work on the reaction of glycerol with diamines, the direct use of glycerol will most likely lead to a mixture of products (Scheme 3.20).[71] Therefore, we decided to start our investigations utilising the 1,2-acetal-protected glycerol derivative 1,2-isopropylideneglycerol (**2**, solketal), with one primary alcohol available for functionalisation, in a direct amination reaction applying hydrogen borrowing methodology (Scheme 4.1)



Scheme 4.1 Amination of solketal.

In this initial screening, solketal was allowed to react with morpholine as the model amine in the presence of a catalyst with toluene as the reaction medium, in a sealed vial under argon and using conventional heating (Table 4.1). One iridium catalyst[43] and two ruthenium catalysts,[50b, 51-52] that have previously proved to effectively aminate alcohols, were investigated. When $[Ru_3(CO)_{12}]$ was used, no product could be observed (entry 1), and although $[Cp^*IrCl_2]_2$ performed well compared to the other catalysts at 110 °C (entry 2), $[Ru(p\text{-cymene})Cl_2]_2$ proved to be superior when the temperature was increased to 120-130 °C (entries 4-8). Both dppf and DPEphos could be employed as ligands.

Table 4.1 Evaluation of the reaction conditions for the amination of solketal with morpholine.



Entry	Catalyst	Catalyst loading [mol%]	Ligand	Temp. [°C]	Time [h]	Yield [%][b]
1	$[Ru_3(CO)_{12}]$	2	-	140	24	<1
2[c]	$[Cp^*IrCl_2]_2$	5	-	110	24	38
3	$[Ru(p\text{-cymene})Cl_2]_2$	1.25	dppf	110	24	12
4	$[Ru(p\text{-cymene})Cl_2]_2$	1.25	dppf	120	24	80
5	$[Ru(p\text{-cymene})Cl_2]_2$	1.25	dppf	130	24	95
6[d]	$[Ru(p\text{-cymene})Cl_2]_2$	1.25	DPEphos	130	24	97
7	$[Ru(p\text{-cymene})Cl_2]_2$	1.25	dppf	130	48	>99
8	$[Ru(p\text{-cymene})Cl_2]_2$	1.25	dppf	130	12	90

[a] Conditions: In a sealed Biotage® microwave-vial was added catalyst, ligand (2.5 mol%) solketal (2 mmol), morpholine (2 mmol) and toluene (2 mL) under argon. The mixture was stirred at room temperature for 5-10 min, and then heated in an oil bath. [b] Measured by ^1H NMR. [c] In 0.1 mL toluene using 5 mol% $NaHCO_3$ as added base. [d] 1 mmol scale.

For the following experiments, we chose to use $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst, with dppf or DPEphos as the ligand at 130 °C and toluene as the solvent. The amine was added in a small excess. Employing these conditions, the morpholine derivative

6 could be isolated in 92% yield (Figure 4.2). Piperazines with different substituents (phenyl, Boc, and methyl) were also applicable, forming amino glycerol derivatives **7**, **8**, and **9** that were all isolated in over 80% yield. The piperidine derivative **10** was isolated in a lower yield, mostly due to purification issues.

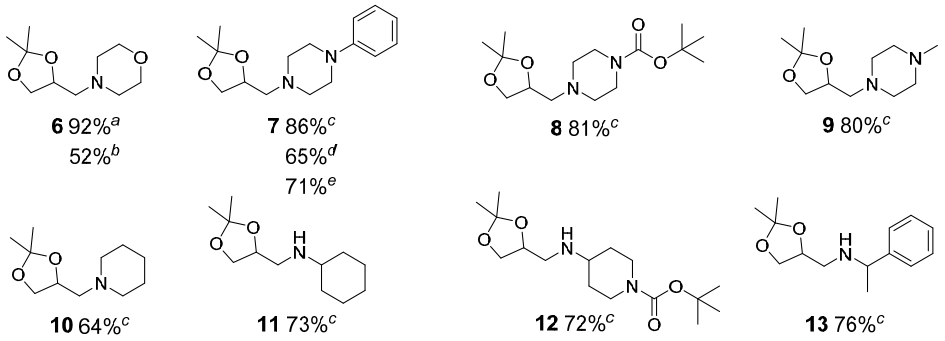
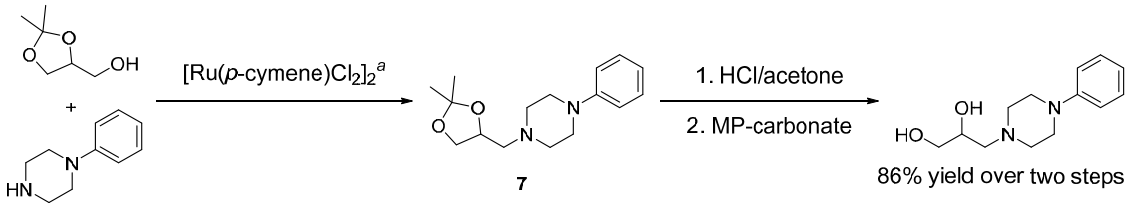


Figure 4.2 Synthesised amino glycerol derivatives.

Conditions: In a sealed Biotage® microwave-vial was added [Ru(*p*-cymene)Cl_2]$_2$ (1.25 mol%), ligand (2.5 mol%) solketal (2 mmol), amine (2.4 mmol) and toluene (2 mL) under argon. The mixture was stirred at room temperature for 5-10 min, and then heated in an oil bath. [a] dppf. [b] *tert*-Amyl alcohol as solvent. [c] DPEphos. [d] Solventless conditions: ratio solketal/amine, 1.5 : 1. [e] Solventless conditions: ratio solketal/amine, 1 : 1.2.

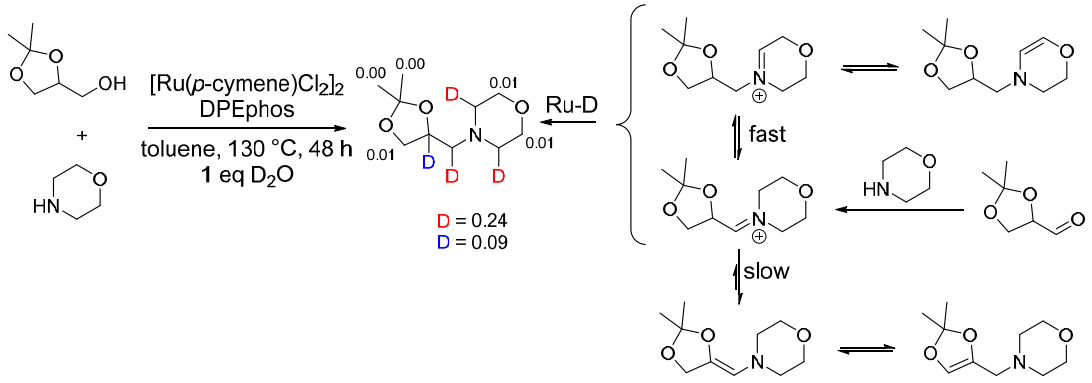
Primary amines with some degree of sterical hindrance such as cyclohexylamine could also be employed, yielding compound **11** in 73% yield. 4-Amino-*N*-Boc-piperidine, of interest in the synthesis of several classes of drugs,[95] was then utilised as the amine, resulting in a highly functionalised glycerol derivative **12** with several possible alternatives for further functionalisation. While the use of α-methylbenzylamine resulted in 76% isolated yield of compound **13**, benzylamine itself gave only low yields of the desired product. For other less sterically hindered primary amine substrates such as *n*-hexylamine, 2-phenethylamine, and *N'*,*N'*-dimethylpropane-1,3-diamine, none of the desired products could be isolated. Possibly, less hindered primary amines undergo homo-coupling under the applied reaction conditions, a reaction that has been previously reported by Williams, albeit employing a more reactive iridium catalyst.[96] MS analysis of reactions employing *n*-hexylamine or benzylamine as the amine nucleophile indicate the formation of such homo-coupled products. The more benign solvent *tert*-amyl alcohol could also be used, but the isolated yield of compound **6** decreased considerably when running the reaction in this solvent (Figure 4.2). Solventless conditions were investigated in the formation of **7** and even though a slight drop in yield was observed as compared to running the reaction in toluene, good yields were nevertheless obtained.

With our amino glycerol derivatives at hand, we moved on to the deprotection of the acetal group. Several conventional deprotection methods were investigated (HOAc, TFA, *p*-TsOH, Dowex-50W-8x exchange resin, HCl in acetone), and it was found that 0.1 M aqueous HCl and acetone in a 1:1 mixture at 40 °C gave the desired HCl-salt of the amino glycerol derivative. Treatment of the hydrochloride salt with a polystyrene-bound carbonate base (MP-carbonate) afforded the free amine. When applying this strategy for the phenyl-piperazine derivative **7**, the antitussive agent dropropizine was isolated in an 86% overall yield from solketal (Scheme 4.2).



Scheme 4.2 Synthesis of dropropizine from solketal. [a] Conditions: see Figure 4.2.

