Stockholm University

Multicomponent Catalytic Reactions

Theoretical and Experimental Studies

Martin Pauze

Doctoral Thesis in Organic Chemistry at Stockholm University, Sweden 2021

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Academic dissertation for the Degree of Doctor of Philosophy in Organic Chemistry at Stockholm University to be publicly defended on Tuesday 28 September 2021 at 10.00 in online via Zoom, public link is available at the department website.

Abstract

In this thesis, Density Functional Theory (DFT) methods have been applied to study the mechanisms of three different multicomponent organic reactions. Also, a new synthetic procedure for the preparation of quinolinium salts is presented, and its mechanism also studied by DFT calculations. The thesis summarizes the work realized in two universities, and is divided in the following way: The first part of the thesis concerns the development of an experimentally simple, but mechanistically complex, reaction for the formation of quaternary quinolinium salts catalyzed by palladium salts. This multicomponent process uses readily available propylamine and its derivatives as starting materials. Through DFT studies a mechanism through the activation of two aliphatic C-H bonds is proposed. The second part focuses on the mechanistic investigation of a three-components reaction, namely terminal alkynes, CO_2 and allylic chlorides, mediated by an *N*-heterocyclic carbene catalyst that yields propargylic esters. By DFT calculations, the rate-limiting step was identified to be the reaction between the carboxylated catalyst and the allylic chloride. Through DFT modelling, we were also able to understand the limitations of this reaction. The mechanism of a multicomponent reaction in which allylic alcohols are transformed into α-functionalized carbonyls was also investigated. The reaction relies on an umpolung strategy that enables to react enol intermediates with different nucleophiles. By DFT studies, a mechanism *via* enolonium intermediates is proposed, which provides an understanding of the selectivity of the reaction. The final chapter of the thesis deals with another multicomponent solvent-free reaction for synthesizing propargylamines catalyzed by manganese *via* a KA^2 coupling. DFT studies were undertaken and a mechanism *via* manganese phenylacetylide species is proposed.

Keywords: *C-H Activation, Quaternary Quinolinium, Organocatalyst, Transition Metal Catalyst, Umpolung Strategy, Multi-step Reactions, Mechanistic Investigation, Density Functional Theory.*

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“I am among those who think that science has great beauty”

Marie Curie

Abstract

In this thesis, Density Functional Theory (DFT) methods have been applied to study the mechanisms of three different multicomponent organic reactions. Also, a new synthetic procedure for the preparation of quinolinium salts is presented, and its mechanism also studied by DFT calculations. The thesis summarizes the work realized in two universities, and is divided in the following way: The first part of the thesis concerns the development of an experimentally simple, but mechanistically complex, reaction for the formation of quaternary quinolinium salts catalyzed by palladium salts. This multicomponent process uses readily available propylamine and its derivatives as starting materials. Through DFT studies a mechanism through the activation of two aliphatic C–H bonds is proposed. The second part focuses on the mechanistic investigation of a three-components reaction, namely terminal alkynes, CO_2 and allylic chlorides, mediated by an *N*-heterocyclic carbene catalyst that yields propargylic esters. By DFT calculations, the rate-limiting step was identified to be the reaction between the carboxylated catalyst and the allylic chloride. Through DFT modelling, we were also able to understand the limitations of this reaction. The mechanism of a multicomponent reaction in which allylic alcohols are transformed into α-functionalized carbonyls was also investigated. The reaction relies on an umpolung strategy that enables to react enol intermediates with different nucleophiles. By DFT studies, a mechanism *via* enolonium intermediates is proposed, which provides an understanding of the selectivity of the reaction. The final chapter of the thesis deals with another multicomponent solvent-free reaction for synthesizing propargylamines catalyzed by manganese *via* a KA^2 coupling. DFT studies were undertaken and a mechanism *via* manganese phenylacetylide species is proposed.

Populärvetenskaplig sammanfattning

Upptäckten av nya kemiska processer för att få tillgång till organiska molekyler är av stor betydelse för vårt samhälle. Läkemedel är oftast organiska föreningar, så även jordbrukskemikalier och andra material. En stor utmaning som organiska kemister står inför idag är dock att utveckla nya metoder som är effektiva, minimerar avfall, och följer principerna för grön kemi. För att ta itu med några av dessa utmaningar i modern organisk syntes är det viktigt att få tillgång till reaktionsmekanismer. Att förstå hur en kemisk reaktion sker ner på molekylär nivå gör det möjligt att förbättra den kemiska processen.

Denna avhandling fokuserar på användningen av teoretiska verktyg, särskilt densitetsfunktionsteori, för studier av tre nya kemiska reaktioner som ger tillgång till organiska molekyler. En viktig aspekt i denna forskning har varit förståelsen av två olika metoder som gör det möjligt att invertera den normala reaktiviteten hos vissa kemikalier, känt som *umpolung* kemi. En annan typ av kemisk reaktion som har studerats i detta arbete ger tillgång till komplexa organiska cykliska molekyler genom att uppnå en selektiv funktionalisering av kol-vätebindningar. Dessa metoder är effektiva för syntes av många funktionella föreningar och har potential att användas för framställning av mer komplexa material.

List of abbreviations

Abbreviations and acronyms are in agreement with standards in the field, following the ACS abbreviations and acronyms in the 2016 guidelines for authors (http://pubsapp.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf). Common abbreviations in this report and other non-conventional abbreviations are listed below:

A^3	aldehyde-alkyne-amine reaction
CMD	Concerted Metalation Deprotonation
DFT	Density Functional Theory
DG	Directing Group
IRC	Intrinsic Reaction Coordinate
KA^2	ketone-alkyne-amine reaction
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
SET	Single Electron Transfer
TBAF	Tetra-*n*-Butyl Ammonium Fluoride
TFE	2,2,2-Trifluoroethanol
TLC	Thin Layer Chromatography
TS	Transition State

List of publications

This thesis is based on the following publications. The authors' contribution to each publication is clarified in a contribution list in Appendix B.

I. **Cascade C–H activation for the synthesis of quaternary quinolinium salts from propylamine and its derivatives.**
Martin Pauze, Enrique Gómez-Bengoa
Manuscript in preparation.

II. **Unprecedented Multicomponent Organocatalytic Synthesis of Propargylic Esters via CO_2 Activation.**
Argyro T. Papastavrou, Martin Pauze, Enrique Gómez-Bengoa and Georgios C. Vougioukalakis
ChemCatChem **2019**, *11*, 5379

III. **An Umpolung Strategy to React Catalytic Enols with Nucleophiles**
Amparo Sanz-Marco, Samuel Martinez-Erro, Martin Pauze, Enrique Gómez-Bengoa and Belén Martín-Matute
Nature Communications **2019**, *10*, 5244

IV. **Manganese-Catalyzed Multicomponent Synthesis of Tetrasubstituted Propargylamines: System Development and Theoretical Study**
Stavros P Neofotistos, Nikolaos V Tzouras, Martin Pauze, Enrique Gómez-Bengoa, Georgios C Vougioukalakis
Advanced Synthesis & Catalysis **2020**, *362*, 3872-3885

Other documents based on this work

The content of this thesis builds partly upon the author´s half-time report, presented on the 24th of November 2020. Chapters III and IV have now been updated. Chapter II and Chapter V are presented in this thesis for the first time.

