New ligands for cooperative metal-organocatalysis

Master’s thesis
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July 2017
New ligands for cooperative metal-organocatalysis

The combination of transition metal catalysis and organocatalysis has received an increasing amount of attention in the recent years. Phosphines have an established position as the most popular ligands, however, NHC carbenes gain in popularity as better alternatives. Very little research has been devoted to molecules bearing two active sites within one catalyst. In the present work, a new NHC carbene is designed and the synthetic route toward the catalyst is presented. Its structure is based on an imidazole moiety with two catalytic centers: gold(I) and an aldehyde functionality, so that it could catalyze the isomerization of propargylic ketones. By modification of the functionality, the reaction scope could be broadened.
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<thead>
<tr>
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<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>$d_3$-ACN</td>
<td>Deuterated acetonitrile</td>
</tr>
<tr>
<td>ACDC</td>
<td>Asymmetric counterion-directed catalysis</td>
</tr>
<tr>
<td>Ad</td>
<td>Adamantyl</td>
</tr>
<tr>
<td>BAIB</td>
<td>Bis(acetoxy)iodobenzene</td>
</tr>
<tr>
<td>Boc</td>
<td>$t$-Butoxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>BrettPhos</td>
<td>2-(Di-tert-butylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
<td>'Bu</td>
<td>$tert$-Butyl</td>
</tr>
<tr>
<td>CAAC</td>
<td>Cyclic alkyl amino carbene</td>
</tr>
<tr>
<td>cat.</td>
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<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>DMS</td>
<td>Dimethyl sulfide</td>
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<td>DMSO</td>
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<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
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<td>Ethanol</td>
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<td>$n$-hex</td>
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<td>Isopropyl</td>
</tr>
<tr>
<td>IPr</td>
<td>2,6-(Diisopropyl)phenyl</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>L</td>
<td>Ligand</td>
</tr>
<tr>
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</tr>
<tr>
<td>NaBARF</td>
<td>Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<tr>
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<td>Nucleophile</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
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<tr>
<td>pK&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Acid dissociation constant</td>
</tr>
<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>Retention factor</td>
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<tr>
<td>RT</td>
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</tr>
<tr>
<td>sat.</td>
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<tr>
<td>SPhos</td>
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<tr>
<td>TCE</td>
<td>1,1,2,2-Tetrachloroethane</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-(Tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TOF</td>
<td>Turnover frequency</td>
</tr>
<tr>
<td>TON</td>
<td>Turnover number</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-Toluenesulphonic acid</td>
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1. Introduction

The use of transition metals to catalyze organic transformations has been determined as one of the most beneficial and effective tools in organic synthesis.\textsuperscript{1} Coinage metals, especially gold, thanks to its Lewis acid properties, are used for activation of unsaturated bonds.\textsuperscript{2} Another approach, making use of small organic molecules that can act as catalysts, has also gained enormous popularity in the past two decades.\textsuperscript{3} The concept of combining transition metal catalysis and organocatalysis may give rise to new and unique processes, which would not be attainable using these strategies alone.

Phosphines have been successfully employed as transition metal ligands in numerous transformations.\textsuperscript{4} However, in the last two decades, N-heterocyclic carbenes (NHC) have experienced an enormous thrust and are nowadays an important and novel class of organic compounds that has found application in catalysis.\textsuperscript{5} They are considered as a promising alternative to commonly used phosphines, which are accessible in a wide range of different properties, suitable for any given transformation.\textsuperscript{6} Despite bearing many similarities, NHCs may provide some additional advantages, being easily synthesized and modified to tune-up their electronic and structural properties.

In the present work, the concept of dual catalysis, as a combination of a transition metal and organocatalyst, will be presented along with selected examples of its application.
1.1 Dual catalysis

Dual catalysis can be classified into three main types, depending on the manner in which the transition metal and the organocatalyst interact with the substrates (Figure 1.1). The first type, cooperative catalysis, requires that both catalysts take part directly in the same catalytic cycle and afford the product by their cooperative work. The second type, synergistic catalysis, is different from the first one, because the substrates are activated by the transition metal and the organocatalyst in two catalytic cycles, that are however directly coupled. The last type of dual catalysis, defined as sequential or relay catalysis, involves the formation of an intermediate in the first catalytic cycle, which is then transformed into the product by the other catalyst present in the reaction medium.

The concept of combining transition metal and organocatalysis has proven to bring a few advantages into catalysis. Firstly, new and previously unachievable processes can be carried out as they were not possible by use of these catalytic systems separately. The problem of a lack or poor enantioselectivity may be solved, since there are more possibilities to create or improve stereochemical control of a reaction. And what is more, the substrate scope and effectiveness of already known transformations may be improved and widen.

However, there are also difficulties and challenges that have to be faced when one wants to apply the idea. The biggest problem in the development of dual catalysis is to provide compatible substrates, catalysts, intermediates and solvents during all stages of reaction series. Proper match of the catalysts is indispensable in that matter. In order to prevent the deactivation of catalysts, a hard Lewis acid and a soft Lewis base (or vice versa) are combined or reagents and catalysts are added sequentially.

So far, transition metals have been used in combination with these types of organocatalysts: (1) secondary and primary amines; (2) Brønsted acids; (3) hydrogen-bonding catalysts; (4) Brønsted bases; (5) Lewis bases; (6) chiral phase transfer catalysts; (7) NHCs. Among these catalyst combinations, the most popular and well investigated are amine- and Brønsted acid- with transition metal catalysts. The following metals have been applied: Pd, Rh, Ru, Cu, Ni, Zn, Fe, Ir, Co, Mn, Ti, Y, In, Nb, Au, Ag, Pt, V. Especially gold catalysis has grown quite rapidly in use in the past decade.
Figure 1.1 Schematic depiction of three working modes in dual catalysis.
1.2 Most common ligands used in catalysis

Carbenes, in their ground state, have two nonbonding electrons that can be either paired, occupying the same orbital (singlet configuration), or unpaired, occupying different orbitals (triplet configuration) (Figure 1.2)\(^{10}\) The properties and reactivity of carbenes are related to the multiplicity of their ground state. In the case of cyclic carbenes, such as NHCs, the bent geometry imposes sp\(^{2}\) hybridization, meaning that the resulting sp\(^{2}\) and p orbitals are not degenerated, as it is with linear species. The energy gap between these two orbitals can be modified by varying atoms adjacent to the carbene carbon. In the case of very electronegative, σ-withdrawing elements, such as nitrogen, the energy gap increases, therefore promoting the singlet ground state, and thus stabilizing inductively the species.\(^{11}\) The lone electron pair is in the plane of the ring, occupying a σ orbital, which renders the compounds nucleophilic.

![Possible electron configuration for carbenes and their frontier orbitals.](image)

**Figure 1.2** Possible electron configuration for carbenes and their frontier orbitals.

In addition to the inductive stabilization described above, NHCs are also stabilized mesomerically. The adjacent nitrogen atoms, being π donors to the carbene carbon, donate some of the electron density into the empty p orbital of the carbon atom, favoring the bent geometry of the molecule. Among singlet state carbenes stabilized by two π donors, NHCs are the most important ones. A few examples are shown in Figure 1.3.\(^{12}\)
Figure 1.3 Electronic stabilization of NHCs and the most popular structures.

They were originally considered as phosphine mimics, however, their steric and electronic characteristics are quite different (Figure 1.4). Phosphines are defined by their cone angle, whereas such generalization cannot be done with NHCs. The steric bulk has a bigger impact on the latter, as the N-substituents are closer to the coordination sphere of the metal, therefore, playing a more important role in tuning metal's activity. In terms of electronic properties, even the most basic phosphines are weaker σ-donors than NHCs. As a consequence, the metal-ligand bond strength is weaker as well.

Figure 1.4 Schematic representation of steric bulk around the metal for NHCs and phosphines.
1.3 Combined amine and transition metal catalysis

Amine catalysis, including secondary amine- and more recently primary amine catalysis, are of enormous importance for the development of organocatalysis.\(^{15}\) There are two ways in which amines activate organic molecules: enamine activation\(^{16,17}\) and imine activation\(^{18,19}\) (Scheme 1.1).\(^7\) They can also be employed in tandem reactions (imine-enamine activation). Aldehydes and ketones activation results in the formation of an enamine, whereas \(\alpha,\beta\)-unsaturated aldehydes and ketones form iminium ions.