The catalytic process for this type of transformation involves initial dehydrogenation, followed by condensation and hydrogenation of the imine intermediate (see Scheme 3.8). In the initial study on the [Ru(*p*-cymene)Cl_2]$_2$-catalysed hydrogen borrowing reaction by Williams, labelling experiments indicated that condensation did not necessarily take place within the coordination sphere of the catalyst and that only one C–H bond needed to be broken for the reaction to occur.[52] The hydrogenated catalytic species can be either a mono- or a di-hydride metal complex (see section 3.2.1). We decided to further investigate the nature of the catalyst by considering the effect of added D_2O. Under standard reaction conditions, using equimolar amounts of solketal and morpholine, 0.5, 1, and 2 eq of D_2O were added, respectively, and allowed to equilibrate before the reaction was started. The reaction mixtures were then analysed by ^1H, ^2H, and ^{13}C NMR, indicating that deuterium was incorporated mainly at the positions highlighted in Scheme 4.2. Major incorporations were seen on all carbons bound to the nitrogen atom (marked in red in Scheme 4.3). A lower degree of incorporation was seen for the position marked in blue, and minor incorporation was observed for all other positions α to heteroatoms.



Scheme 4.3 Deuterium incorporation experiments and plausible mechanism. D = fraction incorporated deuterium.

In the case of a di-hydride route, substantial deuterium incorporation is expected, as the proton and the hydride will lose their identity on the metal species. The mono-hydride route should not lead to any scrambling in the presence of D_2O, as only the α-hydride ends up on the metal. However, if the mono-hydride complex is a redox-labile and long-lived species, there is a possibility that the "hydride" is transferred as a proton to the $D_2O/H_2O/DOH$ in a reversible process, leading to some degree of hydride/proton scrambling between the protic co-solvent and the catalyst. Some degree of deuterium incorporation was indeed observed, indicating that the intermediate ruthenium-species could be either a mono-hydride or di-hydride metal complex that, in a fast reversible reaction, can lose the hydride as a proton to the protic co-solvent. The majority of the deuterium ended up on carbons bound to nitrogen, indicating that the formed iminium ion is in a fast equilibrium with an iminum ion in the morpholine ring, possibly catalysed by the ruthenium catalyst. These intermediates can be reduced by a ruthenium deuteride. For the remaining positions, ruthenium-catalysed alkene isomerisation[97] and reversible formation of enamines via proton loss could lead to this type of incorporation. Imine formation can take place via a coordinated or non-coordinated pathway. In an experiment employing (*S*)-BINAP as the ligand, 18% enantiomeric excess of compound **7** and 5% of **6** was obtained, indicating that the phosphine ligand is involved in the selectivity-determining step.

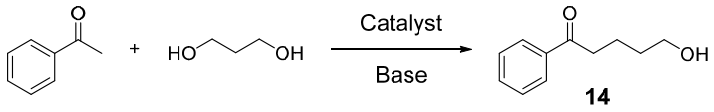
In conclusion, we have shown that solketal can be aminated with cyclic secondary amines and bulky primary amines using a ruthenium catalyst. Less sterically hindered primary amines, did not afford synthetically useful amounts of product, at least in part due to homo-coupling of such amines. Deprotection of the acetal was effected by treating the aminated solketal derivative with HCl/acetone, followed by treatment

with a polymer-bound carbonate base. This method could be employed to synthesise the antitussive agent dropropizine in 86% overall yield from solketal. The nature of the catalyst was briefly examined via deuterium incorporation in the presence of D_2O, indicating that the intermediated metal hydride complex could be long-lived, allowing for the exchange of deuterides/hydrides of the catalyst with the solvent in a redox equilibrium.

5. ALKYLATION OF KETONES

5.1 1,3-PROPANEDIOL AS AN ALKYLATING AGENT (PAPER II)

In the previous chapter, it was shown that the glycerol derivative solketal can be employed in amination reactions to obtain useful building blocks and small functional organic compounds. In the construction of new molecules, it is also of great value to form new carbon–carbon bonds. Therefore, we were interested in examining carbon nucleophiles in conjunction with hydrogen borrowing. Enolisable carbonyl compounds have proven to be useful nucleophiles in the hydrogen borrowing reaction, resulting in α-alkylated ketones.[38h] 1,3-Propanediol has two primary alcohols available for substitution, but lacks the secondary alcohol on the central carbon, eliminating the issue of selectivity in terms of primary/secondary alcohol, but also allowing for substitution at both ends of the glycerol molecule. Although 1,3-propanediol has been used in carbon–nitrogen bond forming reactions via hydrogen borrowing,[73-74, 76-78, 98] the utilisation in carbon–carbon[79] bond forming reactions has only been briefly examined (see section 3.2.4 for more details). We decided to start our investigations by alkylating acetophenone with 1,3-propanediol and we envisioned that under hydrogen borrowing conditions, a ketone with an extended alkyl chain and a terminal hydroxyl group would be formed (Scheme 5.1).

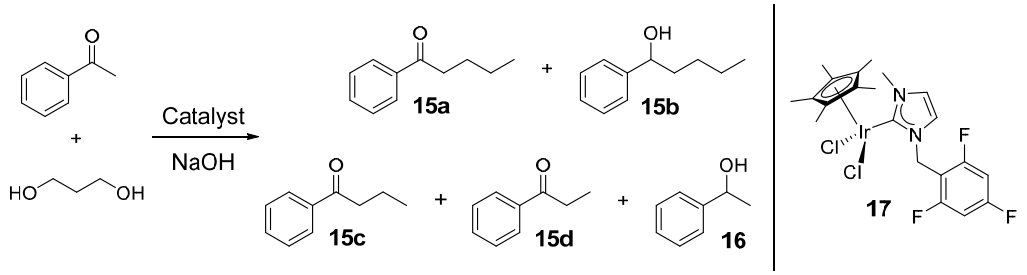


Scheme 5.1 Proposed alkylation of acetophenone with 1,3-propanediol.

First, we examined a number of different catalysts that have proven to efficiently catalyse the alkylation of ketones with alcohols. In a typical reaction setup, acetophenone and 1,3-propanediol were heated in a sealed vessel in the presence of a catalyst, sodium hydroxide, with or without a solvent, at 100–130 °C for 20 h. The reaction mixture was then analysed by GC-MS. Under these conditions, the desired product 5-hydroxy-1-phenylpentan-1-one (**14**) was not detected. Instead, a mixture of five different products was obtained (Table 5.1). Depending on the choice of catalyst, the major products were 1-phenylpentan-1-one (**15a**) and/or 1-phenylethanol (**16**). In addition, smaller amounts of 1-phenylpentan-1-ol (**15b**), 1-phenylbutan-1-one (**15c**), and propiophenone (**15d**) could be detected. Compounds **15a**-**15d** are all formed through carbon–carbon bond formation between acetophenone and 1,3-propanediol (**15a** and **15b**) or fragments of 1,3-propanediol

(**15c** and **15d**), while compound **16** is the result of catalytic transfer hydrogenation of the ketone substrate.

Table 5.1 Catalyst evaluation for the alkylation of acetophenone with 1,3-propanediol.[a]



Entry	Catalyst	Solvent	Conv. [%][b]	Selectivity					
				15a	**15b**	**15c**	**15d**	**16**	Ratio **15:16**
1	$RuCl_2(PPh_3)_3$	-	18	-	-	-	-	100	0 : 100
2[c,d]	$RuH_2(PPh_3)_3(CO)$/ PNP·HCl	*t*-amyl alcohol	21	-	-	-	10	90	10 : 90
3[c]	$Ru_3(CO)_{12}$/ CataCXium PCy	*t*-amyl alcohol	27	15	-	3	4	78	22 : 78
4[c]	$Ru(CO)ClH(PPh_3)_3$/ Xantphos	*t*-amyl alcohol	32	-	-	-	-	100	0 : 100
5	$RuCl_2(DMSO)_4$	-	37	19	5	-	-	76	24 : 76
6[e]	$IrCl_3$/ BINAP	*p*-xylene	2	-	-	-	-	100	0 : 100
7	$[Ir(cod)Cl]_2$/ PPh_3	-	26	50	15	-	-	35	65 : 35
8	$[Cp^*IrCl_2]_2$	-	61	-	-	-	-	100	0 : 100
9[f]	**17**	-	11	100	-	-	-	-	100 : 0

[a] Conditions: In a sealed Biotage® microwave-vial was added catalyst (2 mol%), ligand (8 mol%), NaOH (20 mol%), acetophenone (2 mmol), 1,3-propanediol (3 mmol), and solvent (0 or 1 mL) under argon and heated in an oil bath at 100 °C for 20 h. [b] Measured by GC-MS using naphthalene as internal standard. [c] 130 °C. [d] PNP·HCl = $(Ph_2PCH_2CH_2)NH·HCl$. [e] 140 °C. [f] 0.25 mmol scale, K_2CO_3 as base, 115 °C, 24 h.

Five different ruthenium catalysts were investigated, and in all cases compound **16** was the major product (Table 5.1, entries 1-5). Two of these catalysts, gave complete selectivity for transfer hydrogenation (entries 1 and 4). In the remaining cases, a mixture of transfer hydrogenation and alkylation products was obtained (entries 2, 3, and 5). Three different commercial iridium catalysts were then examined (entries 6-8), as well as iridium carbene complex **17** (entry 9), first reported by Saunders[99] and of the same type previously used by Marr and co-workers for the amination of 1,3-propanediol.[77-79] $[Ir(cod)Cl]_2$ gave the highest overall yield of alkylation products (entry 7), while compound **17**, made available to us by Marr and co-workers, was the only catalyst that was completely selective for one alkylation product (entry 9).

Interestingly, $[Cp^*IrCl_2]_2$ produced substantial amounts of **16** selectively, indicating that 1,3-propanediol can be used as a hydrogen source in the catalytic transfer hydrogenation of aromatic ketones employing this catalyst (entry 8). The results in entries 7 and 9 encouraged us to further investigate $[Ir(cod)Cl]_2$ and **17** in order to improve the yield of the alkylated products.