This thesis summarizes the work performed at the University of Basque Country and at Stockholm University as part of the multi-partner Marie Sklodovska Curie Actions (MSCA) Innovative Training Network (ITN) European Joint Doctorate (EJD) "Catalytic Methods for Sustainable Synthesis. A Merged Experimental and Computational Approach" (CATMEC). Within this program, I aim to obtain a double PhD degree, from Stockholm University, Sweden, and from the University of Basque Country, Spain. Therefore, the content of this thesis will be used to a PhD degree from each university. The thesis at Stockholm University will be published the 07th of September 2021 and the thesis will be deposit at the University of Basque Country in September 2021.

Table of Contents

Abstract i
Populärvetenskaplig sammanfattning ii
List of abbreviations iii
List of publications iv
Other documents based on this work v
I Introduction 1
I.1 Catalysis in organic chemistry 1
I.1.1 Catalysis and catalytic reactions 1
I.1.2 Transition metal catalysis 1
I.1.3 NHC catalysis 2
I.2 Umpolung reactivity 4
I.2.1 Hypervalent Iodine 5
I.2.2 CO_2 Activation by NHC 6
I.3 C_{sp^2}–H and C_{sp^3}–H activations by transition metals 7
I.3.1 Mechanisms of C–H bond activations 7
I.3.2 Directing groups for C–H activation 8
I.3.3 C_{sp^3}–H activation of aliphatic amines 10
I.4 A^3 coupling and KA^2 coupling reactions 11
I.5 Density functional theory for mechanistic investigations 13
I.5.1 Principles of density functional theory and functionals construction 13
I.5.2 Basis sets 14
I.5.3 Solvation model 14
I.5.4 Functionals and basis sets selected in the thesis 15
I.6 Objective of the thesis 16
II Synthesis of substituted alkyl quinoliniums from propylamine and its derivatives (Paper I) 17
II.1 Introduction 17
II.2 Preliminary work and structure determination 19
II.3 Optimization of the reaction conditions 23
II.4 Scope 26
II.4.1 Substrate scope: 26
II.4.2 Scope of the reaction 26
II.4.3 Propylamine as substrate: 28
II.5 Mechanistic investigation 30
II.6 Conclusion 37
III NHC-catalyzed synthesis of propargylic esters with CO_2 capture (Paper II) 38

III.1 Introduction 38
III.2 Experimental results and scope of the reaction 39
III.3 Mechanistic studies 41
III.3.1 Proposed mechanism 41
III.3.2 Methodology for computational investigations 41
III.3.3 Results and discussion 42
III.4 Conclusion 45
IV Reaction of Catalytic Enols with Nucleophiles (Paper III) 46
IV.1 Introduction 46
IV.2 Experimental results and scope of the reaction 47
IV.3 Mechanistic studies 49
IV.3.1 Method and model selection 49
IV.3.2 Intermolecular reactivity mechanism 50
IV.3.3 Intramolecular reactivity mechanism 51
IV.4 Conclusion 52
V Theoretical study of manganese-catalyzed synthesis of propargylamines (Paper IV) 53
V.1 Introduction 53
V.2 Scope of reaction 54
V.3 Mechanism study 55
V.4 Conclusion 56
VI Concluding remarks 57
Acknowledgements 58
Appendix A. Author contribution: 59
Appendix B. Reprint Permissions 60
References 61

I Introduction

I.1 Catalysis in organic chemistry

I.1.1 Catalysis and catalytic reactions

The rate of a reaction depends on various chemical and physical factors (pressure, solvent, stirring conditions, etc.). When those factors are fixed, the rate of reaction relies on the concentration of the reactants and on the energy given to the system, experimentally evaluated by the temperature. Every reaction has an activation energy, which represents a barrier that needs to be overcome in order for the reaction to happen, and to obtain the product. A catalytic reaction is characterized by a lower energy of activation compared to that of the reaction in the absence of the catalyst. A catalyst is a species that increases the reaction rate by lowering the activation energy.[1] Because the energy of activation is lower with catalyst and the entities involved can be different, catalytic reactions may follow pathways that are very different from those of their uncatalyzed reactions. Other characteristic is that the catalyst is not consumed during the reaction.

Catalysis can be divided into three main categories, homogeneous, heterogeneous and bio-catalysis. In homogeneous catalysis, all the components are soluble in the reaction media. One of the main sub-groups in this category is the catalysis mediated by transition metal complexes, where the metal is usually coordinated by anions or neutral ligands.[2] An example can be the Hoveyda-Grubbs catalyst for metathesis reactions.[3] Another important sub-group in homogeneous catalysis is that involving organocatalysts, which are small organic molecules used in processes.[4] An example could be the secondary amines used in Knoevenagel reaction.[5] Heterogeneous catalysts are not soluble in the reaction media (e.g. liquid media) and the physical interactions (adsorption, diffusion, etc…) between the reagents and the catalyst play a key role. The last type of catalysts, at the frontier between organic chemistry and biochemistry, are the enzymes, which catalyse a major part of the reactions needed for life and are becoming of common use in the chemical industry.[6]

I.1.2 Transition metal catalysis

Transition metals are elements that form one or more stable cations with incomplete *d* orbitals.[1] These elements form the *d*-block of the periodic table, including groups 3 to 12 (Figure 1). Interestingly, one of the main particularities of the transition metals is the ability to exhibit a range of possible oxidation states. All of them have at least two different positive states of oxidation.