**Scheme 1.1** Different types of amine catalysis.

This area of research has been investigated since 2000\(^7\) and the first example of dual catalysis using an amine and transition metal was reported by Córdova and Ibrahem.\(^{20}\) It is a challenge to combine an amine catalyst with a Lewis acid and avoid acid-base quenching and therefore deactivation of the catalyst. In this section, several examples of reactions will be presented. Depending on their activation modes, they can be divided into five types (Figure 1.5).\(^{21}\)
**Figure 1.5** Five examples of activation modes in amine catalysis.

Type I involves addition of enamine to a π-allyl–transition metal complex. Type II, addition of enamine to a molecule activated by a σ-electrophilic Lewis acid. Type III, addition of enamine to a cation formed by a σ-electrophilic Lewis acid. Type IV, addition of enamine to a reactive Cu(III) species. Type V, addition of enamine to an alkyne activated π-electrophilic Lewis acids.

Córdova’s group first applied the concept of amino- and metal catalysis. They chose an intermolecular α-allyl alkylation of aldehydes and cyclic ketones. This transformation is problematic due to competing reactions that may take place, namely aldol condensation, Cannizzaro or Tischenko reactions and O- or N-alkylations. The researchers discovered that by using enamine and Pd catalysis, aldehydes and cyclic ketones could undergo α-allylic alkylation with allyl acetate (Scheme 1.2).

![Scheme 1.2](image)

**Scheme 1.2** Córdova's direct α-allylation of aldehydes and cyclic ketones.
In the proposed mechanism, the authors suggest that two catalytically active species participate in the reaction. Substrates are activated in two different catalytic cycles that are directly coupled. Aldehydes or ketones reacting with pyrrolidine generate enamine intermediates which make a nucleophilic attack to catalytically formed palladium–π-allyl species with a subsequent reductive elimination that leads to the regeneration of Pd(0). The following hydrolysis of the iminium intermediates, provides α-allylic alkylated aldehydes or ketones and the amine catalyst is liberated (Scheme 1.3).

Scheme 1.3 The mechanism of the direct α-allylation of aldehydes and cyclic ketones.

About a decade ago, the concept of π-activation by Lewis acids was combined with aminocatalysis to develop innovative processes that could enrich an already very broad scope of reactions. In 2008 Kirsch and co-workers published the results of the direct cyclization of formyl alkynes that was possible thanks to dual catalysis by a cationic gold(I) complex and amine activation of carbonyl group. Two types of products were observed, depending on branching of aldehydes in α position (Scheme 1.4). The advantage of using catalytically formed enamines lies in the possibility of avoiding an additional synthetic step, as it would be the case if enol ethers, silyl enol ethers or silyl ketene amides were used instead, because they must be preformed beforehand. Gold(I) complexes can retain their chemoselectivity towards alkynes despite the presence of amines and water.
Scheme 1.4 Catalyst effects on the reaction product.

The reaction was tested with a formyl alkyne 22 and only 26 was obtained as a product.\textsuperscript{22} The optimal loading for the amine was found to be 20 mol\% and for the metal catalyst – 2-10 mol\%. By varying the metal center, it was concluded that gold(I) produced the highest yield and the structure of the amine seemed to have a smaller impact on the outcome of the reaction. The postulated reaction mechanisms are given in Scheme 1.5. As it was the case in the previous reaction, this is an example of synergistic catalysis.

Scheme 1.5 Possible mechanism of the direct cyclization of formyl alkynes.
One assumption is that an enamine intermediate (Scheme 1.5 A) attacks a Au(I) complex with the alkyne.\(^{22}\) The other one involves the formation of a Au(I)–enolate by the amine. In the case of gold, the mechanism B seems to be more probable since the use of a tertiary amine results in a rather poor yield. What is interesting, when the same base was used with a different metal catalyst (AgOTf), the cyclization product was obtained in 73% yield. This result may suggest that indeed, the pathway B explains correctly the catalytic process for the silver catalyst.\(^{1,22}\)

In the same year, Dixon and co-workers published a very similar procedure, where cyclopentenes were obtained from α,β-unsaturated ketones and propargylated carbon acids (Scheme 1.6).\(^{23}\) They implemented iminium, enamine and metal activation in a cascade sequence. Here, a few transition metals (Cu, Ag, Hg, Au, Pd) were investigated and their catalytic performance compared. All of them demonstrated good activity towards the substrate, however, the highest yield was achieved when Cu(OTf)\(_2\) in the presence of triphenylphosphine was employed.

![Scheme 1.6](image_url)  
**Scheme 1.6** One-pot synthesis of cyclopentenes.

Yet another example of an amine catalyzed reaction, this time in a sequential manner, was provided by Krause, Alexakis and co-workers in 2009 (Figure 1.6).\(^{24}\) This one-pot tandem reaction involves an organocatalytic Michael addition of aldehydes to nitroenynes, acetalization and cyclization of the formed adduct in a gold-catalyzed process. Chiral nitrosubstituted tetrahydrofuranyl ethers can be obtained with high diastereo- and enantioselectivities (Figure 1.6).
Figure 1.6 Scope of the one-pot tandem reaction.

After optimizing the reaction conditions and catalysts, different alcohols were screened. As a result, a wide spectrum of primary and secondary alcohols can be applied.

In order to elucidate the reaction mechanism, the authors used deuterium labeled methanol in the reaction. As confirmed by NMR spectra, the deuterium was positioned on the exocyclic double bond, which led to the following proposal (Scheme 1.7).
Scheme 1.7 Mechanism of the gold-catalyzed acetylation/cyclization reaction.

Taking into account that the reaction proceeds even without a Brønsted acid, it was assumed that the cationic gold catalyst, [PPh₃Au]BF₄ is formed first and initiates the reaction by acting as an oxophilic Lewis acid, that catalyzes the acetalation of aldehyde 41. At this stage, corresponding hemiacetal salt 43 can be formed. As gold catalysts activate alkynes by generating π-complexes, the unsaturated bond is prone to the attack by the oxygen atom, which results in the formation of tetrahydrofuran 44. The latter undergoes protodemetalation by HBF₄ to furnish corresponding tetrahydrofuranyl ether 45.

The study has shown that organocatalysis and gold catalysis can be applied for one-pot transformations as they are compatible and complementary. Thus, it allows to isolate the products in higher yields in comparison with sequential reactions.²⁴
1.4 Hydrogen bond and metal catalysis

Whereas the amine/transition metal catalysis has been the subject of an extensive research, the combination of hydrogen-bonding and transition metal catalysis has been arguably left behind. The first reported procedure was the work of Jørgensen and co-workers who have carried out a sequential enantioselective Mannich-type/hydroamination reaction to obtain functionalized optically active 2,3,3,5-tetrasubstituted 2,3-dihydro-1H-pyrroles (Scheme 1.8).²⁵

![Scheme 1.8 Sequential enantioselective Mannich-type/hydroamination reaction.](image)

It has been demonstrated by previous studies that chiral hydrogen-bond donors, for example thioureas and phosphoric acid, are able to effectively activate simple N-Boc-protected imines and pronucleophiles toward numerous nucleophilic addition through acid-base interactions.²⁶ Moreover, chiral hydrogen-bond acceptors, for example cinchona alkaloids, have exhibited the ability to activate malonates and their derivatives toward conjugate additions.²⁷ That is how the idea of using cinchona alkaloid derivatives and similar molecules with a thiourea functionality has arisen (Figure 1.7).
Jørgensen has also proven that those interactions are imperative for the reaction to take place. The highest enantioselectivity was obtained for catalysts bearing a thiourea functionality. It may also happen that the catalyst self-associates in solution, which can be problematic and the solvent needs to be changed. The importance of the basic groups of the catalyst was investigated by using TFA as an additive. The reaction was slowed down and upon a higher amount of acid, the catalyst was deactivated.