First, we considered the reaction with $[Ir(cod)Cl]_2$ and a number of different ligands were used to replace triphenylphosphine. Both bidentate (dppe, dppp, dppb, dppf, BINAP, SEGPHOS, and Xantphos) and monodentate ligands (PPh_2Me, (*p*-$CF_3C_6H_4)PPh_2$, CataCXium PCy, RuPhos, XPhos, and PipPhos) were less effective in terms of alkylation compared to PPh_3, although the selectivity for transfer hydrogenation could be increased in some cases (see supporting information for Paper II). The reaction conditions were then further evaluated using PPh_3 as the ligand. The effect of temperature, base loading and substrate ratio were then briefly examined, and it was found that temperatures around 100-120 °C, with the addition of 20 mol% base and 150-200 mol% of 1,3-propanediol as compared to acetophenone was most beneficial for the formation of alkylation products (see supporting information for Paper II).

A number of different bases and solvents were then explored and compared (Table 5.2). The base screening was performed using toluene as the reaction medium and for all the examined bases, a mixture of products were obtained (entries 1-8). In the case of CsOH, LiOH, KOH and K_3PO_4, transfer hydrogenation was favoured (entries 3-6) while alkylation was favoured by K_2CO_3, albeit in a low yield in this case (entry 7). Using NaOH as the base, the effect of solvent was then evaluated. Less polar solvents (toluene and xylene) slightly favoured transfer hydrogenation (entries 1 and 9). More polar solvents such as dioxane, *t*-butanol and *t*-amyl alcohol, however, favoured the formation of alkylation products, and the overall conversion increased (entries 10-12), while neat conditions further improved the selectivity (entry 13). Under neat conditions, other reaction temperatures and previously examined bases were reconsidered. Increasing the temperature resulted in slightly lower selectivity and lower conversion, in the latter case, possibly due to faster catalyst deactivation (entry 14). NaO*t*-Bu under these conditions, gave a higher selectivity but a lower conversion (comparing entries 2 and 16), while the use of LiOH and CsOH resulted in higher conversions and better selectivity under neat conditions (entries 17-19).

For $[Ir(cod)Cl]_2$, the best results were obtained using NaOH as the base in dioxane or under solventless conditions at 110 °C. Under these conditions, the GC yields were still not synthetically useful and for this reason, we decided to investigate catalyst **17** further, as our initial studies showed that this catalyst could selectively give compound **15a**.

Table 5.2 Effect of base and solvent for the alkylation of acetophenone with 1,3-propanediol.[a]

Entry	Base	Solvent	Conv. [%][b]	Selectivity					
				15a	**15b**	**15c**	**15d**	**16**	Ratio **15:16**
1	NaOH	toluene	35	28	3	6	6	57	43 : 57
2	NaO*t*-Bu	toluene	33	36	3	9	9	43	57 : 43
3	$CsOH·H_2O$	toluene	28	32	3	4	4	57	43 : 57
4	$LiOH·H_2O$	toluene	21	24	-	-	-	76	24 : 76
5	KOH	toluene	34	15	3	6	3	73	27 : 73
6	K_3PO_4	toluene	24	21	-	8	4	67	33 : 67
7	K_2CO_3	toluene	17	53	-	18	trace	29	71 : 29
8	Cs_2CO_3	toluene	14	36	-	14	trace	50	50 : 50
9	NaOH	xylene	38	29	3	5	5	58	42 : 58
10	NaOH	dioxane	40	48	trace	20	22	10	90 : 10
11	NaOH	*t*-butanol	36	50	5	17	14	14	86 : 14
12	NaOH	*t*-amyl alcohol	43	51	2	19	16	12	88 : 12
13	NaOH	-	42	67	7	9	5	12	88 : 12
14[c]	NaOH	-	29	69	-	7	7	17	83 : 17
15[d]	NaOH	-	35	63	14	9	-	14	86 : 14
16	NaO*t*-Bu	-	22	82	-	-	-	18	82 : 18
17	$CsOH·H_2O$	-	33	52	6	6	-	36	64 : 36
18	$LiOH·H_2O$	-	38	45	18	5	3	29	71 : 29
19[c]	$LiOH·H_2O$	-	36	47	8	6	6	33	67 : 33

[a] Conditions: In a sealed Biotage® microwave-vial was added $[Ir(cod)Cl]_2$ (2 mol%), PPh_3 (8 mol%), base (20 mol%), acetophenone (2 mmol), 1,3-propanediol (3 mmol), and solvent (0 or 1 mL) under argon and heated in an oil bath at 110 °C for 20 h. [b] Measured by GC-MS using naphthalene as internal standard. [c] 130 °C. [d] 100 °C, 112 h.

In the initial screening, the use of catalyst **17** resulted in the selective formation of compound **15a**, albeit in low conversion (Table 5.3, entry 1). Increasing the reaction time gave a higher yield without lowering the selectivity (entry 2). However, an increase in temperature with lower base loading or the addition of molecular sieves did not improve the yield (entries 3-4). Interestingly, NaOH afforded complete

selectivity for transfer hydrogenation, albeit in very low yields (entry 5), while LiOH resulted in an increase of the yield, accompanied with a loss in selectivity. No short chain products (**15c** and **15d**) were obtained using this catalyst.

Table 5.3 Investigation of catalyst **17** in the alkylation of acetophenone with 1,3-propanediol.

Entry	Base	Time	Conv.	Selectivity					
		[h]	[%][b]	**15a**	**15b**	**15c**	**15d**	**16**	Ratio **15:16**
1	K_2CO_3	24	11	100	-	-	-	-	100 : 0
2	K_2CO_3	48	17	100	-	-	-	-	100 : 0
3[c]	K_2CO_3	48	10	100	-	-	-	-	100 : 0
4[d]	K_2CO_3	48	15	100					100 : 0
5	NaOH	24	6	-	-	-	-	100	0 : 100
6	$LiOH·H_2O$	24	58	48	4			48	52 : 48
7[e]	$LiOH·H_2O$	24	19	42	trace	-	-	58	42 : 58
8	$LiOH·H_2O$	48	27	67	trace	-	-	33	67 : 33
9[f]	$LiOH·H_2O$	24	20	75	-	-	-	25	75 : 25

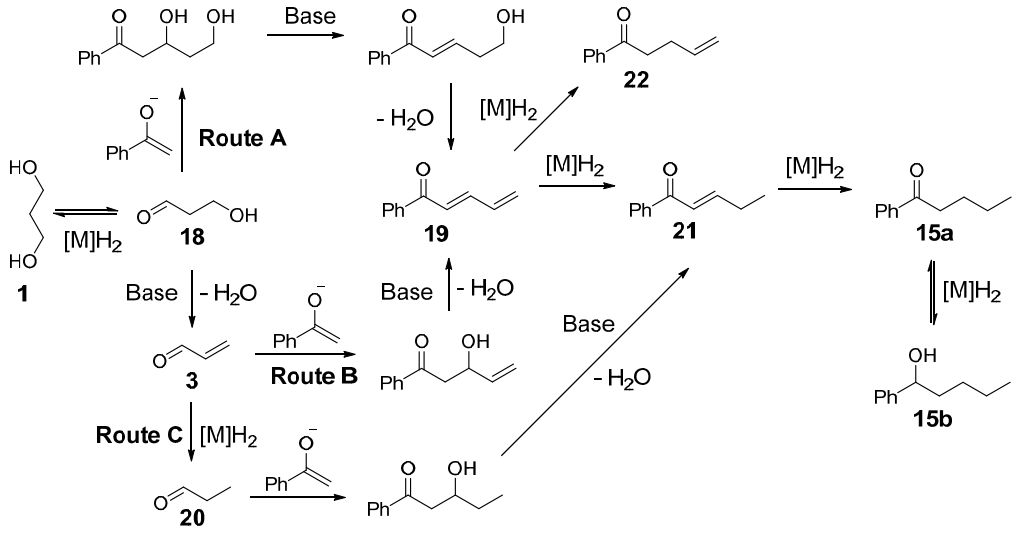
[a] Conditions: In a sealed Biotage® microwave-vial was added **17** (2 mol%), base (20 mol%), acetophenone (1 mmol), and 1,3-propanediol (1.5 mmol) under argon and heated in an oil bath at 115 °C for 24 or 48h. [b] Measured by GC-MS using naphthalene as internal standard. [c] 150 °C, 10 mol% base. [d] 4Å molecular sieves as additive. [e] 40 mol% base. [f] $N_{1,8,8,8}NTf_2$ (ionic liquid) as solvent.

The results above give indicate that 1,3-propanediol can potentially be used as a green propylation agent. However, this type of transformation poses several difficulties in terms of selectivity and mechanism. We did not observe the initially expected 5-hydroxy-1-phenyl-pentan-1-one **14** (Scheme 5.1). Instead, we could see the formation of **15a**, together with transfer hydrogenation products **16** and **15b**. In addition, the short chain coupling products **15c** and **15d** were also observed.

We were interested in understanding how the observed products were formed. It seemed as if the first step, the dehydrogenation of 1,3-propanediol (**1**) to give hydroxypropanal (**18**), was the first reaction step in the formation of all products, but the fate of this intermediate differed depending on the final product (Schemes 5.2 and 5.3).