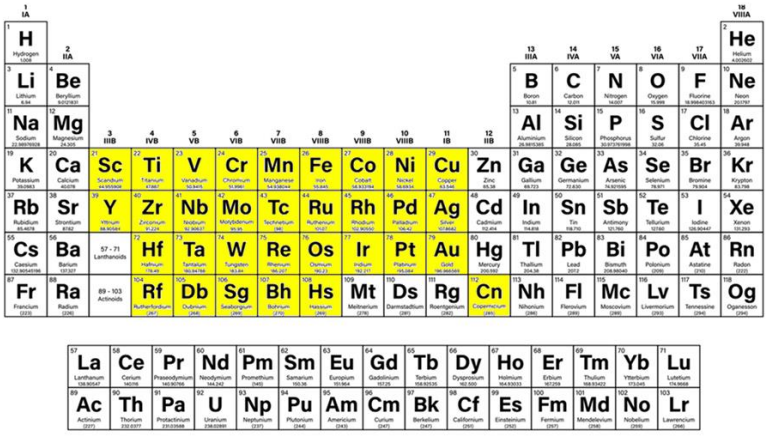


Figure 1. Transition metals (in yellow) on the periodic table

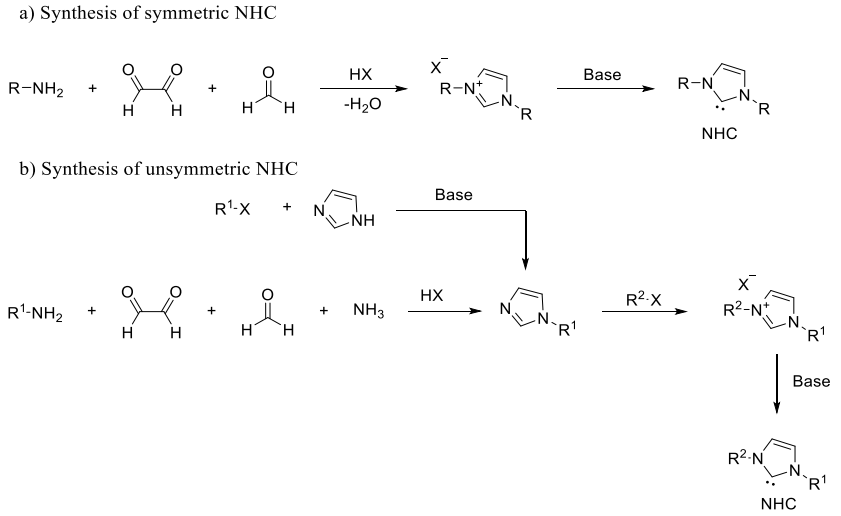
In recent years, transition metals have fulfilled an important role in the synthesis of organic compounds. Numerous organic transformations need transition metals, as it happens for example in the family of cross-coupling and related reactions. Mizoroki-Heck,[7] Suzuki-Miyaura[8] or Buchwald-Hartwig[9] coupling reactions are widely used in academia and in industry.

There are two major drawbacks for the general use of transition metals in synthetic chemistry. The first one is related to the supply chain. Noble metals are not abundant and others, like cobalt, are produced in socially and politically unstable countries. The second problem is toxicity, which can be of great concern for an industrial use.

I.1.3 NHC catalysis

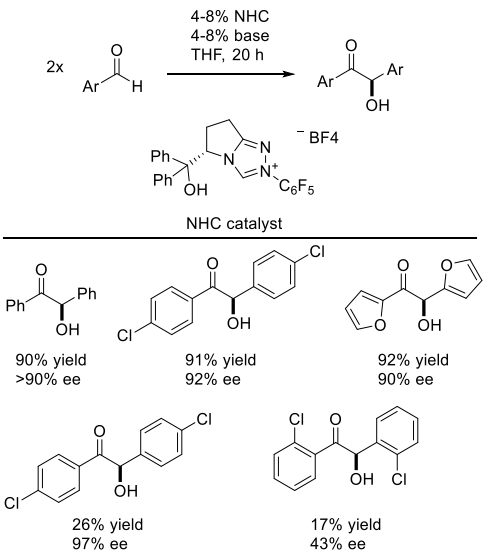
N-Heterocyclic carbenes (NHCs) are organic molecules used in a wide range of applications, and they can also function as organocatalysts. The first evidence of the existence of *N*-heterocyclic carbenes was provided during the 50's, but the first stable and isolable ones were developed by Arduengo and co-workers in 1991.[10] NHCs serve as ligands for organometallic complexes[11] as well as catalysts in their own right, more prominently as nucleophilic species in umpolung chemistry,[12] but also as Brønsted bases in organic transformations.[13]

Many NHCs are readily accessible and even commercially available, mainly from imidazolonium salts upon deprotonation with a base (Scheme 1).[14,15] They allow a rapid development of new synthetic methodologies, giving access to a wide range of structures. The introduction of chirality in the carbenes has also been exploited for the asymmetric construction of organic molecules.[16]



Scheme 1. Two different strategies to synthesize NHCs

An example of a reaction involving an NHC catalyst is the benzoin condensation reaction, where two aldehydes react together to form α-hydroxy ketones (Scheme 2), important intermediates in the synthesis of bioactive molecules. These processes show in general high yields and high enantiomeric excess.[17]



Scheme 2. Synthesis of α-hydroxy ketones in high yields and with enantiomeric excess.[18]

In addition, the use of carbenes has been expanded to other related reactions, like cross benzoin condensations, cross aza-benzoin reactions, and the Stetter reaction.[19] It has to be noticed that a base is necessary to *in situ* generate the catalyst and initiate the reaction. The base is used in the same amount as the catalyst, and its strength can vary from mild

bases (such as carbonate salts and tertiary amines) to stronger ones, such as potassium *tert*-butoxide. For the last case, the scope can be limited due to the absence of orthogonality of reaction between the base and certain substituents, especially protecting groups.

The N-heterocyclic carbene family includes a sub-group called "non-classical carbenes". Their main characteristic is that they have a significantly lower heteroatom stabilization by adjacent heteroatoms (Figure 2).[20] Those non-classical carbenes recently discovered have been used mainly for complexation with metals (palladium, nickel, rhodium), with implications for C–C formation,[21] hydrogenation[22] and metathesis reactions.[23] A characteristic of non-classical NHCs is that they have less donor ability. Their complexes are less stable than those of classical NHC, widening the scope of catalytic species.

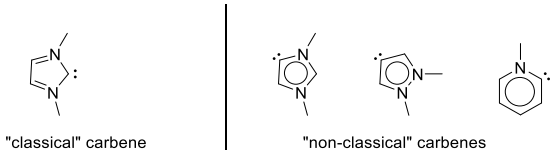
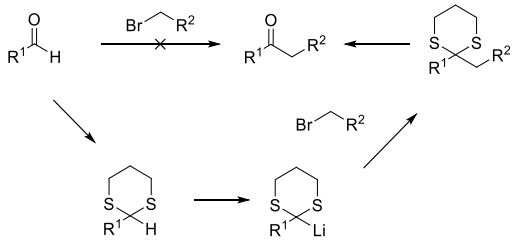