As far as the second catalyst is concerned, only a gold(I) salt was able to activate the triple bond of the alkynes. Surprisingly, Cu, Ag, Pd, Ni, Rh, Fe, Pt, Zn and In showed no activity in the reaction system. Another problem that had to be faced, was the deactivation of the catalysts. When gold was used in excess or in equimolar amount, the Mannich reaction was inhibited. Employing an excess of thiourea resulted in deactivation of the gold catalyst. Having taken that into consideration, the authors decided to carry out the reaction in a sequential one-pot procedure.
Later on, by combining silver catalysis and organocatalysis, Enders et al. have demonstrated a sequential Michael addition and hydroalkoxylation for the synthesis of coumarin derivatives. They have employed silver salts and primary amines for a one-pot sequential transformations of 4-hydroxycoumarins and enynes. The enyne is activated by a primary amine, which in the case of the study were cinchona derivatives 35-38 (Figure 1.8).

The reaction in Figure 1.8, however, did not show a satisfying enantioselectivity. Therefore, a strategy of changing TFA as an additive to a weaker acid could bring beneficial results. It has been demonstrated by Moran and Melchiorre that N-Boc-protected amino acids could provide a higher level of stereocontrol. The essential role of the acid co-catalyst lays in its assistance of the enyne and the amine catalyst condensation (Scheme 1.9). Then, the formed imine interacts with the acid building-up a well-structured ion-pair supramolecular catalytic assembly that is held together by multiple hydrogen bonds. Due to these interactions, the reaction proceeds with enhanced enantioselectivity. The concept of such catalysis is known as asymmetric counteranion-directed catalysis (ACDC). One of the iminium sides is shielded for the nucleophilic attack and the other
molecule of amino acid directs the attack by 4-hydroxy-coumarin to the iminium ion. After hydrolysis, intermediate 68 enters the second catalytic cycle, where the alkyne moiety is activated by Ag(I) and a cyclization takes place.

Scheme 1.9 Stereoselective amino acid-assisted synthesis of coumarin derivatives.
1.5 Functionalized phosphine and NHC ligands

So far, the presented examples of dual catalysis always involved at least two different molecules of catalyst. In this section, a few examples of a novel approach toward ligand design will be demonstrated. In recent years, the idea of combining two active sites within one catalytic species was born. A functionalized ligand could bring many advantages in transition metal catalysis.

In 2014, Frémont et al. designed an NHC ligand bearing an additional hydroxyl group on its side arm, that could, along with a Au(I/III) metallic center, potentially catalyze tandem 3,3-rearrangement–Nazarov reactions of enynyl acetate (Scheme 1.10).\(^{30}\)

![Scheme 1.10 Products of tandem 3,3-rearrangement–Nazarov reactions.](image)

The structures of the synthesized and characterized ligands are shown in Figure 1.9.

![Figure 1.9 Hydroxyl-functionalized NHC ligands for dual catalysis.](image)
The reaction of the 3,3-rearrangement followed by the Nazarov reaction and the subsequent 1,2-hydrogen shift was first studied by Zhang et al. (Scheme 1.1), when they discovered that the efficiency of cyclopentenones formation was dramatically increased when the reaction was carried out in wet DCM. It was an interesting observation, as the hydrogen shift reactions have generally a fairly low activation energy and they are usually not the rate-determining step in multistep processes. As a result, Shi et al. decided to further investigate the mechanism of that tandem reaction and by carrying out a computational study, explain the role of water in the whole transformation.

Scheme 1.11 Mechanism of tandem 3,3-rearrangement–Nazarov reactions.

The proposed mechanism of these transformations is shown in Scheme 1.10. The process is initiated by the coordination of the cationic gold catalyst to enynyl acetate 91 which forms oxonium ion 92 as intermediate. The ring opens up, generating dialkene 93 in a 3,3-rearrangement process. Intermediate 94 undergoes a Nazarov-type reaction in an electrocyclic ring closure. Finally, a 1,2-hydride shift proceeds, which is the rate-limiting step for the reaction. The presence of water does not affect the first two processes of the tandem reaction. It has a beneficial influence on the hydride-shift, which was proven by deuterium labeling. The detailed mechanism is presented in Scheme 1.12. A molecule of
water can create a cationic complex, which is stabilized by two types of hydrogen bonds. The subsequent two steps are proton-transfer processes catalyzed by water. The function of the water molecule is to transfer a proton to the adjacent carbon atom, while the acetoxy group behaves as a proton acceptor. The performed calculations confirm that the 1,2-hydride shift occurs easier in a wet solvent.

Scheme 1.12 Mechanism of water-assisted 1,2-hydride shift.

Taking into account the results of Shi and his colleagues, a mechanism for the 1,2-hydride shift using hydroxyl-functionalized NHCs as ligands is proposed in Scheme 1.13.

Scheme 1.13 Mechanism of 1,2-hydride shift and hydrolysis by a hydroxyl-functionalized NHC ligand.
All hydroxylated ligands successfully catalyzed the last step of the reaction and, as expected, they also promoted the following hydrolysis step to form a cyclopentenone. However, it turned out that water was still more efficient than just a hydroxyl group for the proton transfer as it is a better nucleophile. The reaction provided a higher yield for an unfunctionalized ligand in wet DCM.

The reaction presented above certainly demonstrates that the concept of functionalized ligands for dual catalysis is arguably very promising for catalysis. Although it lacks a real advantage, since more efficient protocols exist. The ligand design that will be presented in the following section is a conceptually new and possibly allowing gold catalysis with ultra-low loadings.\textsuperscript{33}

As a consequence of the linear structure of gold complexes between the ligand and the alkyne, and what is more, because of the anti-nucleophilic approach, the introduction of bonding interactions between the nucleophile and the ligand is really problematic, considering their obvious spatial distance (Figure 1.10). Up until 2014, there was no reported reaction employing such strategy.

\textbf{Figure 1.10} Steric considerations in gold catalysis.

However, Wang, Zhang \textit{et al.} proposed that if a ligand had a rigid and extending framework that would be able to project a functional group far enough, it could interact with an approaching nucleophile and hence direct the attack at the gold-activated triple bond (Figure 1.11). The rigidity of the framework would prevent the ligand from coordination to the metallic center by the functionality on the extending arm.
The design of the framework would also minimize the entropy cost of the reaction and it is believed that the strategy would render the nucleophilic attack much easier by turning it from an intermolecular operation into a quasi-intramolecular process. Therefore, a greater TON and therefore much more productive catalysis should be anticipated.

The chosen reaction to investigate was addition of carboxylic acids to alkynes and to further demonstrate the general applicability of the design, hydration and hydroamination of alkynes were carried out (Scheme 1.14).

**Figure 1.11** Beneficial nucleophile-functional group interaction.

**Scheme 1.14** Reaction scope for the catalyst.
Modification of phosphine ligands for gold catalysis is not very common. They have successfully found applications in this type of catalysis, being especially used with palladium complexes. Their bulkiness and electron-richness make them very versatile for different transformations. As far as biarylphosphines are concerned, their two linked aromatic rings could provide a good backbone and function as an extending arm that allows to reach a molecule with a functional group on the opposite side of the coordinated alkyne. By implementing bulky groups on the phosphorus atom, the rotation of P-C bond can be fixed, thus aligning the P-Au-alkyne axis with two phenyl rings (Figure 1.12).

**Figure 1.12** Modes of substrate activation for a dual catalyst.

If the activated alkyne is located in a close proximity to the lower phenyl ring, it is expected that by functionalizing the ring with H-bond acceptors, they could interact with nucleophiles and direct their attack toward the alkyne in a quasi-intramolecular process.

To verify if the idea would be successful, a series of functionalized phosphine ligands was designed that are shown in Figure 1.13.
After running the reaction with ligands 117 and 118, no improvement was observed for the ligand substituted in para position, meaning that ortho substitution might be better. A more efficient reaction was carried out when the dimethylamino group was changed to piperidin-1-ylcarbonyl group (ligands 119 and 123), which suggested that an amide was a proper functional group for the reaction. Then the catalyst loading was lowered down as much as possible, finding the ultimate value of 220 ppm with 1681 TON for ligand 123. The amide group was modified to further optimize the reaction (ligands 120-124). Ligand 124 proved to be the most efficient among the other ones with 25 ppm of its cationic gold complex and 34400 TON. A correlation between the reaction yield and the H-bond capability of the oxygen from the amide group was observed.

The reaction scope was further examined with different carboxylic acids and alkynes, resulting in mostly quantitative yields, showing the broad applicability of the method.