First we considered the formation of compounds **15a** and **15b** (Scheme 5.2). In order to produce these compounds, 3-hydroxypropanal (**18**) can either react with the enolate ion obtained from acetophenone (Route A), followed by dehydration to give **19** and then hydrogenation of the formed dienone to give compound **15a** and subsequently compound **15b** after a reduction of the carbonyl group. Alternatively,

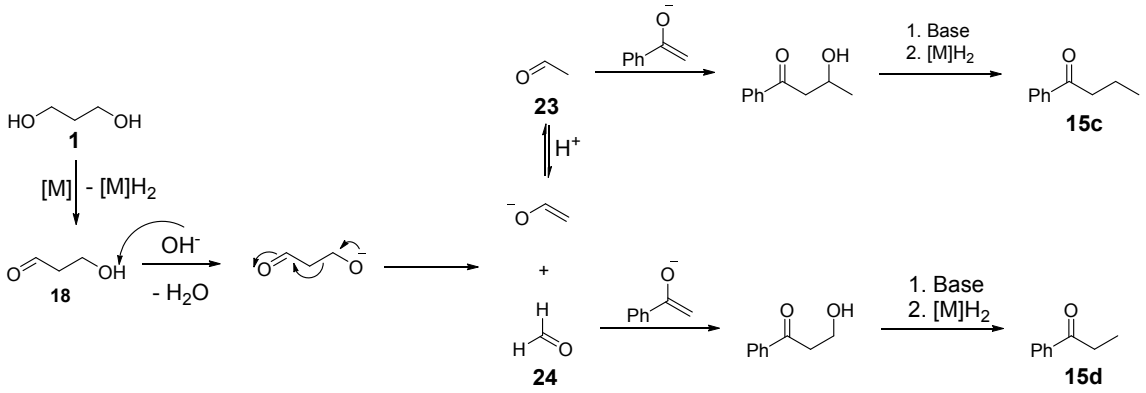
hydroxypropanal may undergo a base promoted dehydration to form acrolein (**3**), which can then react in a condensation reaction with the enolate ion to give **19** after dehydration (Route B), followed by hydrogenation to form **15a** and **15b**. Finally, acrolein can instead be directly reduced to propanal (**20**, Route C), which may then react through a condensation reaction with the enolate ion to give intermediate **21** after dehydration. DFT calculations using the anion of acetone and 3-hydroxypropanal as the model reactants revealed that although the reversible aldol addition should be considerably faster than elimination at the relatively high temperatures used here, elimination is irreversible and should therefore dominate at the actual reaction conditions. This, together with the fact that **22** was never detected, indicates that Route C is a more probable pathway to the final products.



Scheme 5.2 Potential pathways to compounds **15a** and **15b**.

The short-chain coupling products **15c** and **15d** are most likely formed through initial base promoted retro-aldol fragmentation of 3-hydroxypropanal (**18**), yielding acetaldehyde (**23**) and formaldehyde (**24**), which can both react in an aldol condensation with the enolate anion to give **15c** and **15d** (Scheme 5.3).

Selective *N*-substitution on one side of 1,3-propanediol, with the other alcohol moiety retained, has been previously reported by Börner,[98] as well as Marr.[78] Furthermore, substitution on both sides of 1,3-propanediol has also been carried out in good yields.[73] The behaviour of 1,3-propanediol to act as a propylation agent has also been seen as a side reaction[74, 76] or as the major pathway leading to the main product under optimised conditions.[78]



Scheme 5.3 Potential pathways to **15c** and **15d**.

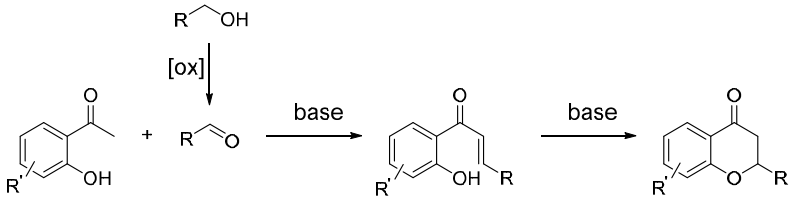
In the case of the enolate ion, it can be speculated that the reactivity of the enolate poses problems, as it is also a good enough base to efficiently promote E1cB elimination of 3-hydroxypropanal (**18**), instead of directly acting as a nucleophile, yielding acrolein that can react in one of the described pathways. It is also possible that the catalyst is involved in the transformation of 3-hydroxypropanal into acrolein and/or propanal. If so, the catalyst may be involved in the selectivity for the different products.

In conclusion, we have shown that the alkylation of acetophenone with 1,3-propanediol is a challenging transformation, as a number of competing processes can take place in parallel. While full selectivity could be obtained in some cases, the yields were not synthetically useful. These results do however suggest that catalyst development may be a possible way to gain better control of this transformation, even though it is clear that the search for such a catalyst will most likely not be straightforward. The selectivity obtained with catalyst **17** is also encouraging as this type of catalyst is compatible with directly coupling the alkylation process with fermentation of crude glycerol to 1,3-propanediol, indicating that glycerol could indirectly be employed as an alkylating agent.[77]

5.2 SYNTHESIS OF CHROMAN-4-ONES VIA HYDROGEN TRANSFER CATALYSIS

Throughout the course of the work described in this chapter, we became interested in connecting the hydrogen borrowing reaction with other transformations. During discussions with colleagues in the medicinal chemistry field, working on the synthesis of chroman-4-one-based sirtuin 2 (SIRT2) selective inhibitors,[100] it became clear to us that hydrogen transfer catalysis bears the potential to overcome certain issues in this area.

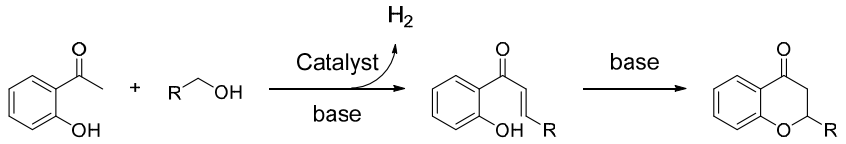
More specifically, Luthman and co-workers have developed an efficient protocol for the synthesis of chroman-4-ones from 2´-hydroxyacetophenones and aldehydes via an aldol condensation forming a chalcone intermediate, that subsequently cyclises in an intramolecular oxa-Michael addition to give the final product (Scheme 5.4).[100]



Scheme 5.4 Chromanone synthesis.[100]

Although the substrate scope is wide, the variety of available aldehydes is limited, and for certain aldehydes the reaction suffers from low yields due to high degree of homo-aldol coupling. Furthermore, some of the aldehydes have to be synthesised from the corresponding alcohols and can be difficult to isolate.

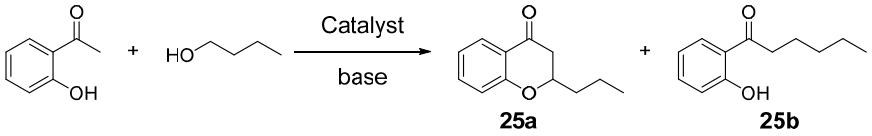
We envisioned that the use of a hydrogen transfer approach, allowing for the direct use of alcohols in the chroman-4-one synthesis, could solve several of these problems (Scheme 5.5). First of all, the scope of commercially available alcohols is much wider than the commercial scope of aldehydes. Moreover, a hydrogen transfer approach would lead to a low concentration of aldehyde present in the reaction mixture, minimising the formation of homo-aldol by-products. In addition, this new approach would eliminate the need of isolating sensitive aldehydes that are not commercially available.



Scheme 5.5 Proposed pathway to chroman-4-ones directly from alcohols.

2'-Hydroxyacetophenone and 1-butanol were chosen as the model substrates and were allowed to react in the presence of different catalysts at 130-170 °C (Table 5.4). Two products were observed, the desired chromanone **25a** and the alkylated acetophenone **25b** that is formed as the result of a standard hydrogen borrowing reaction. First, $[Ir(cod)Cl]_2$ was investigated with and without 1-dodecene, as the added hydrogen acceptor, and it was found that the product distribution was improved without the addition of 1-dodecene (entries 1-2). An increase in the reaction temperature from 130 °C to 150 °C resulted in slightly higher yields, but going up to 170 °C also resulted in increased formation of **25b** (entries 2-4). $[RuCl_2(PPh_3)_3]$ afforded the highest selectivity for the hydrogen borrowing product **25b** (entry 5).

Table 5.4 Investigation of reaction conditions for the chroman-4-one synthesis.[a]



Entry	Catalyst	Solvent	Temp [°C]	Time [h]	Yield [%][b] **25a**	**25b**
1[c]	$[Ir(cod)Cl]_2/PPh_3$	toluene	130	76	8	17
2	$[Ir(cod)Cl]_2/PPh_3$	toluene	130	76	9	11
3	$[Ir(cod)Cl]_2/PPh_3$	*p*-xylene	150	90	15	19
4	$[Ir(cod)Cl]_2/PPh_3$	mesitylene	170	90	18	27
5	$[RuCl_2(PPh_3)_3]$	*p*-xylene	150	26	10	29
6	**17**	*p*-xylene	150	22	19	-
7	**5**	*p*-xylene	150	72	27	15
8	**26**	*p*-xylene	150	72	18	14

[a] Conditions: 2'-Hydroxyaectophenone (0.5 mmol), 1-butanol (0.9 mmol), catalyst (2mol%), LiOH (40 mol%), and solvent (2 mL) stirred in a sealed Biotage® microwave-vial under argon for the indicated temperature and time. Products were isolated by column chromatography. [b]Isolated yield. [c] 1-Dodecene (1 eq) added.

Finally, three different iridium carbene catalysts were tested (Table 5.4 entries 6-8, and Figure 5.1). Interestingly, catalyst **17** was completely selective for the desired chromanone product, however this product was isolated in a low yield (entry 6).