Figure 2. Examples of classical and non-classical carbenes

I.2 Umpolung reactivity

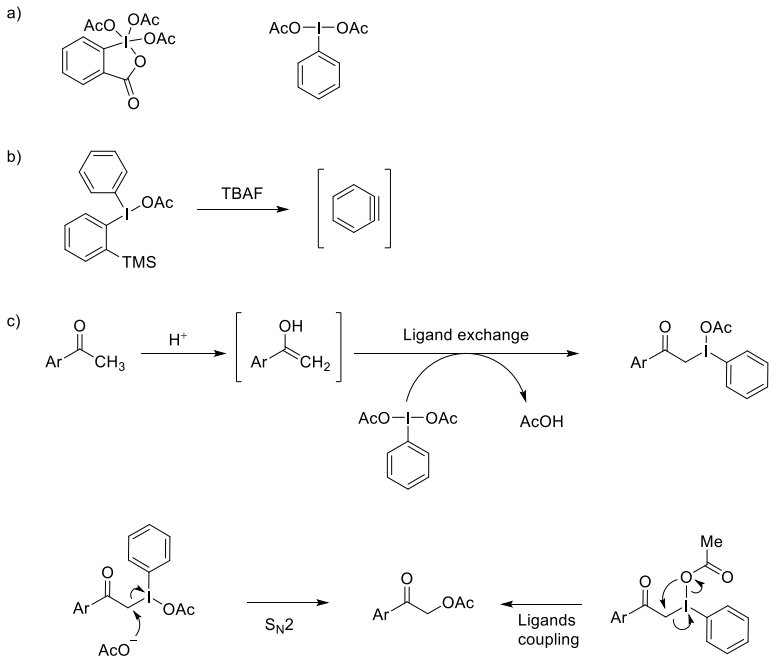
The principle of umpolung is the inversion of the natural reactivity of a synthon.[24] A major part of the reactivity in organic chemistry is based on the reaction between an electrophile and a nucleophile. According to this model, two entities with the same polarity (nucleophile-nucleophile, or electrophile-electrophile) would not react together. Umpolung is a process that allows this kind of reactivity to happen, by switching the polarity of one of the reagents. An example could be the reaction between an aldehyde and an alkyl bromide, which are both electrophilic by nature. However, reacting the aldehyde with 1,3-propanedithiol yields a thioketal, which can form a nucleophilic organolithium reagent. This species can then react with the electrophilic alkyl bromide, and after removal of the 1,3-propanedithiol, the ketone is obtained (Scheme 3).[25]



Scheme 3. Umpolung strategy to make aldehydes nucleophilic species.

I.2.1 Hypervalent Iodine

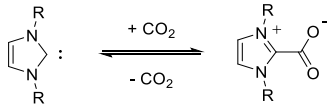
Polyvalent iodine compounds overpass the octet rule, providing specific reactivity. Those compounds are built around iodine atoms with an oxidation state of III or V, and they can be cyclic. They have three main types of applications. The first one is as oxidation reagents, such as the Dess-Martin periodinane (Scheme 4a), used for the mild oxidation of alcohols, or (diacetoxyiodo)benzene (PIDA) commonly used for reoxidizing transition metal catalysts.[26] A second usage is as reagents for organic synthesis.[27] For example, they are precursors of benzyne, which can be produced *in-situ* with fluorine donor reagents (Scheme 4b).[28] Finally, hypervalent iodine reagents can also work as umpolung reagents. The electrophilicity of the iodine atom allows access to electrophilic synthons starting from nucleophiles,[29,30] due to their capacity to induce ligand exchange, reductive eliminations or ligand couplings.[31] For example, Ochiai's group reported the α-acetylation of ketones with iodobenzene diacetate.[32] After formation of the enolate, a ligand exchange happens with the hypervalent iodine reagent, followed by either a S_N2 reaction with the acetate anion or either an intramolecular ligands exchange to form the desired product and iodobenzene, which could be then reoxidized and used in catalytic amount (Scheme 4c).



Scheme 4. a) Hypervalent reagents used as oxidants. b) Precursor of aryne. c) Example of an umpolung reaction mediated by PIDA.

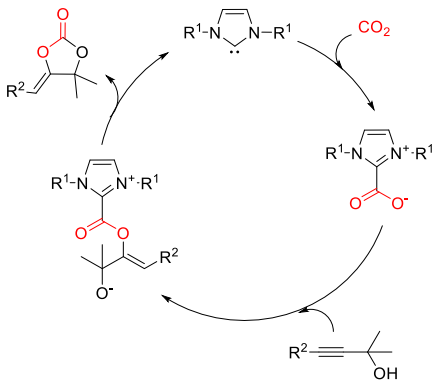
I.2.2 CO_2 Activation by NHC

As previously shown, NHCs are nucleophilic entities, and are able to react with carbon dioxide to form imidazole-2-carboxylates. The first example of this adduct was reported by the Kuhn group, from a preformed NHC.[33] The NHC–CO_2 adduct has a relative low stability, because CO_2 can be released if the adduct is heated above 100 °C. The NHC-CO_2 adduct can be used as a precursor of NHCs, or it can be used as a temporary carrier of CO_2 (Scheme 5).



Scheme 5. Synthesis of NHC-CO_2 adduct.

The NHC-CO_2 adduct is a neutral zwitterionic species, where the carboxylate holds a formal negative charge. CO_2 is normally a kinetically stable, weak electrophile; it can react only with strong nucleophiles, like phenylmagnesium bromide, forming benzoic acid in this case. After formation of the NHC-CO_2 adduct, due to the negative charge at the oxygen atom, the CO_2 molecule can act as a nucleophile. This fact enriches and expands enormously the reactivity of carbon dioxide, like in the formation of cyclic carbonates by reaction between NHC-CO_2 adducts and propargylic alcohols.[34] The carboxylate group of the adduct attacks the alkyne, and the carbanion then deprotonates the alcohol. The catalytic cycle is closed after a cyclization step, releasing the NHC catalyst (Scheme 6).



Scheme 6. Mechanism of the synthesis of cyclic carbonates *via* NHC-CO_2 adducts.[35]

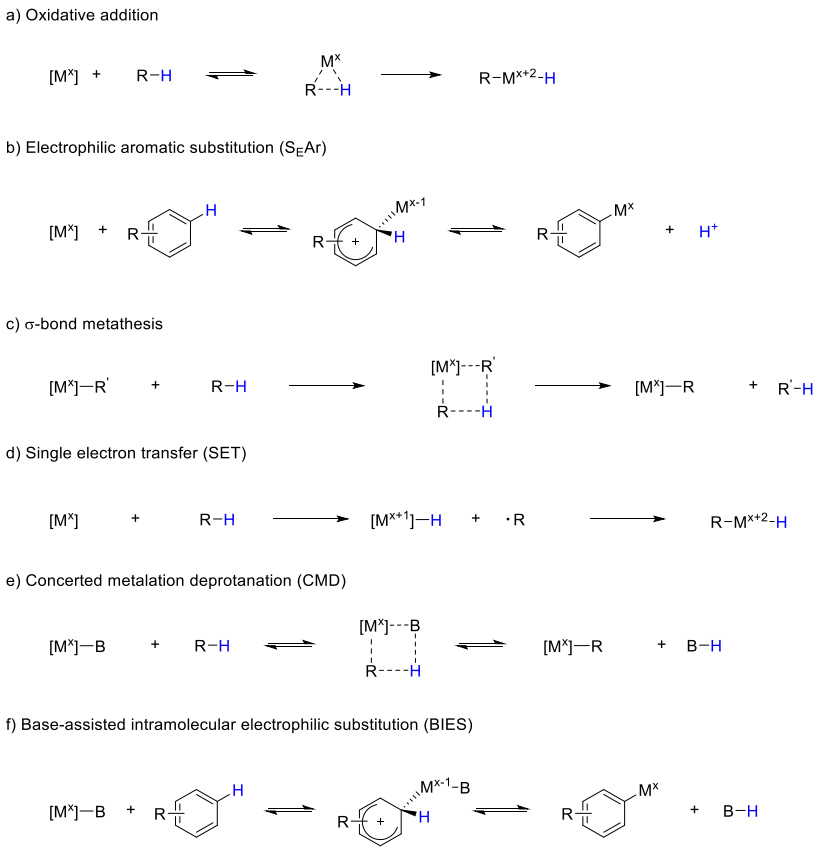
I.3 C_{sp^2}–H and C_{sp^3}–H activations by transition metals