In the same year, three authors of the publication presented above decided to explore the idea more and continued the research toward isomerization of alkynes into 1,3-dienes. The ligand design was based on the same biaryl framework. Here, the deprotonation of the alkyne could be achieved using a very mild base, a tertiary amino group as the functionality in the lower phenyl ring. It stays in analogy with enolization of carbonyl compound by a ‘push-pull’ approach. An oxophilic Lewis acid coordinates to the carbonyl
group, increasing the acidity of α protons, whereas a soft Lewis base deprotonates the compound. In the case of alkynes, a gold complex would function as a Lewis acid and the amine group deprotonate the molecule. It was the first time that such a weak base as tertiary aniline (pKₐ in DMSO ~5) could deprotonate a propargylic C-H bond (pKₐ in DMSO >30). By appropriately varying electronic properties of the catalyst, the amino group becomes more basic if electron donating substituents are placed in the lower phenyl ring and the gold metal center becomes more acidic if the phenyl ring directly attached to the phosphorus is substituted with electron withdrawing groups. Therefore, the reaction efficiency can be improved. The reaction mechanism is presented in Figure 1.14 along with the most efficient ligand.

![Figure 1.14](image_url) Suggested mechanism of alkynes isomerization into 1,3-dienes.³⁴

Later on, the same researchers published another example of this reaction.³⁵ This time it was a regiodivergent and stereoselective isomerization of propargylic esters into dienyl esters (Figure 1.15). Both steps of the transformation have already been presented in this study.
Figure 1.15 Stereoselective isomerization of propargylic esters into dienyl esters.\textsuperscript{35}
2. Summary

The concept of combining transition metal catalysis and organocatalysis has become very attractive over the course of the last decade. The selected examples of dual catalysis show how various transformations can be achieved, employing a wide range of transition metals and several types of organocatalysts, which would be impossible by use of these catalysts alone. Aminocatalysis has particularly received a lot of attention due to its versatility and numerous modes of activation. Notwithstanding the developments that have been made in the field, the number of applications is still limited. This may change in the near future, as new catalysts, with unprecedented bifunctional properties, are being discovered and successfully applied, as they can serve both as Lewis acid for unsaturated bonds activation and organocatalysts simultaneously. Especially NHCs are very promising ligands that can without a doubt compete with traditionally used phosphines or even overtake their popularity in catalysis, owing to the simplicity of their modification and functionalization.
Experimental part:

Synthesis of a NHC gold complex equipped with a rigid aldehyde functionalized sidearm for cooperative dual catalysis of ynone transposition
3. Aim of the study

The aim of the work was the design, synthesis and characterization of a new NHC ligand with a functionalized and extending side arm for dual catalysis. Its catalytic performance as a ligand for a gold(I) metal center would be examined (Figure 3.1).

![Figure 3.1 The concept of the ligand design.](image)

The structure of the ligand was chosen to be based on a rigid framework which can be provided by a 1,1-bis substituted cyclohexyl ring with two phenyl groups, one bearing an imidazole moiety and the other a tertiary amino group, in para positions (Scheme 3.1). In this way, the NHC structure would be able to reach the approaching molecule of alkyne from opposite sides and direct it to the metallic center. Our research hypothesis was that by performing a catalytic reaction in an intramolecular, rather than via bimolecular intermediates, there is a potential chance to increase TOF and TON values dramatically.

![Scheme 3.1 Structure of the designed ligand.](image)
The aldehyde functionality could potentially catalyze an isomerization reaction of propargylic ketones (Scheme 3.2), while the model reaction is presumed to proceed via cyclic acetal intermediate 127.\(^{37}\)

![Scheme 3.2 Model reaction.]

The designed ligand should be able to mediate the reaction in an analogous manner through cyclic acetal intermediate 130 (Scheme 3.3).

![Scheme 3.3 Postulated mechanism of cooperative catalysis.]

If the concept proved successful, further modifications of the ligand would be undertaken in order to find its best performance and broaden the reaction scope.
4. Results and discussion

4.1 Synthesis of 1,1-bis(4-aminophenyl)cyclohexane

The first synthetic step was initiated with the formation of the backbone of the ligand. The reaction between cyclohexanone 132 and aniline 133 was carried out according to a reported procedure (Scheme 4.1).38

\[ \text{Cyclohexanone} + \text{Aniline} \xrightarrow{\text{HCl}} \text{Product} \]

Scheme 4.1 Synthesis of 134.

A plausible reaction mechanism is presented in Scheme 4.2. Firstly, the carbonyl group of 132 is protonated with hydrochloric acid, forming an acyl cation which attacks an electron-rich molecule of 133 in a Fried-Crafts acylation reaction. At this stage, the formed molecule can either undergo water elimination or further react with another molecule of 133, giving 134 as product. The yield of the product was a few times lower than expected, despite varying the reaction conditions (temperature, quantities of substrates, reaction time, pressure). The structure of the product was confirmed with \(^1\)H-NMR spectroscopy. It was very important to distill the unreacted aniline as the purification process becomes easier afterwards.

Scheme 4.2 Proposed mechanism of formation of 134.
It was necessary to protect one of the amino groups of 134 for further synthetic steps, because the imidazole moiety was supposed to be built up on only one amino group. Boc was chosen as a convenient protecting agent with its stability in a broad range of pH values.\textsuperscript{39} The reaction was monitored by TLC and 0.8 equiv. of Boc\(_2\)O gave the highest yield of the monoprotected product. After purification the product of double protection could be deprotected in TFA and reused.

**4.3 Synthesis of the imidazole moiety**

There are many different pathways to form an imidazole ring, depending on its substitution patterns and the nature of substituents.\textsuperscript{40} Here, the heterocyclic ring should be unsymmetrically substituted with two aromatic groups. The following procedure allows the synthesis of 1-substituted imidazole derivatives with good yields from glyoxal, ammonium chloride and formaldehyde (Scheme 4.3).\textsuperscript{41} In the case of the target molecule, the yield did not exceed 10\% in any of the trials. It may have been worth to try the reaction in different solvents (e.g. EtOH) instead of MeOH, as it was also mentioned in the original publication. Formed iminoacetaldehyde 136 tends to precipitate from a methanol solution. However, a variation of the reaction time did not have any impact on the overall yield. An interesting fact is that the amino group remained protected over the course of the reaction, despite the introduction of orthophosphoric acid, which was determined by \(^1\)H-NMR spectroscopy. The molecule was deprotected with TFA for the further step.

![Scheme 4.3 Synthesis of 137.](image-url)
4.4 Reductive amination

Reductive amination is a convenient way to obtain N-substituted amines by introducing an aliphatic group. Here, benzaldehyde was chosen, as the formed imine can be reduced to the benzyl group (Scheme 4.4). The synthesis can be carried out as a one-step or two-step procedure, depending on the reducing agent. If sodium tetraborohydride is used, it is necessary to form an imine first and then add the reductant, to avoid the reduction of the aldehyde. If sodium cyanoborohydride is used, the reductant can be added along with the amine and aldehyde, as aldehydes are reduced very slowly in such conditions. It is also advantageous to equip the reaction vessel with a Dean-Stark apparatus in order to evacuate forming water from the reaction environment and therefore, switch the reaction equilibrium in favor of the forming product.

![Scheme 4.4 Synthesis of 139.](image)

4.5 Introduction of an aldehyde functionality

4.5.1 Buchwald amination

A few protocols exist in order to introduce an aryl group to a primary or secondary amine. Buchwald-Hartwig amination involves a reaction between amines and aryl halides via the palladium-catalyzed cross-coupling reaction. It has become a very general and popular way to obtain aromatic amines as many precatalysts and ligands have been developed for that purpose. In a procedure reported by Buchwald et al., two ligands are used: BrettPhos and RuPhos, depending on whether a primary or secondary amine is used, respectively (Figure 4.1). It is claimed that they provide the widest scope of amines and aryl chlorides that can undergo cross-coupling reactions.
In the case of this study, a different ligand and precatalyst were used. SPhos was available as the ligand, which has a similar structure to RuPhos (Figure 4.2) and Pd(OAc)$_2$ was chosen as the precatalyst.

Figure 4.2 Structure of SPhos ligand.

This modified procedure was tested on 139 with acetal 145 (Scheme 4.6). Unfortunately, the reaction turned out to be unsuccessful as no product was isolated, despite providing required reaction conditions. No oxidative addition to the aryl chloride was observed.