Employing catalyst **5** (entry 7), resulted in the highest isolated yield of **25a**, and in this case **25b** was also isolated, while the last catalyst **26** was less successful, both in terms of selectivity and yields (entry 8).

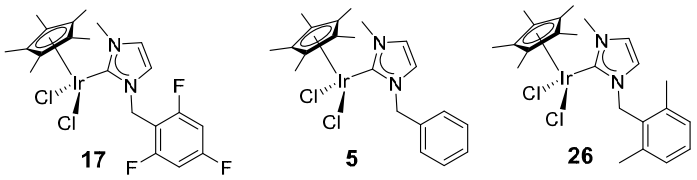


Figure 5.1 Iridium carbene catalysts.

Although the reported yields remain low, these results have encouraged us to further investigate this type of transformation, and a few issues need to be addressed for the success of future efforts. First of all, the catalyst should be capable of releasing hydrogen as H_2(g) after dehydrogenation of the alcohol, or should be able to leave hydrogen to a scavenger such as an alkene. Furthermore, in order to simplify this process, it would most likely be beneficial if the condensation occurred after decomplexation of the formed aldehyde, and that reduction of the intermediate chalcone would be slower or less favoured than the cyclisation. As in the case with the alkylation of acetophenone with 1,3-propanediol in the previous section, the nature of the catalyst is most likely very important for the product distribution and by careful catalyst design there is a chance that higher yields could be obtained.

Both of these carbon–carbon bond forming reactions suffer from poor selectivity and/or low yields of the desired product. This illustrates the difficulties but also the possibilities of these types of transformations. If mastered, these reactions could be powerful and environmentally friendly tools for the formation of new molecules.

6. SYNTHESIS OF TRIAZOLE AMINO ACIDS VIA A RuAAC REACTION (PAPER III)

Peptidomimetics are a class of compounds that mimic the function and structure of natural peptides, although their construction may differ considerably from the natural ones, adding features such as metabolic stability, or higher activity and selectivity.[101] 1,2,3-Triazoles, described in more detail in section 3.3, have received considerable attention in this area of research thanks to their geometric and electronic resemblance to the amide bond, in combination with their stability towards a range of conditions including enzymatic stability.[102] Depending on the substitution pattern on the triazole, the geometry may resemble different types of amide bonds. The 1,5-disubstituted triazole has structural similarities with *cis*-amide bonds, while the 1,4-disubstituted triazole bears resemblance to a *trans*-amide bond.[102]

Foldamers are polymers or oligomeric structures that in solution can adopt a well-defined three-dimensional structure, or conformationally fold into an ordered state, in a similar fashion to how proteins fold.[19-20] Peptidic foldamers can, for example, be constructed of different non-natural amino acids, and 1,2,3-triazoles have emerged as promising scaffolds for such compounds.[103] Previous work in our group has considered the ruthenium-catalysed construction of monomeric triazole δ-amino acid derivatives and the structural investigations of these monomers, as well as the corresponding oligomerised foldameric structures.[104] Similar 1,5-disubstituted triazole amino acid monomers have been synthesised for incorporation into proteins as *cis*-amide bond substitutes[105] and as disulfide bond auxiliaries.[106]

As a continuation to the previous work in our group on triazole δ-amino acids in foldameric structures,[104] we were interested in investigating the effect of chiral groups on the three-dimensional structure of such compounds. We therefore decided to synthesise a set of new triazole monomers with different combinations of alanine derivatives. In the earlier studies, the commercially available unsubstituted azide and alkyne derivatives **27** and **28** were used to construct 1,5-triazole monomers (Figure 6.1).[104a] We reasoned that if we combined these two monomers with the two enantiomers of the corresponding alanine-derived alkyne and azide **29** and **30**, respectively, a set of four monochiral triazoles could be synthesised. Furthermore, **29** and **30** could be combined with each other, yielding four stereoisomers of the disubstituted triazole monomer.

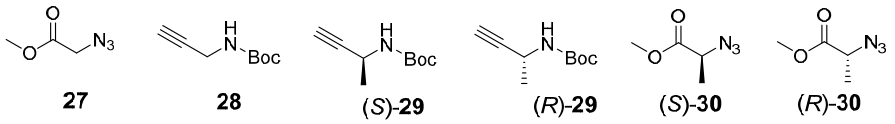
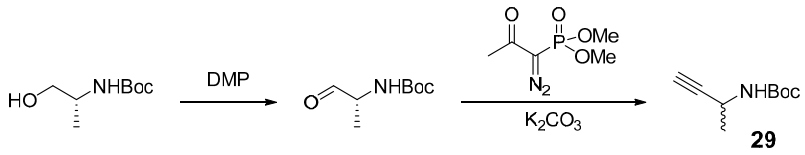


Figure 6.1 Azides and alkynes used for the triazole monomer synthesis.

Initially, we attempted to synthesise the two enantiomers of alkyne **29** from the corresponding chiral amino alcohols via an oxidation reaction using Dess-Martin periodinane,[107] followed by treatment of the intermediate aldehyde with the Bestmann-Ohira reagent[108] to give the corresponding alkyne (Scheme 6.1). Unfortunately, this approach proved to cause extensive racemisation of the stereogenic centre, and we instead opted to purchase these substrates from a commercial source. The chiral azides **30** were synthesised using a diazo-transfer reaction to the primary amine of the alanine methyl ester.[109]

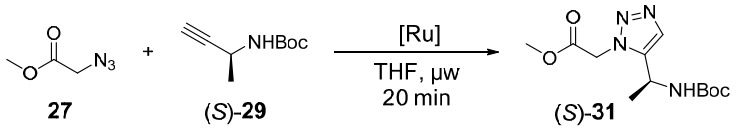


Scheme 6.1 Attempted synthesis of chiral alkynes.

With these compounds at hand, we started investigating their use in the RuAAC reaction. First, we had to find a catalyst that was suitable for coupling these building blocks without affecting the enantiomeric purity of the chiral moieties. Four different ruthenium catalysts were examined in the reaction between azide **27** and alkyne (*S*)-**29** (Table 6.1, entries 1-4). The two substrates were allowed to react in the presence of the ruthenium catalyst in THF under microwave irradiation for 20 minutes at 60-80 °C and the generated product ((*S*)-**31**) was purified by flash chromatography or HPLC.

The two most commonly used catalysts in this type of reaction, [Cp*RuCl(PPh_3)$_3$] and [Cp*RuCl(cod)], as well as [Cp*$RuCl_2$]$_n$ gave moderate to good yields, while the tetramer [Cp*RuCl]$_4$ was the only catalyst that performed poorly in terms of yield. The enantiomeric purity was to our delight not notably affected by any of the catalysts, although the use of [Cp*RuCl(cod)] maintained slightly higher enantiomeric purity in the product, possibly due to the lower temperature used in this case. We then decided to synthesise the different triazole monomers using either [Cp*RuCl(cod)] or [Cp*$RuCl_2$]$_n$.

Table 6.1 Catalyst evaluation for the RuAAC reaction.[a]



27 (*S*)-**29** (*S*)-**31**

Entry	Catalyst	Temp [°C]	Yield [%][b]	ee [%][c]
1	$[Cp^*RuCl(PPh_3)_3]$	80	42	97.7
2	[Cp*RuCl(cod)]	60	73	98.4
3	$[Cp^*RuCl]_4$	80	5	97.5
4	$[Cp^*RuCl_2]_n$	80	57	97.3

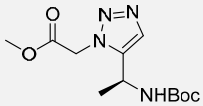
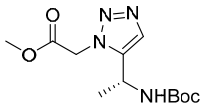
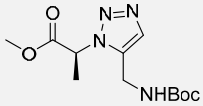
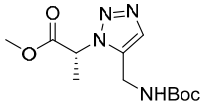
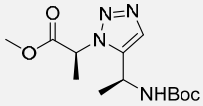
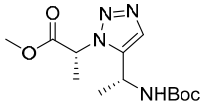
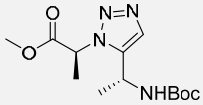
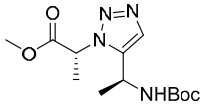
[a] Conditions: Azide (0.4 mmol), alkyne (0.4 mmol), and ruthenium-catalyst (5 mol%) in THF (3 mL) heated under microwave irradiation at the given temperature for 20 mins. The product was purified by HPLC or flash chromatography. [b] Isolated yield. [c] Determined by chiral HPLC.

First, the achiral azide was combined with the other enantiomer of the chiral alkyne (*R*)-**29** using $[Cp^*RuCl_2]_n$, resulting in a 52% yield of the triazole monomer (Table 6.2, entry 2). Thereafter, *N*-Boc-propargylamine was combined with the two different enantiomers of the chiral azide **30** yielding monomers (*S*)-**32** and (*R*)-**32** in 87% and 84% yield, respectively (entries 3-4). However, the enantiomeric excess (ee) for these two compounds had surprisingly dropped to 81.8% and 79.2%, respectively, showing that either the diazo-transfer reaction or the RuAAC reaction causes racemisation of this stereogenic center. This, however, still remains unclear as the unstable nature of the azides complicates the ee-investigation of these compounds, and further investigations of this matter are in progress. Finally, the two enantiomers of the chiral azide **30** were combined with the two enantiomers of the chiral alkyne **29** to give the four different stereoisomers of monomer **33** (entries 5-8). Compounds (*R*,*S*)- and (*R*,*S*)-**33** were obtained in higher yields than (*R*,*R*)- and (*S*,*S*)-**33**, possibly due to higher steric hindrance in the latter. In all cases, the regiochemistry could be confirmed by 2D NMR techniques such as 2D NOESY. The enantiomeric excess has not yet been determined for these compounds, and we will continue our structural investigations.