I.3.1 Mechanisms of C–H bond activations

Unrelated to any functional groups, C–H bonds have low intrinsic reactivity.[36] The energy barrier to cleave them is so high that, without harsh chemical conditions (high temperature, strong bases or acids), uncatalyzed reactions are unlikely to happen. However, some reactions as difficult as the C–H bond activation of methane to form methanol have been achieved, like in the platinum catalyzed process reported by Shilov.[37] And, in past decades, an abundant literature has been developed.[38] Due to the potential for atom economy and shorter synthetic paths, important research efforts have been dedicated to seek catalysts and potential substrates for attainable C–H activation processes.

In the case of transition metal catalyzed C–H activations, different mechanisms have been proposed. Among them, one of the fundamental variants is the oxidative addition to the C–H bond, forming a metal hydride and increasing the oxidation state of the metal atom (Scheme 8a); other mechanisms involve electrophilic aromatic substitution (S_EAr) (Scheme 7b); σ-bond metathesis (Scheme 7c); or single-electron transfer (SET) with radical intermediates (Scheme 7e).

More closely related to our work, two other approaches have recently appeared. First, the concerted metalation deprotonation (CMD), where the formation of the carbon-metal bond and the cleavage of the C–H bond are concerted. The proton departure is assisted by a base, in a single elementary step. The electropositivity of the metal, while approaching the carbon, increases the acidity of the proton. CMD is one of the most proposed mechanisms for palladium C–H activation (Scheme 7e). On the other hand, the base-assisted intramolecular electrophilic substitution (BIES), is a mechanism with two elementary steps, where the metal first coordinates with the carbon and then the proton is removed by the base (Scheme 7f). The bases involved in both mechanism are commonly carboxylates, carbonate, amide or phosphine oxide.[39,40]



Scheme 7. Mechanisms of C–H activations by transition metals.

I.3.2 Directing groups for C–H activation

A great interest of C-H activation is the possibility of controlling the regioselectivity. This is achieved by the introduction of directing groups (DG). When using Pd complexes, once the C–H bond is cleaved, a palladacycle is formed. The size of the cycle may vary from three to ten atoms, although the most stable ones are the five- and six-membered rings.[41] Many of these metallacycles have been isolated.[42–44] Thus, the position of the directing group on the molecule dictates the position of the C–H bond that will be activated. For palladium, numerous types of functional groups can direct the activation. Those based on oxygen as the coordinating atom commonly include carboxylic acids (carboxylate form in the palladacycle), esters or alkoxides.[45] Among the family based on nitrogen as the coordinating group, amines, imines, oximes, amides, N-oxides and sulfamides have been reported.[46] A classification of the strength of those directing groups has been reported by Norrby and co-workers (Figure 3).[47]

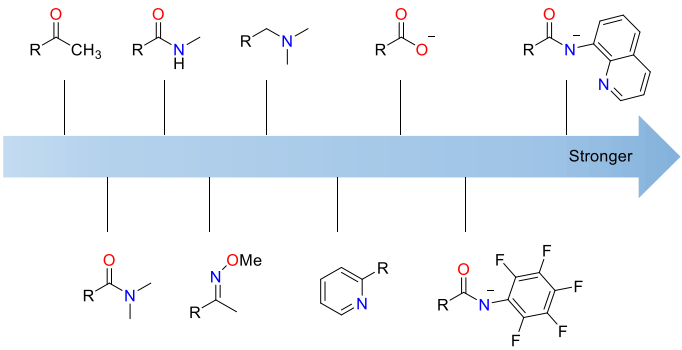
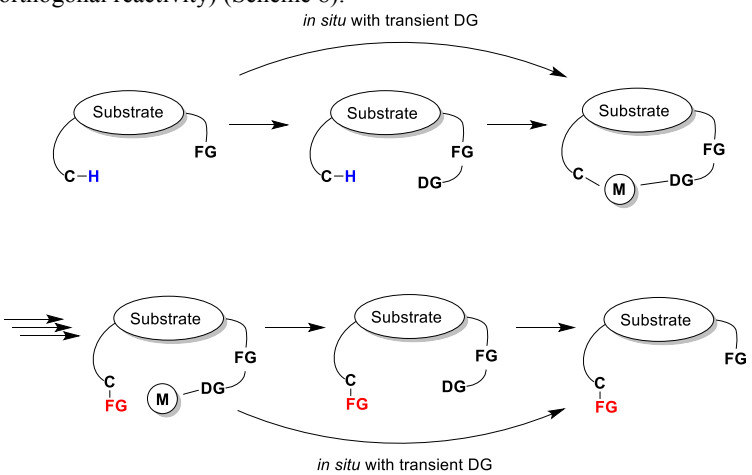


Figure 3. Qualitative scale of strength of selected directing groups.[47]

If the starting material contains a weak directing functional group, it can be modified to create a DG with the expected length. Then the metal can coordinate at the desired position and activate the desired C–H bond. Two categories exist, a functionality with a covalent link to the molecule, or with a removable link. The covalent linked one's can be, for example, of an amide made from the carboxylic acid and amines, such as 8-aminoquinoline, picolinamide[48] or sulfamide. In these cases, the substrate and the metal can proceed to the activation with harsher conditions thanks to a stable DG. This type of directing group can be challenging if the desired functional group do not have and orthogonal reactivity with the other ones (if other functional groups can react in the same reaction conditions for setting or removing the DG). On the other hand, the second category are the, so called, transient directing groups. They are incorporated in the molecule *in situ* upon reaction with a functionality already present in the molecule. As before, the aim is to generate the DG with the wanted characteristics (strong chelating ability and regioselectivity).

To have a good transient DG, the following criteria need to be fulfilled: a) the introduction of the DG has to be reversible, b) the formation should be chemo-selective, and c) they should be stable enough to allow the C–H activation and the subsequent transformations. It is also necessary that the DG do not interact with other functional groups (orthogonal reactivity) (Scheme 8).