Scheme 4.6 Tested Buchwald amination reaction.
Due to the synthetic problem described above, an alternative way to introduce the aldehyde functionality had to be found.

4.5.2 Use of furfural

It has been reported that anilines react with furfural giving 2-formylpyrroles as products of this condensation, as shown in the mechanism in Scheme 4.7.45

Scheme 4.7 Mechanism of 2-formylpyrroles formation.

A model reaction between furfural and aniline was carried out, according to the reported procedure, but no product could be isolated. The problem lies in the electronic properties of the amine. Only electron deficient anilines give products in good yields (above 70% for \( p \)-nitroaniline, Scheme 4.8), therefore, this strategy was discarded.

Scheme 4.8 Synthesis of 153.
4.5.3 Use of Kojic acid

While the previous attempts to introduce a group with an aldehyde functionality being unsuccessful, a new promising alternative was found (Scheme 4.9).

\[
\text{HN}_\text{Boc} \quad 154 \quad 2\% \text{ HCl} \quad \rightarrow \quad \text{OH} \quad 155
\]

Scheme 4.9 Introduction of an aldehyde functionality.

\(\gamma\)-pyrones can be converted into \(N\)-aryl-\(\gamma\)-pyridones in weakly acidic conditions as reported by Looker et al. It is believed that the following equilibria shown in Scheme 4.10 enable the reaction.\[46\]

\[
\text{HO} \quad \text{O}^+ \quad \text{OH} \quad \leftrightarrow \quad \text{HO} \quad \text{O}^+ \quad \text{OH} \quad \leftrightarrow \quad \text{HO} \quad \text{O}^+ \quad \text{OH}
\]

Scheme 4.10 Resonance equilibria of protonated 154.

The hydroxyl group can be easily oxidized to the corresponding aldehyde. Kojic acid, transformed into methyl monoether, was tested in a model reaction with \(p\)-\(tert\)-butylaniline 156, providing the \(N\)-aryl-\(\gamma\)-pyridone 157 with a good yield of 77\% (Scheme 4.11).

\[
\text{156} \quad 154 \quad 2\% \text{ HCl} \quad \rightarrow \quad \text{157}
\]

Scheme 4.11 Model reaction for 157.

Consequently, 135 was used in the same reaction with Kojic acid (Scheme 4.9). Formation of a tar was observed, which lowered the yield of the reaction to around 35\%. This could
possibly be avoided if the amine was used in the form of hydrochloride, but then the protecting group would be cleaved off.

4.6 Synthesis of imidazole moiety on the sidearm

As the reaction shown in Scheme 4.9 was successful, although with a low yield (28.2%), a heterocoupling leading to a double N-substituted imidazole with 2,6-diisopropylphenyl (IPr) halide was not very promising due to its apparent bulkiness. These couplings usually involve unsubstituted or monosubstituted phenyl rings, however, in the case of the latter, the yield decreases significantly. Therefore, a different approach was chosen to continue the synthesis of 125. Fürstner et al. reported a procedure allowing the synthesis of imidazolium salts with substitution patterns that were not achievable with other pathways. It is especially useful for obtaining unsymmetrically substituted imidazolium salts. Even sterically hindered and weakly nucleophilic amines give good results.

This procedure had another advantage in the case of this project, because it changes the synthetic route from a single sequence of transformations into two parallel pathways, thus lowering the impact of individual reactions on the overall yield (Scheme 4.12).

Scheme 4.12 New synthetic route.

The key step is the reaction between an amine and oxazolinium salt which leads to the imidazolium salt. Oxazolinium salts can be prepared in a short and very effective sequence of reactions. The starting amine 158, which will be employed as the N-substituent for the quaternary nitrogen atom of the imidazolium salt, reacts with the commercially available 2-bromoacetaldehyde diethylacetal 159 to afford 160. Upon formylation and subsequent
hydrolysis, the product 161 is treated with acetic anhydride in the presence of a strong mineral acid, such as HClO₄ or HBF₄, furnishing the oxazolinium salt 162. A few difficulties were encountered with purification of 161. After Kugelrohr distillation and recrystallization from EtOH, the product did not show the aldehyde protons in the ¹H-NMR spectrum. When the hydrolysis step in formic acid was repeated, the product was used for the next step without any purification. Another difficulty was encountered at the last stage, when the amine 155 was not soluble in toluene and the addition of MeOH was required to overcome this problem. The reaction could also be carried out in an aprotic solvent, such as TCE. The purification of 163 was not as straightforward as reported by Fürstner and co-workers. Flash column chromatography was applied with the eluent being a mixture of DCM and MeOH 40:1 (v:v) respectively, with the addition of aqueous ammonia. The procedure turned out to be very time- and solvent-consuming as the Rf values of the product and starting material were very close to 0.

4.7 Oxidation of the Kojic acid moiety
The transformation of 163 into an aldehyde (Scheme 4.13) was performed with 2,2,6,6-(tetramethylpiperidin-1-yl)oxyl (TEMPO) (cat.) with bis(acetoxy)iodobenzene (BAIB) acting as the terminal oxidant.

Scheme 4.13 Oxidation of 163.

It is a very mild and environmentally-friendly oxidant that transforms activated primary alcohols into aldehydes if the reaction is carried out in non-aqueous conditions. Another advantage is a very straightforward work-up and high tolerance for various functional groups. The oxidation mechanism is shown in Scheme 4.14.
**Scheme 4.14** Mechanism of TEMPO-catalyzed oxidation of alcohols.

**4.8 Insertion of gold**

There are three general synthetic routes towards NHC-gold(I) complexes (examples 1-3 in Scheme 4.15). Each of them has advantages and limitations. The first one seems to be the most straightforward, however, it requires the most effort, which means that the reaction needs to be carried out in dry solvents and under an inert atmosphere. The preformed free carbenes are highly reactive and the reaction yield is unsatisfactory.

**Scheme 4.15** General synthetic routes towards Au(I)-NHC complexes.
In the other two approaches, a thioether ligand is substituted from a gold(I) precursor complex. They are more effective and commonly used. The second method was applied in the case of this study. Due to its bulkiness, 164 had to be refluxed in DCM for several hours, otherwise the generally fast reaction did not occur.\textsuperscript{52}
5. Conclusions

The synthesis of the ligand and its gold complex was successfully achieved despite a few synthetic problems that had to be resolved. It is a novel and complex molecule, so the development of an efficient synthetic strategy may be time-consuming. As a result, the study was limited to one molecule and the catalytic performance of the ligand will be characterized outside of this study. However, it is highly expected that owing to its design, it will act as a dual catalyst towards the isomerization of propargylic ketones, according to the equation in Scheme 3.2. The concept of functionalized ligands has not been reported yet in the literature for NHCs, but given the success of its implementation in phosphines, it is a very promising strategy. The local concentration of the formyl group in regard to the approaching nucleophile can be immensely increased by the intramolecular manner of the reaction. We anticipate that the synthesized gold complex provides efficient catalysis with respect to ynone transposition reaction. However, to get reliable knowledge about the catalytic reaction kinetics, reaction progress monitoring studies (with NMR spectroscopy) and related kinetic analysis are needed. This is of importance, because in principle catalytic conversions could be also mediated by decomposition e.g. gold nanoparticles products. The kinetic information will be further utilized with computational study to find evidence of desired cooperative dual catalysis. Unfortunately, this part of the study could not be included in the present work.

This work has been a part of a bigger project that will be continued in the future. Ultimately, the reaction scope will be broadened by employing another functional group and nucleophile. The aldehyde can be easily transformed into an amine that could direct a molecule of CO$_2$ or a carbonate anion towards activated triple bonds.
6. Experimental

$^1$H-NMR (299.952 MHz) and $^{13}$C-NMR (75.430 MHz) spectra were done on a Varian 300 MHz spectrometer at 27 °C. Solvents and chemicals used in synthesis and purification procedures were HPLC quality and used as received. Dry THF and toluene were obtained from Vacuum Atmospheres Solvent purifiers.