However, theoretical conformational studies could still be carried out at this stage and these were based on earlier computations performed in our research group on achiral triazole monomers.[104a] The earlier published quantum mechanical calculations for the achiral monomers were adapted to the 8 current structures, considering the (*R*)- and (*S*)-conformers as enantiomer pairs (Table 6.2). For compounds (*S*)-**31** and (*R*)-**31**, 7 and 9 low energy conformers were found, respectively. All of these

conformers could be part of low energy secondary structures, meaning that there are several folding possibilities for each monomer. For (*S*)-**32** and (*R*)-**32**, there were 11 and 6 stable conformers, respectively. For compounds **33**, the number of stable monomer conformers was slightly lower, most likely as a result of the higher steric hindrance.

Table 6.2 Chiral triazole monomers.[a]

Entry	Compound no.	Structure	Yield [%][b]	Number of stable conformers
1	(*S*)-**31**		73	7
2	(*R*)-**31**		52	9
3	(*S*)-**32**		87	11
4	(*R*)-**32**		84	6
5	(*S*,*S*)-**33**		68	5
6	(*R*,*R*)-**33**		67	3
7	(*S*,*R*)-**33**		79	7
8	(*R*,*S*)-**33**		78	3

[a] Conditions: Azide (0.4 mmol), alkyne (0.4 mmol), and ruthenium-catalyst (5 mol%) in THF (3 mL) heated under microwave irradiation at 60-80 °C for 20 mins and the product was purified by HPLC or flash chromatography. [b] Isolated yield.

In conclusion, we have synthesised eight triazole δ-amino acids for further structural investigations. However, problems were encountered during the synthesis of these compounds and some of these issues still need to be solved. For example alternative methods to synthesise the azides that avoid racemisation could be considered. The computational conformational studies indicate that all monomers could be part of well-defined polymeric structures, and we plan to investigate these structures further.

7. SYNTHESIS OF 1,5-FUSED TRIAZOLE PIPERAZINES VIA A RuAAC–HYDROGEN BORROWING ROUTE (Paper IV)

In the previous section, the RuAAC reaction was used to access non-natural 1,2,3-triazole amino acids. Such amino acids bear a potential as building blocks for non-natural peptides (for example as *cis*-amide bond isosters or in peptidic foldamers), or for the construction of other organic compounds. The spatial arrangement of the substituents on the 1- and the 5-positions of a 1,2,3-triazole also provides the possibility of forming fused triazole-containing compounds. Such fused triazoles occur in various types of biologically active compounds with for example anticancer[110] and antiviral[111] properties (Figure 7.1). Triazole-fused bicyclic scaffolds have earlier been synthesised using for example tandem,[112] sequential,[113] or multi-component[114] reactions.

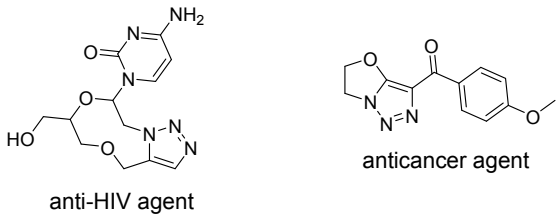
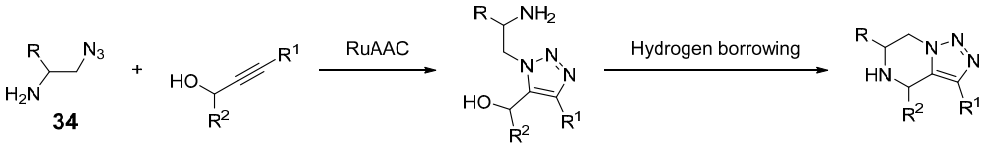


Figure 7.1 Biologically active fused 1,2,3-triazoles.[110-111]

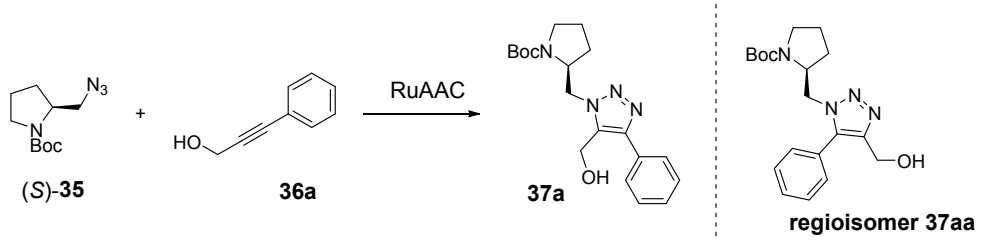
When designing this project, we anticipated that fused triazoles could be constructed by first forming the 1,4,5-trisubsituted triazole scaffold via a RuAAC reaction involving an internal alkyne, and that the nature of the substituents in the 1- and 5-positions would allow for a subsequent intramolecular hydrogen borrowing reaction, leading to the formation of the second ring. With this in mind, we reasoned that if an amino acid-derived azide such as compound **34** (Scheme 7.1) was reacted with a propargylic alcohol via a RuAAC reaction, the amine and the alcohol moiety would be positioned so that a hydrogen borrowing reaction between the two would lead to the formation of a 1,5-fused triazole piperazine with one substituent on the piperazine ring (Scheme 7.2, substituent R) and a second substituent in the 4-position of the triazole (R^1). Moreover, as secondary alcohols are also applicable in the hydrogen borrowing reaction, a substituent could potentially be introduced adjacent to the alcohol (R^2).



Scheme 7.1 Sequential RuAAC and hydrogen borrowing reactions yielding 1,5-fused triazole piperazines.

We started our investigation by allowing commercially available proline-derived azide (*S*)-**35** and 3-phenyl-2-propyn-1-ol **36a** to react in a RuAAC reaction yielding triazole **37a** (Table 7.1). In a general reaction setup, the azide and the alkyne were stirred in equimolar amounts under argon in the presence of a ruthenium catalyst for 24-72 hours, using conventional heating. The product was isolated using flash chromatography. Four different catalysts were examined (Table 7.1, entries 1-5), with [Cp*RuCl(cod)] giving the highest yield at the shortest reaction time (entries 4-5). The best results were obtained using toluene as the solvent at 40 °C. Increasing or decreasing the temperature did not improve the yield (entries 6-7).

Table 7.1 Investigation of reaction conditions for the RuAAC reaction.[a]



Entry	Catalyst	Solvent	Temp. [°C]	Time [h]	Yield [%][b] **37a**
1	$[Cp^*RuCl]_4$	toluene	40	62	9
2	$[Cp^*RuCl_2]_n$	toluene	40	62	40
3	$[Cp^*RuCl(PPh_3)_3]$	toluene	40	62	59
4	[Cp*RuCl(cod)]	toluene	40	48	85
5[c]	[Cp*RuCl(cod)]	toluene	40	21	67
6	[Cp*RuCl(cod)]	toluene	50	23	56
7	[Cp*RuCl(cod)]	toluene	25	48	45
8	[Cp*RuCl(cod)]	THF	40	41	41
9[d]	[Cp*RuCl(cod)]	CH_2Cl_2	25	24	51

[a]Conditions; Azide (0.4 mmol) and alkyne (0.4 mmol) were added to a mixture of ruthenium-catalyst in the solvent (5 mL). The mixture was stirred under argon at the stated reaction temperature for the indicated time. [b]Isolated yield. [c]Reaction performed using (*R*)-**35**. [d] Regioisomer **37aa** observed in higher yields (approx. 10%).

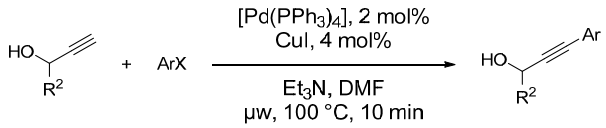
Changing the solvent to THF resulted in lower yields (entry 8), while the use of dichloromethane afforded acceptable amounts of the desired product, but in this case substantial amounts of the unwanted regioisomer **37aa** was also formed (entry 9). In most other cases, the undesired regioisomer was not seen or it was detected in trace amounts. We therefore decided to use [Cp*RuCl(cod)] on a slightly larger scale (0.6 mmol) in toluene at 40 °C for the triazole synthesis. This enabled the isolation of (*R*)-**37a** in 94% yield.