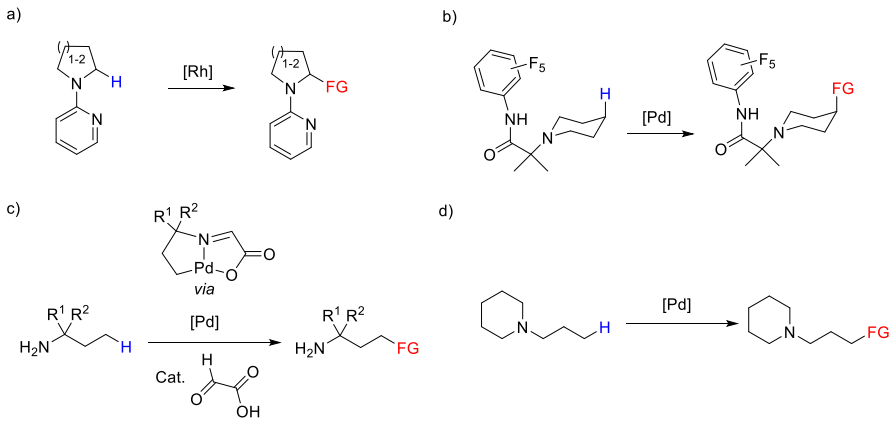


Scheme 8. Strategy for incorporation of directing group.

I.3.3 C_{sp^3}–H activation of aliphatic amines

C–H activation is a great synthetic strategy to reach new potential drugs. Nitrogen containing molecules are prevalent in bioactive compounds, methods towards the C–H activation of aliphatic amines have recently emerged. Those methods represent a powerful synthetic strategy, especially for late stage functionalization.[49] The number of such valuable reactions keeps continuously growing. However, universal methods for activating any position of the alkyl chains of an aliphatic amine do not exist. Therefore, inventive and convenient procedures have been developed to suit with the different constraints of the substrates for achieving the reaction.[50]

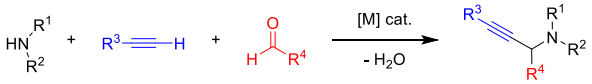
The most popular approach to reach C–H activation of amines is the use of a directing group. For example, the group of Maes reported the use of a pyridine moiety to activate the α-position of piperidines (Scheme 9a).[51] Also, the γ-position of alicyclic amines has been activated by the Sandford group with an innovative directing group (Scheme 9b).[52] The Ge group succeeded in the selective γ-functionalization of polysubstitued aliphatic amines with glyoxylic acid as transient directing group (Scheme 9c).[44] Methods with no directing group added exist, but only with secondary/tertiary amines or in the presence of protective groups on the nitrogen (Scheme 9d).[53] So far, the C–H activation of free amines, with no additional directing groups, remains a challenge.



Scheme 9. Examples of functionalization of aliphatic amines through C–H activation.[44,45,52,53]

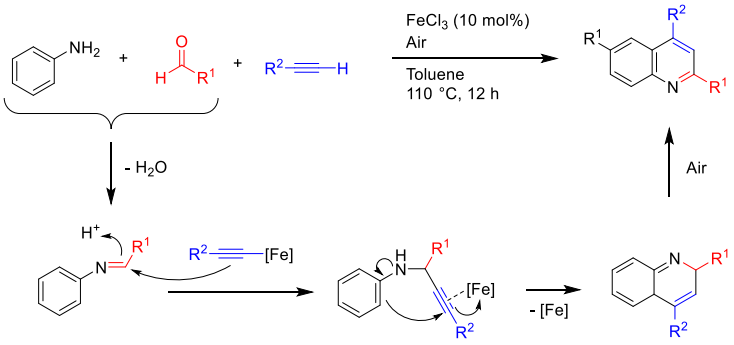
I.4 A^3 coupling and KA^2 coupling reactions

A^3 stands for Aldehyde-Alkyne-Amine reaction, a multicomponent synthesis of propargylamines (Scheme 10), with water as by-product. This denomination was first proposed by Li,[54] but the first reaction of this type was reported by Dax and co-workers.[55] The reaction needs a metal catalyst, and several transition metal complexes have been reported to mediate this transformation.[56] The most common are copper, ruthenium, gold or even silver.[57,58] Recently, more earth abundant metals are also able to catalyze the reaction, such as zinc, or iron.[59]



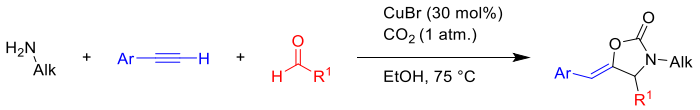
Scheme 10. General A^3 coupling reaction.

Propargylamines prepared through this method may be reacted further towards the synthesis of more complex molecules. An example is the synthesis of quinoline by Tu and co-workers.[60] They reacted the three components, aniline, aldehyde and terminal alkylne, in the presence of an iron salt. The same catalyst mediated the nucleophilic functionalization of the triple bond, resulting in a cyclization, which is followed by a final oxidation by air (Scheme 11).



Scheme 11. Synthesis of quinolines by tandem A^3 / cyclization reaction reactions.

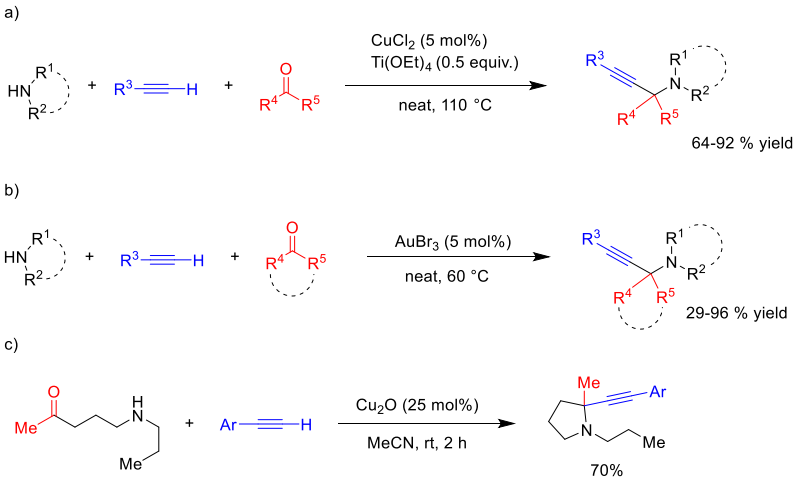
Another modified version was reported by Li and co-workers,[61] consisting on performing the A^3 reaction in the presence of CO_2 (1 atm), resulting in the synthesis of carbamates in a one-pot reaction. The catalyst used was CuBr (Scheme 12).



Scheme 12. Modified A^3 coupling reaction for the synthesis of carbamates.

The KA^2 coupling stands for Ketone, Alkyne and Amine coupling, and affords fully α-substituted propargylamines.[62] Changing the aldehydes to ketones have an impact on the reaction rate, as ketimines, the intermediates formed in this instance, are less reactive than aldimines. Despite these difficulties, several examples of KA^2 couplings have been reported, also mediated by transition metal catalysts.