**Characterized compounds:**

- **1,1-bis(4-aminophenyl)cyclohexane (134)**

  
  
  ![Image of 1,1-bis(4-aminophenyl)cyclohexane](image)

  Excess aniline (100 ml, 1.1 mol, 3.44 equiv.) was added to cyclohexanone (31.205 g, 0.318 mol, 1.0 equiv.) in 37% HCl (110 ml). The mixture was refluxed at 130 °C for 44 h in closed microwave vessels. Then pH was raised to 13 with NaOH, the oily layer was separated and the excess of unreacted aniline distilled. Purification by column chromatography (SiO$_2$, EtOAc:n-hex from 1:10 to 1:1). Yield: 11.5% (9.74 g)

**$^1$H-NMR (300 MHz, CDCl$_3$):** $\delta$ 7.04 (d, J=8.7 Hz, 4H), 6.60 (d, J=8.7 Hz, 4H), 3.54 (br s, 4H), 2.17 (m, 2H), 1.53 (m, 8H)

The obtained $^1$H-NMR spectrum matches the reported one.

- **tert-butyl (4-((1-(4-aminophenyl)cyclohexyl)phenyl)carbamate (135)**

  
  ![Image of tert-butyl (4-((1-(4-aminophenyl)cyclohexyl)phenyl)carbamate](image)

  Boc$_2$O (6.39 g, 29.3 mmol, 0.8 equiv.) was added to a solution of 134 (9.74 g, 36.6 mmol, 1.0 equiv.) in DCM (400 ml) and stirred at RT overnight. Purification by column chromatography (SiO$_2$, EtOAc:n-hex from 1:5 to 1:1). Yield: 50% (5.37 g)
**1H-NMR** (300 MHz, CDCl₃): δ 7.19 (m, 4H), 7.02 (d, J=8.7 Hz, 2H), 6.59 (d, J=8.7 Hz, 2H), 6.37 (s, 1H), 3.53 (br s, 2H), 2.18 (m, 2H), 1.50 (s, 15H)

- 4-((1H-imidazol-1-yl)phenyl)cyclohexyl)aniline (137)

```
\[ \text{NH}_2
```

40% glyoxal (0.5 ml, 11.77 mmol, 1.0 equiv.) was added to a solution of 135 (4.314 g, 11.77 mmol, 1.0 equiv.) in MeOH (50 ml) and left for 20 h at RT. NH₄Cl (1.26 g, 22.54 mmol, 2.0 equiv.) and formaldehyde (35% in H₂O, 1.88 ml, 22.54 mmol, 2.0 equiv.) were added and refluxed for an hour. Then H₃PO₄ (85%, 1.64 ml, 2.0 equiv.) was added slowly and the reflux was continued for another 8 h. After removal of the solvent, the residue was mixed with ice and neutralized with 40% KOH. The product was extracted with EtOAc (3x30 ml) and purified by column chromatography (SiO₂, EtOAc:n-hex 1:1). Yield: 9.7% (362 mg)

**1H-NMR:** (300 MHz, CDCl₃): δ 7.80 (s, 1H), 7.35 (d, J=8.6 Hz, 2H), 7.24 (m, 3H), 7.17 (s, 1H), 7.06 (d, J=8.7 Hz, 2H), 6.62 (d, J=8.7 Hz, 2H), 3.56 (br s, 2H), 2.23 (m, 2H), 1.56 (m, 8H)

**13C-NMR** (300 MHz, CDCl₃): δ 149.4, 144.2, 138.0, 135.8, 134.8, 130.4, 128.7, 128.2, 121.4, 118.5, 115.4, 45.6, 37.4, 26.6, 23.1

- 2-(3-chlorophenyl)-1,3-dioxolane (145)

```
\[ \text{Cl}
```

Ethylene glycol (2.8 ml, 50 mmol, 1.7 equiv.) was added to a solution of 3-chlorobenzaldehyde (4.068 g, 28.9 mmol, 1.0 equiv.) in toluene (160 ml) with TsOH (cat.). The mixture was refluxed overnight equipped with a Dean-Stark apparatus. The product was purified by distillation. Yield: 92% (4.91 g)
**1H-NMR** (300 MHz, CDCl₃): δ 7.49 (s, 1H), 7.32 (m, 3H), 5.79 (s, 1H), 1.10 (m, 2H), 4.03 (m, 2H)

The obtained ¹H-NMR spectrum matches the reported one.⁵³

- **N-benzylaniline (139)** ⁵⁴

To a solution of aniline (1.0 g, 10.74 mmol, 1.0 equiv.) in EtOH, benzaldehyde (1.37 g, 12.88 mmol, 1.2 equiv.) and sodium cyanoborohydride (1.34 g, 21.48 mmol, 2 equiv.) were added and the mixture was refluxed for 18 h equipped with a Dean-Stark apparatus. The reaction was quenched with 1M NaOH. The product was extracted with DCM, dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography (SiO₂, EtOAc:n-hex 1:3). Yield: 55% (1.082 g)

**1H-NMR** (300 MHz, CDCl₃): δ 7.42 (m, 5H), 7.27 (t, J=7.2 Hz, 2H), 6.82 (t, J=7.2 Hz, 1H), 6.72 (d, J=8.7 Hz, 2H), 4.40 (s, 2H), 4.06 (br s, 1H)

The obtained ¹H-NMR spectrum matches the reported one.⁵⁴

- **1-(4-nitrophenyl)-1H-pyrrole-2-carbaldehyde (153)** ⁵⁵

To a solution of p-nitroaniline (690 mg, 5.0 mmol, 2.0 equiv.) in EtOH (10 ml) at 100 °C, furfural (250 mg, 2.5 mmol, 1.0 equiv.) was added and 2M HCl (12 ml) was added dropwise. After 2h, the mixture was diluted with water (100 ml). The precipitate was filtered off and washed with EtOH. Yield: 85% (459 mg)

**1H-NMR** (300 MHz, CDCl₃): δ 9.61 (s, 1H), 8.31 (d, J=9.3 Hz, 2H), 7.51 (d, J=9.3 Hz, 2H), 7.26 (s, 1H), 7.19 (m, 1H), 7.11 (m, 1H), 6.48 (m, 1H)

The obtained ¹H-NMR spectrum matches the reported one.⁵⁵
• 2-(hydroxymethyl)-5-methoxy-4H-pyrane-4-one (154)\textsuperscript{46}

![Structure of 2-(hydroxymethyl)-5-methoxy-4H-pyrane-4-one](image)

To a solution of Kojic acid (5.02 g, 35.3 mmol, 1.0 equiv.) in 10% KOH (25 ml, 38.9 mmol, 1.1 equiv.), dimethyl sulfate (3.34 ml, 35.3 mmol, 1.0 equiv.) was added over the period of 30 min. The temperature was kept below 25 °C. Stirring was continued for another 30 min. The mixture was kept at -20 °C overnight and the precipitate was filtered off and recrystallized from MeOH. The product was obtained as a light-yellow solid. Yield: 47% (2.59 g)

\textsuperscript{1}H-NMR (300 MHz, \textit{d}\textsubscript{6}-DMSO): δ 8.06 (s, 1H), 6.27 (s, 1H), 5.64 (t, \textit{J}=6.9 Hz, 1H), 4.27 (d, \textit{J}=6.9 Hz, 2H), 3.63 (s, 3H)

The obtained \textsuperscript{1}H-NMR spectrum matches the reported one.\textsuperscript{46}

• 1-(4-(tert-butyl)phenyl)-2-(hydroxymethyl)-5-methoxypyridin-4(1H)-one (157)\textsuperscript{46}

![Structure of 1-(4-(tert-butyl)phenyl)-2-(hydroxymethyl)-5-methoxypyridin-4(1H)-one](image)

To a suspension of 154 (1.89 g, 12.1 mmol, 1.0 equiv.) in 2% HCl (35 ml), \textit{p}-tertbutylaniline (2.5 ml, 15.73 mmol, 1.2 equiv.) was added and the mixture was refluxed for 24 h. After cooling down, the acid was neutralized with solid Na\textsubscript{2}CO\textsubscript{3}, the solution was extracted with EtOAc (2x10 ml), which was discarded. Half of the solvent was evaporated and the precipitate filtered off. Yield: 77.6% (2.70 g)

\textsuperscript{1}H-NMR (300 MHz, \textit{d}\textsubscript{6}-DMSO): δ 7.54 (d, \textit{J}=8.7 Hz, 2H), 7.38 (d, \textit{J}=8.7 Hz, 2H), 7.28 (s, 1H), 6.34 (s, 1H), 5.49 (br s, 1H), 3.98 (s, 2H), 3.61 (s, 3H)