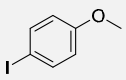
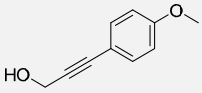
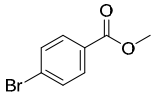
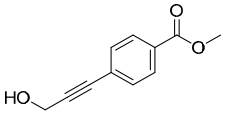
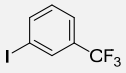
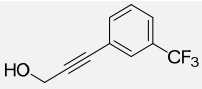
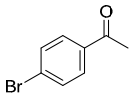
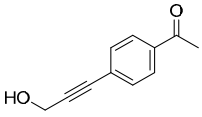
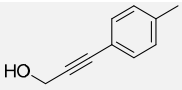
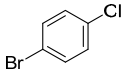
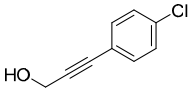
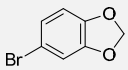
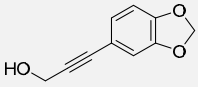
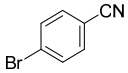
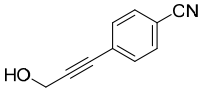
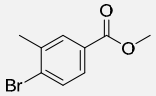
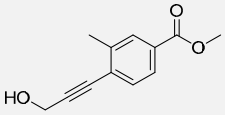
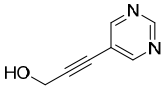
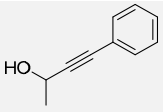
We now planned to investigate internal alkynes with different substituents on the aromatic moiety. In order to do so, a series of alkynes were synthesised from propargylic alcohols and aryl halides employing a microwave-assisted Sonogashira reaction (Table 7.2).[115] Under the influence of $[Pd(PPh_3)_4]$ in combination with CuI, ten different internal propargylic alcohols were synthesised and isolated in low to excellent yields using these conditions. However, the 4-metyl substituted compound **36f** could only be obtained in trace amounts and therefore, an alternative procedure employing $[PdCl_2(PPh_3)_2]$ as the catalyst at ambient temperature was used instead, giving the desired product in excellent yield (entry 5).[116]

With these alkynes at hand, we started investigating the scope of alkynes that could be used in the RuAAC reaction with azide (*R*)-**35** (Figure 7.2). In cases where the alkyne was not soluble in toluene, dioxane was added as co-solvent. Functional groups such as methoxy, methyl ester, trifluoromethyl, acetyl, methyl, and even nitrile groups were unaffected and these substrates were obtained in good to excellent yields (compounds (*R*)-**37b**-**37f**, (*R*)-**37i**). Lower yields were obtained for heteroatom-containing aromatic groups such as dioxole ((*R*)-**37h**), and pyrimidine ((*R*)-**37k**), as well as the ortho-methyl substituted compound (*R*)-**37j**. In the case of the dioxole and the pyrimidine group, the lower yields were partly due to purification issues, as these polar products were more difficult to separate from the catalyst. For the ortho-substituted compound (*R*)-**37j**, we suspect poor coordination of the alkyne (**36j**) to the catalyst due to steric hindrance, resulting in a sluggish reaction. A secondary propargylic alcohol was also applicable, resulting in compound **37l**. Both enantiomers of the azide were allowed to react with a racemic mixture of 4-phenyl-3-butyn-2-ol (**36l**), in both cases resulting in a 1:1 mixture of the two diastereomers in very good yields. Aliphatic groups on the alkyne such as methyl alcohol and an ethyl group could also be used resulting in compounds (*R*)-**37m** and (*R*)-**37n**. Compound (*R*)-**37n** was isolated in a moderate yield, mostly due to problems with

the purification as a large portion of the desired compound co-eluated with what we suspect is the undesired regioisomer.

Table 7.2 Songashira reaction for synthesis of internal alkynes.[a]



Entry	ArX	R^1	Product		Yield [%][b]
1		H	**36b**		59
2		H	**36c**		82
3		H	**36d**		82
4		H	**36e**		82
5[c]		H	**36f**		91
6		H	**36g**		44
7		H	**36h**		18
8		H	**36i**		80
9		H	**36j**		39
10		H	**36k**		93
11		Me	**36l**		43

[a] Conditions: Aryl halide (2 mmol), CuI, and $[Pd(PPh_3)_4]$ were added to a pre-dried 2-5 mL Biotage® microwave-vial that was sealed and the vial was purged with argon. Triethylamine (2 mL) and DMF (1mL) were added, followed by propargyl alcohol. The mixture was heated in a microwave reactor for 10 min at 100 °C. [b] Isolated yield. [c] $[PdCl_2(PPh_3)_2]$ (5 mol%) was used as the catalyst and the reaction was stirred overnight at room temperature.

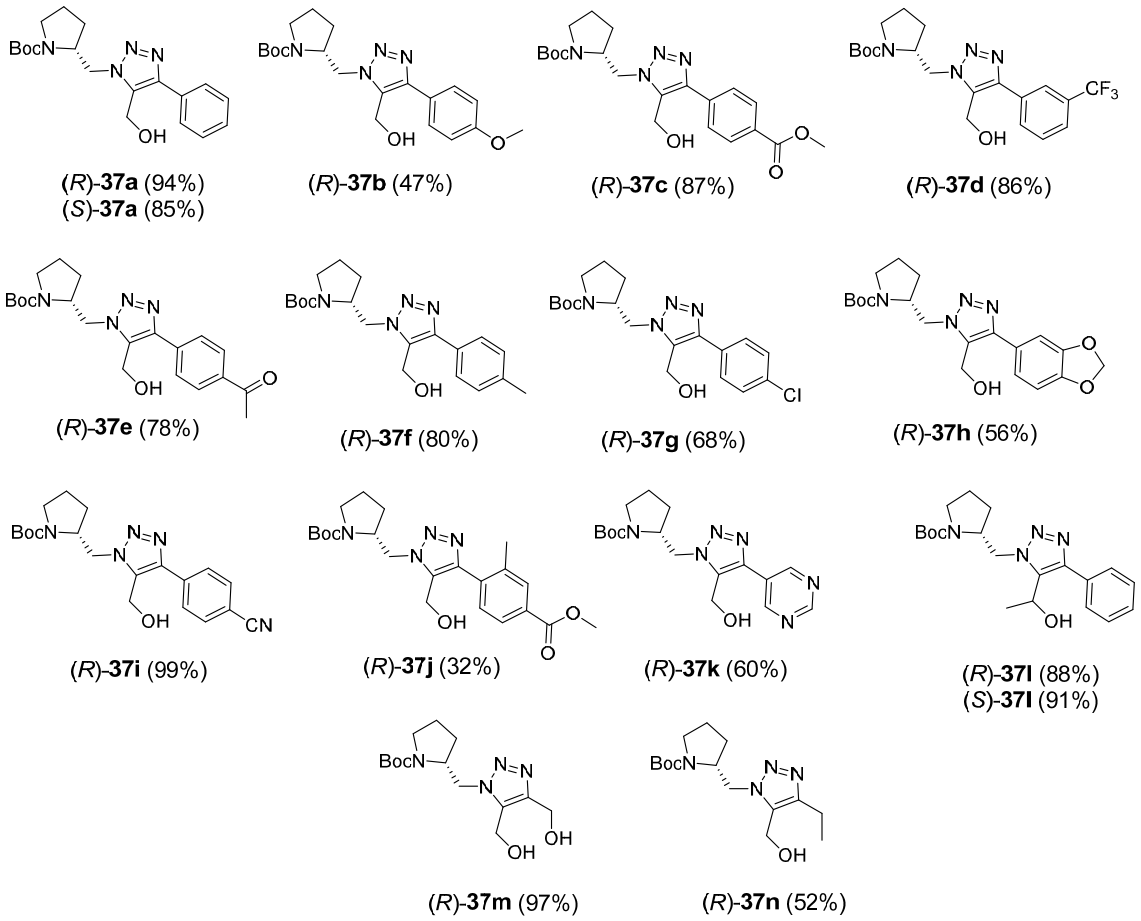
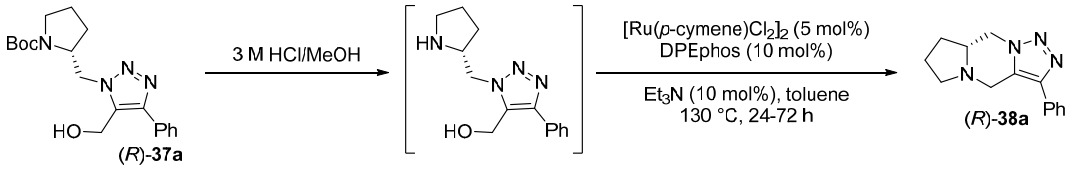


Figure 7.2 Synthesised triazoles.

Somewhat surprisingly, terminal alkynes did not result in any considerable product formation. The azide was recovered in these cases, but the fate of the alkyne was less clear and it is possible that these alkynes were consumed by competing reactions such as cyclotrimerisation.[117]

The model triazole (*R*)-**37a** was then deprotected and cyclised (Scheme 7.2). Boc-removal was effected by treatment of the triazole with 3 M HCl in methanol, yielding the HCl-salt that was neutralised using aqueous NaOH or a polymer-bound carbonate base. Alternatively, TFA/CH_2Cl_2 could be used to provide the corresponding TFA-salt, but using the crude product after applying this deprotection method was associated with unwanted side reactions in the final hydrogen borrowing cyclisation reaction. The amino alcohol was then directly treated with [Ru(*p*-cymene)Cl_2]$_2$ using DPEphos as the ligand. In order to obtain reproducible results, unusually high catalyst loadings were needed (5 mol%), in combination with 10 mol%

triethylamine. These conditions afforded the desired product in high yields (>90% calculated by ^{1}H NMR).



Scheme 7.2 Deprotection and cyclisation of (*R*)-**37a**.

However, the final product (*R*)-**38a** (Scheme 7.2 and Figure 7.3) proved to coordinate well to the ruthenium catalyst, a property that has been previously reported[118] and that resulted in purification issues. Standard flash chromatography was not powerful enough here and we therefore investigated the possibility to use an ion-exchange resin, a metal-scavenger resin or a combination of the above mentioned methods. However, using a sequence of these purification methods resulted in a relatively large loss of material. To circumvent this problem, we briefly investigated the use of $[Cp^*IrCl_2]_2$ as the catalyst for the hydrogen borrowing reaction, in hope that our final compound would not bind as strongly to the iridium complex. Unfortunately, this catalyst did not afford acceptable yields of the final product. Instead, we found that purification of compound (*R*)-**38a** could be carried out by first applying the crude product on a pad of amine functionalised silica, which was then directly placed on top of a standard silica column and further purified using standard flash chromatography using a slow gradient of 0-60% ethyl acetate in petroleum ether, followed by 0-30% methanol in dichloromethane. This sequence afforded the pure fused triazole piperazine in 70% yield for (*R*)-**38a** and 58% yield for (*S*)-**38a** over two steps.