An example of KA^2 reaction is the one reported by Larsen and co-workers,[63] who used $CuCl_2$ as catalyst and $Ti(OEt)_4$ as Lewis acid, without solvent. The Lewis Acid is necessary to form the ketimine, and also acts as a dehydrating agent (Scheme 13a). Ji's group reported the first KA^2 catalyzed by gold ($AuBr_3$), also in neat conditions (Scheme 13b).[64] Intermolecular KA^2 reactions have also been reported. For example, Tehrani and co-workers reacted amino ketones with terminal alkynes under copper catalysis, yielding α-substituted pyrrolidines in good yield (Scheme 13d).[65]



Scheme 13. KA^2 coupling reactions. a) KA^2 coupling catalyzed by copper and Lewis acids. b) KA^2 reaction mediated by a gold catalyst. c) Cu-catalyzed intramolecular KA^2 reaction.

I.5 Density functional theory for mechanistic investigations

I.5.1 Principles of density functional theory and functionals construction

The Schrodinger equation (Equation 1)[66] describes the wave function of a quantum-mechanical system, where $\hat{H}$ is the time dependant Hamiltonian operator, ψ the wave function and *E* the total energy of the defined system.

$$\hat{H}\psi = E\psi$$

Equation 1. Schrodinger equation

In spite of its apparent simplicity, it is not possible to find a solution of the Schrödinger equation for systems containing two or more electrons, and some particular approximations and cases are required to describe multi-electronic systems.

Density Functional Theory (DFT) is one of the most commonly used computational approaches for the calculation of the energies and structures of complex chemical structures. The idea behind DFT is to use a different approach, describing the chemical systems based on their electron density function,[67] and not its wave function, providing an accurate answer in a reasonable time, without too much simplification.

The electron density is represented by a function, noted ρ, giving the probability of finding an electron in certain position of the space. This function ρ depends on three variables (x, y, z), while the wave function depends on 3*N* variables, where *N* is the number of electrons. This is the main advantage of DFT, to greatly reduce the complexity of the equation and the cost of computation.

Two theorems founded the grounds of DFT, and were stated by Hohenberg and Kohn[68]: 1) the ground state electronic energy can be calculated as a function of the electron density, and 2) the electron density follows the variational principle, thus the calculated electronic energy must be greater or equal to the true ground state value (Equation 2).

$$E(\rho) \geq E(\rho_{exact}) = E_{exact}$$

Equation 2. Mathematical description of the Hohenberg-Kohn theorems

From there, they showed that the energy can be calculated from the electron density functional (a mathematic object using electron density function), without explicitly giving the nature definition of the functional. Shortly after, as Kohn and Sham noticed,[69] if the system is considered with non-interacting electrons, the functional can be written as the sum of specific terms (Equation 3):

$$E(\rho) = T_{ni}(\rho) + V_{ne}(\rho) + V_{ee}(\rho) + E_{XC}(\rho)$$

$$\text{With: } E_{XC}(\rho) = \Delta T(\rho) + \Delta V_{ee}(\rho)$$

Equation 3. Composition of the total energy

$T_{ni}(\rho)$ is the kinetic energy of the non-interacting electrons, $V_{ne}(\rho)$ the potential energies due to nuclear-electron interaction and $V_{ee}(\rho)$ the term for the electron-electron repulsion. The exchange-correlation energy $E_{XC}(\rho)$ is composed by the correction to the kinetic energy due to electronic interactions $\Delta T(\rho)$ and the non-classical corrections to

the electron-electron repulsion energy $\Delta V_{ee}(\rho)$. Except the exchange-correlation energy, all the terms can be classically calculated.

This last term, the exchange-correlation energy cannot be exactly calculated. Therefore, functionals have been developed with different approximations of this term.[70] They can be ranked by their type of approximation and the accuracy associated. More complex functional leads to a better accuracy, accompanied at the same time by higher computational cost.

I.5.2 Basis sets

Basis sets in DFT are necessary in order to describe the shape of the different atomic orbitals, as are linear combinations of different functions. Two different types of functions exist. The Slater Type Orbitals, STO, and the Gaussian Type Orbitals, GTO. Whilst the STO are more accurate for the description of the orbitals, the GTO are used due to their simplicity and lower computational cost.

The number of functions per orbital is free to be set. A perfect basis set would have an infinite number of functions, but this is obviously impossible from a practical point of view. If a basis set contains one function per orbital, it is called minimum basis set. However, most of the basis set used contain more than one function. A basis set with two functions per orbital will be named double-zeta, with three triple-zeta, etc.

With the idea to have a lower computational cost without a high loss of accuracy, the number of function can differ between the core orbital and the valence orbitals. As bonds formation rely on the valence orbitals, more functions are used for a better description. This is called a split valence set.

Too take into account the polarization, when electronic charges are altering the shape of the orbitals, functions can be added too.

To describe more accurately the behaviour of the electrons far from the nucleus, diffusion functions can be added to the basis set. This is needed in case of ions or radicals for example.

I.5.3 Solvation model

Most of the chemical reactions are done in a solvent media, and the solvent is an important parameter of the reaction conditions. As the components of a given reaction interact differently with different solvents, the energy associated to the system can differ accordingly.

Two main approaches exist for the description of the solute/solvent interaction. The first one is the explicitly model, where molecules of solvent are surrounding the molecule. In DFT, the cost of this approach is too high to be used on system with 50-100 atoms.[67]

The second approach is the implicit model. The most used is the Polarized Continuum Model, PCM, where the system is placed in a cavity with a suitable shape.[71] The most important parameter of the PCM is the dielectric constant, than can be known by experimental or computational means. The free energy of solvation can be then calculated (Equation 4):

$$\Delta G_{sol} = \Delta G_{cav} + \Delta G_{disp} + \Delta G_{rep} + \Delta G_{elec}$$

Equation 4. Composition of the free energy of solvation

With ΔG_{cav} is the cavitation energy, it is the energy difference with and without the cavity in the continuum. ΔG_{disp} is the dispersion energy between solute and solvent, ΔG_{rep} represents the repulsion between solute and solvent and ΔG_{elec} is the term for the electrostatic polarization caused by the charge distribution of the solute molecules in the solvent, or the opposite.

I.5.4 Functionals and basis sets selected in the thesis

In the second chapter, the B97D functional was used for optimization of the different structures. It is an adequate method for the calculation of structures containing palladium.[72] Also, the 6-311G(d,p) basis set was used, known to be cost effective and providing accurate geometries. M06/Def2TZVPP were used together for energy refinement. Considering the physical interactions between atoms, the accuracy is much higher with Def2TZVPP,[73] set although presenting the drawback of an increase in the calculation time, becoming not applicable for iterative geometry optimizations. Iodine and palladium are not defined in the Pople basis set 6-311G, but an appropriate alternative exist, known as the SDD basis set. Both atoms are defined within the Def2TZVPP basis set.

In the third chapter, M06-2X and 6-31G(d,p) were used for geometry optimization as functional and basis set, respectively. Recent literature examples also use this pair for the study or pure organic reactions,[74] and in addition, it has been demonstrated that they perform well in cases involving zwitterionic species and halogen-ions.[75]

In the fourth chapter, the study was done with using the B97D functional for the structure optimizations, together with the 6-31G(d,p) basis sets for all the atoms.