\textsuperscript{13}C-NMR (300 MHz, \textit{d}\textsubscript{6}-DMSO): δ 172.0, 152.4, 149.5, 148.9, 138.9, 127.2, 127.0, 125.0, 113.6, 59.7, 56.6, 35.2, 31.7
To a suspension of 154 (3.827 g, 24.51 mmol, 1.0 equiv.) in 2% HCl (70 ml), 135 (11.680 g, 31.87 mmol, 1.3 equiv.) was added and the mixture was refluxed for 24 h. The solution was extracted with EtOAc (2x15 ml), which was discarded. After cooling down, the acid was neutralized with solid NaHCO₃. The precipitate was filtered off, washed with water and Et₂O, and purified by column chromatography (SiO₂, DCM:MeOH 9:1 v/v). Yield: 28.2% (2.79 g)

\[ ^1H-NMR \text{ (300 MHz, } d_6-\text{DMSO): } \delta 7.37 \text{ (d, } J=9.0 \text{ Hz, } 2\text{H}), 7.30 \text{ (d, } J=8.7 \text{ Hz, } 2\text{H}), 7.24 \text{ (s, } 1\text{H}), 6.98 \text{ (d, } J=8.7 \text{ Hz, } 2\text{H}), 6.48 \text{ (d, } J=8.7 \text{ Hz, } 2\text{H}), 6.30 \text{ (s, } 1\text{H}), 5.37 \text{ (t, } J=5.7 \text{ Hz, } 1\text{H}), 4.85 \text{ (s, } 2\text{H}), 3.92 \text{ (d, } J=6.3 \text{ Hz, } 2\text{H}), 3.59 \text{ (s, } 3\text{H}), 2.25 \text{ (m, } 3\text{H}), 1.45 \text{ (m, } 8\text{H)} \]

The reaction was carried out in anhydrous conditions and under an inert atmosphere. \textit{n}-BuLi (1.6 M in \textit{n}-hex, 70 ml, 110.2 mmol, 1.1 equiv.) was added to a solution of 158 (18.7 ml, 100.2 mmol, 1.0 equiv.) in THF (200 ml) at 0°C. The mixture was stirred for 30 min at RT before 159 (16.5 ml, 110.2 mmol, 1.1 equiv.) was added. The mixture was left overnight before the solution was poured into a mixture of sat. aq NaHCO₃ and water (200 ml, 1:1 v/v). The aqueous phase was extracted with Et₂O (2x150 ml), the combined organic layers were washed with water (100 ml), brine (150 ml), dried over MgSO₄,
filtered and the filtrate was evaporated. The product was purified by distillation and obtained as a yellow oil. Yield: 94.5% (27.79 g)

**1H-NMR** (300 MHz, CDCl$_3$): $\delta$ 7.10 (m, 3H), 4.70 (t, $J=5.4$ Hz, 1H), 3.79 (tt, $J=9.3$, 6.9 Hz, 2H), 3.61 (tt, $J=9.6$, 7.2 Hz, 2H), 3.34 (sept, $J=6.9$ Hz, 2H), 3.04 (d, $J=5.4$ Hz, 2H), 1.29 (m, 18H)

The obtained 1H-NMR spectrum matches the reported one.$^{48}$

- N-(2,6-diisopropylphenyl)-N-(2-oxoethyl)formamide (161)$^{48}$

![Structure](image)

A mixture of Ac$_2$O (17.6 ml, 189.4 mmol, 1.0 equiv.) and HCOOH (17.6 ml, 473.7 mmol, 5.0 equiv.) were stirred at RT for 2 h before it was added to an ice-cooled solution of 160 in THF (400 ml). Stirring continued for 30 mins at RT. The resulting mixture was poured into a solution of 10% NaOH (450 ml), the aqueous phase was extracted with Et$_2$O (200 ml), the combined organic layers were washed with brine (300 ml), dried over MgSO$_4$ and the solvents were evaporated. HCOOH (200 ml) was then added to the residue at 0°C and the resulting mixture was stirred at RT for 3 h before all volatile materials were distilled off. The crude product was dissolved in Et$_2$O (150 ml) and successively washed with sat. NaHCO$_3$ (2x80 ml) and brine (80 ml), before the organic layer was dried over MgSO$_4$ and evaporated. The product was used in the next synthetic step without purification. Yield: 87.6% (41.04 g)

**1H-NMR** (300 MHz, CDCl$_3$): $\delta$ 9.79 (s, 1H), 8.19 (s, 1H), 7.39 (t, $J=8.7$ Hz, 1H), 7.23 (d, $J=6.3$ Hz, 2H), 4.16 (s, 2H), 3.08 (sept, 8.7 Hz, 2H)

The obtained 1H-NMR spectrum matches the reported one.$^{48}$
• 5-acetoxy-3-(2,6-diisopropylphenyl)-4,5-dihydrooxazol-3-ium perchlorate (162)\textsuperscript{48}

\[
\text{\includegraphics[width=0.2\textwidth]{image1.png}}
\]

161 (2.0 g, 8.1 mmol, 1.0 equiv.) was dissolved in Ac\textsubscript{2}O (8.1 ml) and 60\% HClO\textsubscript{4} (0.95 ml, 9.32 mmol, 1.15 equiv.) was slowly added at RT. The mixture was stirred overnight and the formation of a precipitate was observed. Et\textsubscript{2}O (40 ml) was introduced, the solid was filtered off, washed with Et\textsubscript{2}O (40 ml) and dried. No purification was needed. Yield: 83.6\% (1.97 g)

\textsuperscript{1}H-NMR (300 MHz, d\textsubscript{3}-ACN): δ 8.97 (m, 1H), 7.62 (m, 1H), 7.46 (d, J=8.7 Hz, 2H), 7.40 (dd, J=6.9, 3.1 Hz, 1H), 4.72 (ddd, J=14.9, 6.0, 3.1 Hz, 1H), 4.31 (ddd, J=14.9, 3.9, 1.3 Hz, 1H), 2.88 (m, 2H), 2.26 (s, 3H), 1.30 (m, 12H)

The obtained \textsuperscript{1}H-NMR spectrum matches the reported one.\textsuperscript{48}

• 3-(2,6-diisopropylphenyl)-1-(4-(1-(4-(2-hydroxymethyl)-5-methoxy-4-oxopyridin-1(4H)-yl)phenyl)cyclohexyl)phenyl)-1H-imidazol-3-ium perchlorate (163)

\[
\text{\includegraphics[width=0.2\textwidth]{image2.png}}
\]

To a solution of 155 (1.15 g, 2.843 mmol, 1.2 equiv.) in a mixture of MeOH in toluene (10 ml, 10\% v/v), 162 (923 mg, 2.37 mmol, 1.0 equiv.) was added and the mixture was stirred at RT overnight. The solvents were evaporated and toluene (10 ml) added. Then, 60\% HClO\textsubscript{4} (0.75 ml, 3 equiv.) was added and the mixture was stirred at 80\°C for 20 h. The solvent was evaporated and DCM (5 ml) added. 7M NH\textsubscript{3} in MeOH was added and the
precipitate was filtered off on Celite. The solvent was evaporated and the product purified by column chromatography (SiO₂, DCM:MeOH:NH₄OH 10:1:0.1). Yield: 45.6% (774 mg)

**¹H-NMR** (300 MHz, d₆-DMSO): δ 10.17 (s, 1H), 8.67 (s, 1H), 8.29 (s, 1H), 7.81 (d, J=8.4 Hz, 2H), 7.72 (d, J=8.7 Hz, 2H), 7.64 (t, J=7.8 Hz, 1H), 7.39 (d, J=8.7 Hz, 2H), 7.39 (d, J=8.7 Hz, 2H), 7.29 (d, J=8.1 Hz, 2H), 7.17 (s, 1H), 3.62 (s, 3H), 2.48 (m, 15H), 1.45 (m, 8H), 1.14 (dd, J=6.3, 6.3 Hz, 16H)