We then further investigated this deprotection–hydrogen borrowing cyclisation sequence for the different triazole substrates (Figure 7.3). Five compounds ((*R*)-**38b**, (*R*)-**38d**, (*R*)-**38e**, and (*R*)-**38f**) could be isolated in yields comparable to the model compound. To our surprise, no reduction of the acetyl group in (*R*)-**38e** was observed, as seen in Paper II (section 5.1). Compound (*R*)-**38g** was produced in a lower yield possibly due to the presence of the chloride on the aryl group. It has been shown that aryl halides can react with ruthenium(II) complexes in an oxidative addition reaction,[119] a process that could generate a number of different by-products as well as causing deactivation of the catalyst. Compound (*R*)-**38j** was then isolated in a moderate yield after the deprotection–cyclisation sequence. This could partly be

a result of the smaller scale, due to the low yield obtained of this substrate in the RuAAC reaction ((*R*)-**37j**, Figure 7.2). We are currently investigating the behaviour of the remaining triazoles in this final reaction sequence.

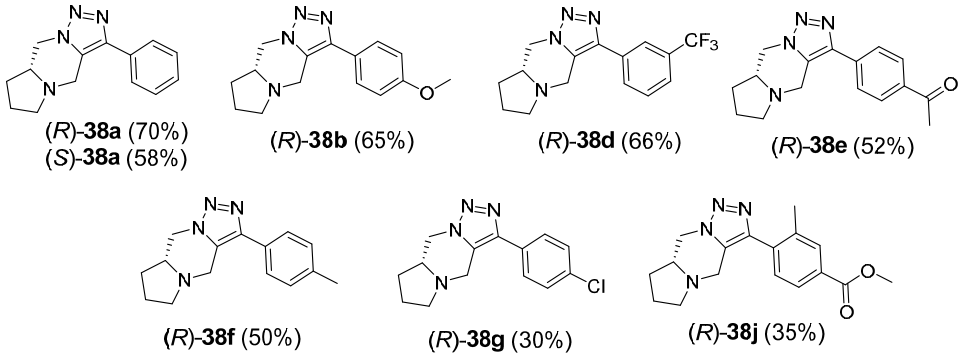


Figure 7.3 1,5-Fused triazole piperazines.

In conclusion, we have shown that it is possible to construct 1,5-fused triazole piperazines via sequential RuAAC–hydrogen borrowing route. This type of approach allows for the variation of substituents in at least three different positions of the scaffold. Furthermore, the appeal of such a transformation increases with the possibility of finding a catalyst that can mediate both of the ruthenium-catalysed reactions, enabling the fast and facile one-pot construction of complex fused molecules, from simple propargylic alcohols and amino acid-derived azides. We are currently investigating such an approach, as well as exploring a wider substrate scope for the deprotection-cyclisation sequence. It would also be of interest to evaluate a set of the obtained compounds for biological activities such as antimicrobial, antiviral or anti-proliferative properties, which have been seen for other triazole-containing structures.[17]

8. CONCLUDING REMARKS AND FUTURE OUTLOOK

This thesis describes the development of atom-economic and efficient chemistry adapted for the valorisation of renewable building blocks into more complex structures. Furthermore, seemingly simple transformations such as alkylation and amination reactions have been investigated for polyfunctionalised renewable starting materials.

The first part of the thesis covered the upgrading of glycerol derivatives via hydrogen borrowing. The amination of solketal was high yielding, allowing for the isolation of tertiary and sterically demanding secondary amino glycerol derivatives. However, the use of less sterically hindered primary amines afforded no or only small amounts of products, partly due to competing homo-coupling of the primary amine substrates. The α-alkylation of acetophenone with 1,3-propanediol proved to be much more challenging. Although a mixture of products were obtained, more knowledge about these types of transformations was gained and chromanone scaffolds could be synthesised using this type of chemistry, albeit in low yields so far. Most likely, further catalyst development is needed in order to solve these problems.

Future investigations within this part of the project could include amination of 1,3-protected glycerol-derivatives to enable substitution on the secondary alcohol, as well as the development of methods for the further functionalisation of the obtained amino glycerol derivatives. For the α-alkylation reactions, catalyst development would be an important start for increasing the selectivity and yields of these reactions. Moreover, it would be of great interest to investigate the possibility of combining the use of 1,3-propanediol as an alkylation agent with the biocatalytic conversion of glycerol into 1,3-propanediol, i.e. employing glycerol indirectly as an alkylation agent.[77, 79] Furthermore, recent advances in double α-alkylation of ketones are encouraging for further functionalisation of the obtained glycerol functionalised substrates, as well as for introducing substituents on the position α to the carbonyl-group of chromanones. It would also be interesting to investigate the possibility of using catalysts based on more abundant metals such as iron or cobalt.

The RuAAC reaction has proven to be a powerful tool in the construction of triazole δ-amino acids from natural amino acids, but the introduction of chiral moieties was not as straightforward as anticipated, mainly due to the lack of reliable methods for the synthesis of the necessary enantiopure alkyne and azide building blocks. Thus, the development of such methods would be of great value for future use of the

RuAAC reaction in this context. Moreover, it would be interesting to synthesise one or several oligomers of the obtained monomers in order to study their behaviour as possible foldamers.

The RuAAC reaction could be successfully employed in the formation of a large set of triazoles, designed for a subsequent hydrogen borrowing cyclisation reaction resulting in the formation of 1,5-fused triazole piperazines. The presented results show that this is a viable method for the construction of such scaffolds. To the best of our knowledge, it is the first example of triazole substrates in the hydrogen borrowing reaction, showing how the combination of RuAAC and hydrogen borrowing reactions could be used as a powerful tool in the fast and atom economic formation of complex heterocyclic structures.

For this final part of the project, it would be of great interest to investigate the possibility of finding a catalyst that can mediate both the RuAAC and the hydrogen borrowing reaction. This would allow for a one-pot approach to this sequence. Furthermore, the use of for example a homopropargylic alcohol would allow for forming a seven-membered 1,5-fused ring. The azide coupling partner could also be varied in a similar manner by changing the chain length or substituent pattern, allowing for the formation of new structurally related compounds. The evaluation of the final compounds as well as the intermediate triazoles, against for example antiviral or anticancer targets, alternatively for their use as catalysts and ligands in other reactions would also be of interest.

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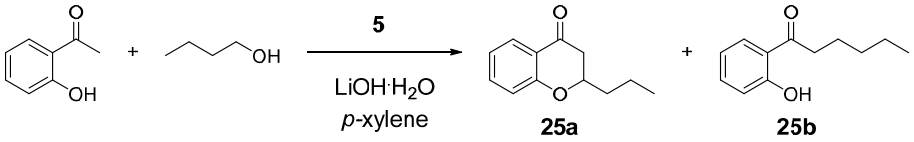
APPENDIX

General procedure for the synthesis of 25a and 25b (Section 5.2).



To a 2-5 mL Biotage® microwave-vial were added catalyst **5** (0.01 mmol, 5.7 mg) and $LiOH \cdot H_2O$ (0.2 mmol, 16.8 mg) followed by 2'-hydroxyacetophenone (0.5 mmol, 60 μL) and 1-butanol (0.5 mmol, 46 μL). The vial was capped and purged with argon. *p*-Xylene (2 ml) was then added and the mixture was stirred at 150 °C for 72 h. The crude reaction mixture was cooled to room temperature and filtered through a pad of neutral activated aluminium oxide. The solvent was removed under reduced pressure and the product was isolated using flash chromatography on silica gel, eluting with 0-40% ethyl acetate in petroleum ether yielding the desired chromanone as a brown oil (26 mg, 27%). Known compound, analytical data were in accordance with published data. δ_H NMR (400 MHz, $CDCl_3$) 0.99 (t, J = 7.3 Hz, 3H), 1.42-1.74 (m, 4H), 1.88 (dddd, J = 5.1, 7.5, 9.6, 13.3 Hz, 1H), 2.66-2.71 (m, 2H), 4.42-4.49 (m, 1H), 6.94-7.03 (m, 2H), 7.47 (ddd, J = 1.8, 7.2, 8.3 Hz, 1H), 7.87 (ddd, J = 0.5, 1.8, 7.8 Hz, 1H); δ_C NMR (100 MHz, $CDCl_3$) 14.0, 18.3, 37.2, 43.2, 77.8, 118.1, 121.2, 121.3, 127.1, 136.1, 161.8, 192.9.[120]

The alkylation product was isolated as a brown oil (14 mg, 15%). Known compound, analytical data were in accordance with published data. δ_H NMR (400 MHz, $CDCl_3$) 0.89-0.95 (m, 3H), 1.32-.143 (m, 4H), 1.70-1.80 (m, 2H), 2.98 (t, J = 7.5 Hz, 3H), 6.87-6.92 (m, 1H), 6.96-7.00 (m, 1H), 7.42-7.49 (m, 1H), 7.74-7.79 (dd, J = 1.6, 8.0 Hz, 1H), 12.41 (s, 1H); δ_C NMR (100 MHz, $CDCl_3$) 13.9, 22.5, 24.1, 31.4, 38.2, 118.4, 118.8, 119.3, 130.0, 136.1, 162.5, 206.8.[121]