**¹³C-NMR** (300 MHz, d₆-DMSO): δ 172.0, 164.5, 150.1, 149.2, 148.0, 146.0, 142.1, 136.9, 132.8, 132.3, 131.2, 129.4, 127.7, 126.5, 125.4, 125.1, 124.0, 122.7, 56.6, 46.1, 36.5, 30.0, 28.6, 26.2, 24.7, 24.4, 23.1

- 3-(2,6-diisopropylphenyl)-1-(4-(1-(4-(2-formyl-5-methoxy-4-oxopyridin-1(4H)-yl)phenyl)cyclohexyl)phenyl)-1H-imidazol-3-ium perchlorate (164)

![Structural diagram](image)

To a solution of 163 (1.113 g, 1.56 mmol, 1.0 equiv.) in DCM (15 ml), BAIB (551 mg, 1.71 mmol, 1.1 equiv.) and TEMPO (25 mg, 0.156 mmol, 0.1 equiv.) were added and the mixture was stirred at RT overnight. The solvent was evaporated and the product purified by column chromatography (SiO₂, DCM:MeOH 40:1). Yield: 78.6% (878 mg)

**¹H-NMR** (300 MHz, CDCl₃): δ 9.57 (t, J=1.5 Hz, 1H), 9.39 (s, 1H), 8.21 (t, J=1.8 Hz, 1H), 7.76 (d, J=8.7 Hz, 2H), 7.54 - 7.42 (m, 7H), 7.26 (m, 5H), 7.17 (s, 1H), 6.83 (s, 1H), 3.67 (s, 3H), 2.32 (m, 7H), 1.94 (s, 2H), 1.55 (m, 8H), 1.13 (dd, J=9.3, 6.6 Hz, 15H)

**¹³C-NMR** (300 MHz, CDCl₃): δ 184.8, 174.0, 172.1, 151.9, 150.7, 150.5, 145.4, 139.8, 137.4, 135.7, 132.3, 130.3, 129.7, 129.2, 126.8, 126.2, 124.9, 124.3, 122.4, 117.6, 56.7, 46.6, 37.0, 28.9, 26.2, 24.5, 24.2, 22.9, 21.2
- Chloro(dimethyl sulfide)gold(I) (165)

\[
\begin{array}{c}
\text{Au} \\
\text{Cl} \\
\text{S}
\end{array}
\]

Me₂S (79 mg, 1.27 mmol, 1.0 equiv.) was added to the solution of HAuCl₄·3H₂O (500 mg, 1.27 mmol, 1.0 equiv.) in MeOH (2 ml). The resulting suspension was protected from light and stirred for 20 min. The product was filtered off and washed with MeOH. Yield: 93% (348 mg)

- (1-(2,6-diisopropylphenyl)-3-(4-(1-(4-formyl-5-methoxy-4-oxopyridin-1(4H)-yl)phenyl)cyclohexyl)phenyl)-2,3-dihydro-1H-imidazol-2-yl)silver (166)

\[
\begin{array}{c}
\text{N} \\
\text{A} \\
\text{g}
\end{array}
\]

Ag₂O (33 mg, 0.144 mmol, 1.0 equiv.) was added to a solution of 164 (103 mg, 0.144 mmol, 1.0 equiv.) in DCM (6 ml) and refluxed for 18 h. The complex was protected from light and subsequently used without purification.

**¹H-NMR (300 MHz, CDCl₃):** δ 9.36 (s, 1H), 7.71 (m, 3H), 7.61 - 7.51 (m, 9H), 7.26 (m, 5H), 7.05 (s, 1H), 3.70 (m, 1H), 3.45 (s, 3H), 2.40 (m, 7H), 1.75 (s, 1H), 1.55 (m, 7H), 1.25 - 1.15 (m, 16H)

**¹³C-NMR (300 MHz, CDCl₃):** δ 184.0, 171.9, 150.8, 150.3, 149.3, 145.9, 140.0, 137.4, 136.7, 131.0, 129.4, 127.0, 126.3, 125.1, 124.6, 124.1, 122.7, 57.6, 53.7, 46.7, 37.3, 28.6, 26.2, 24.8, 24.5, 23.0
• (1-(2,6-diisopropylphenyl)-3-(4-(1-(4-formyl-5-methoxy-4-oxopyridin-1(4H)-yl)phenyl)cyclohexyl)phenyl)-2,3-dihydro-1H-imidazol-2-yl)gold(I) chloride (167)

165 (43 mg, 0.144 mmol, 1.0 equiv.) was added to a solution of 166 in DCM and stirred at RT for 5 h. The product was protected from light and filtered through Celite. The complex was dissolved in a small amount of DCM and precipitated with the addition of n-hex. After a few minutes, the milky suspension formed a dark oil (crude: 124 mg).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 9.41 (s, 1H), 7.73 (m, 2H), 7.50 (m, 4H), 7.28 (m, 5H), 6.92 (s, 1H), 3.77 (s, 3H), 2.49 - 2.33 (m, 9H), 1.54 (m, 5H), 1.22 (m, 6H), 1.11 (d, J=6.6 Hz, 5H)

$^{13}$C-NMR (300 MHz, CDCl$_3$): $\delta$ 184.7, 172.0, 151.9, 150.7, 150.0, 146.0, 139.8, 137.4, 135.9, 133.9, 131.3, 129.4, 129.2, 126.8, 125.1, 124.6, 123.1, 117.7, 60.5, 56.9, 53.8, 46.6, 37.1, 28.7, 26.2, 24.7, 24.5, 23.2, 23.0, 21.2, 14.4
7. References


(6) In *Hydroformylation*; Wiley-VCH Verlag GmbH & Co. KGaA, 2016; pp 73–266.


8. Appendix

Figure 8.1 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of 134 (signals marked with an asterisk come from: 7.26 ppm - CHCl$_3$; 4.12 ppm, 2.05 ppm, 1.27 ppm - EtOAc).

Figure 8.2 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of 135 (signals marked with an asterisk come from: 7.26 ppm - CHCl$_3$; 4.12 ppm, 2.04 ppm, 1.26 ppm - EtOAc).
Figure 8.3 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of 137 (signals marked with an asterisk come from: 5.29 ppm - DCM).

Figure 8.4 $^{13}$C-NMR (300 MHz in CDCl$_3$) spectrum of 137.
Figure 8.5 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of **139** (signals marked with an asterisk come from: 4.22 ppm, 2.13 ppm, 1.35 ppm - EtOAc).

Figure 8.6 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of **145**.
Figure 8.7 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of 153 (signals marked with an asterisk come from: 3.71 ppm, 1.23 ppm - EtOAc' 1.43 ppm - water).

Figure 8.8 $^1$H-NMR (300 MHz in $d_6$-DMSO) spectrum of 154.
Figure 8.9 $^1$H-NMR (300 MHz in $d_6$-DMSO) spectrum of 155 (signals marked with an asterisk come from: 3.29 ppm - water; 2.49 ppm - DMSO).

Figure 8.10 $^1$H-NMR (300 MHz in $d_6$-DMSO) spectrum of 157 (signals marked with an asterisk come from: 3.33 ppm - water; 2.48 ppm - DMSO).
Figure 8.1 $^{13}$C-NMR (300 MHz in $d_6$-DMSO) spectrum of 157.

Figure 8.12 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of 160.
Figure 8.1 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of 161.

Figure 8.14 $^1$H-NMR (300 MHz in $d_3$-ACN) spectrum of 162.
**Figure 8.15** $^1$H-NMR (300 MHz in $d_6$-DMSO) spectrum of 163 (signals marked with an asterisk come from: 3.33 ppm - water)

**Figure 8.16** $^{13}$C-NMR (300 MHz in $d_6$-DMSO) spectrum of 163.
Figure 8.17 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of 164.

Figure 8.18 $^{13}$C-NMR (300 MHz in CDCl$_3$) spectrum of 164.
**Figure 8.19** $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of 166 (signals marked with an asterisk come from: 5.29 ppm - DCM).

**Figure 8.20** $^{13}$C-NMR (300 MHz in CDCl$_3$) spectrum of 166.
Figure 8.21 $^1$H-NMR (300 MHz in CDCl$_3$) spectrum of 167 (signals marked with an asterisk come from: 5.24 ppm - DCM; 4.06 ppm, 1.97 ppm - EtOAc).

Figure 8.22 $^{13}$C-NMR (300 MHz in CDCl$_3$) spectrum of 167.