I.6 Objective of the thesis

The aims of the thesis are the development of efficient methods for the formation of complex molecules from simple and easily accessible materials. The thesis is divided into four independent projects with different inherent objectives.

The first project (Chapter II) reports a new synthetic method to produce alkylated quinoliniums, as molecules of high value, which are prepared from simple propylamine and its derivatives. In addition, the focus was put on the comprehension of the mechanism for further development.

The second project (Chapter III) focuses on the comprehension of an organocatalytic reaction that yields propargylic esters from simple reagents, as alcohols, carbon dioxide and propargyl halides. The study by DFT aims to give a clear view of the mechanism, and to try to explain certain intriguing reactivity in some cases. Also, the aim was to understand the limitation of the scope and highlight the possible incompatibilities between the different reagents.

The third project (Chapter IV) has for objective to understand how hypervalent iodine enables the reaction of two nucleophiles, an enolate and an alcohol, *via* an umpolung reaction. The enolate is generated under the reaction conditions from allylic alcohols *via* an iridium-catalyzed isomerization. A second objective is to understand the selectivity obtained when there exist two different nucleophiles that may react with the enolate produced *via* isomerization.

The last project (Chapter V), used the experimental result of a KA2 coupling reaction, in order to understand the mechanism. For the first time, manganese is used as a catalyst for this reaction, therefore, it is interesting to study his role. To proceed, DFT calculations were used.

II Synthesis of substituted alkyl quinoliniums from propylamine and its derivatives (Paper I)

II.1 Introduction

Quinoliniums and quinolines represent an important class of molecules with strategic applications in many fields of chemistry. Looking to their bioactivity, they are found in antiviral, antibacterial, analgesic, and antidepressant drugs.[76] Well-known molecules such as quinine are emblematic in organic chemistry, and its derivatives are essential for anti-malarial treatments. Quinoliniums are used as tools in biology as DNA dyes and intercalants. They are essential for studies of cells and their environment, and in flow cytometry the main known dye is thiazole orange. Other applications in chromatography have been reported (Figure 4).[77]

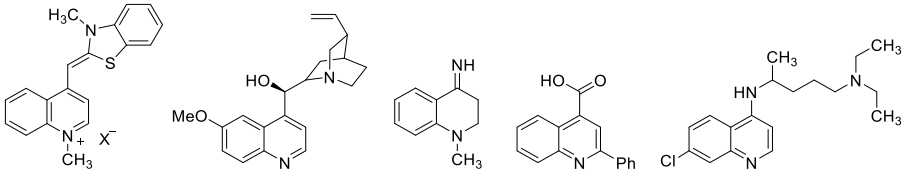
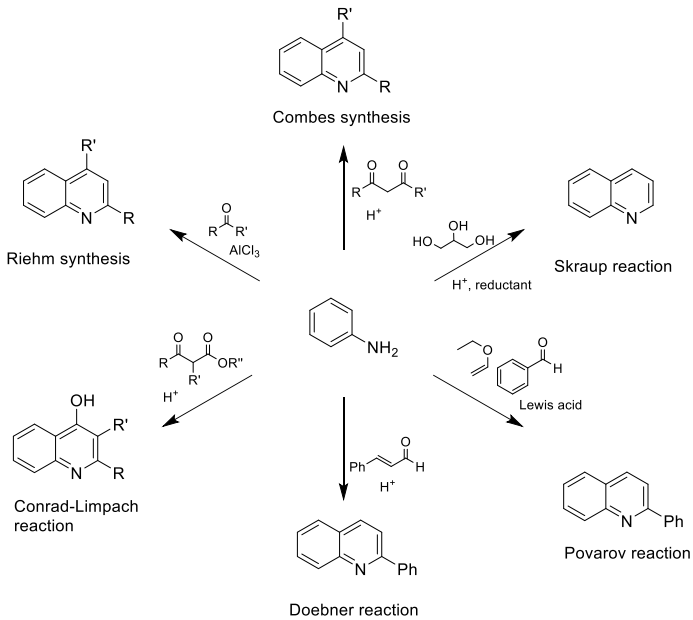


Figure 4. Examples of high-value molecules with quinoline scaffolds.

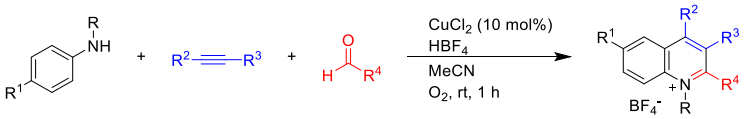
New methods for the synthesis of quinolines are continuously reported, and some of them are part of the most well-known reactions in organic chemistry. However, those syntheses, with few exceptions, need C_{sp^2}-N bond containing starting material, in the form of substituted anilines or nitrobenzenes. For example, the Combes synthesis needs anilines with 1,3-diketone and acid as catalyst to render the quinoline.[78] The drawback of this simplicity is the difficulty to reach regioselectivity. Regioselectivity can be achieved by using steric effects and kinetics, but the scope is meanwhile reduced.

To obtain the desired structure of quinoline, the development of methodologies has been prolific during the last decades.[79] However, the complexity of the starting materials needed for those transformations may be high, and incompatibilities may exist with the desired substituents on the final molecule (Scheme 14).



Scheme 14. Classical synthetic routes to form quinolines from aniline

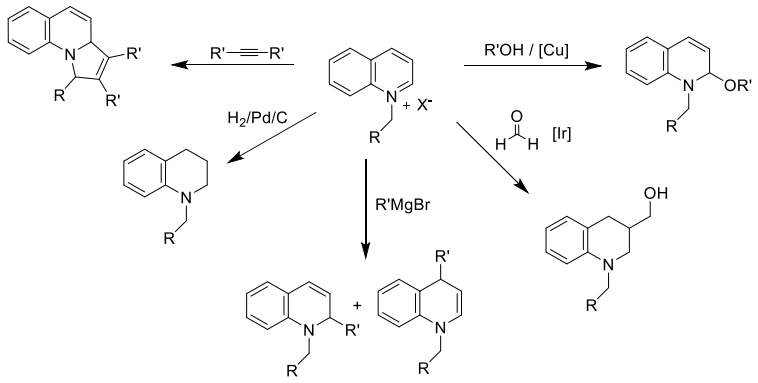
Most of the quaternary quinolinium species are synthetized from quinolines through alkylation with halogenated building blocks. For the direct preparation of quinolinium salts, only few examples are reported. One method was developed by L. Cheng *et al*.,[80] using *N*-substituted anilines, aldehydes and alkynes, in a reaction catalyzed by copper (scheme 15).



Scheme 15. Three components reaction for the synthesis of substituted quinolinium salts.

In addition to the mentioned applications of the quinolinium compounds, they can be used also as intermediates for the synthesis of complex molecules. For example, positions 2 and 4 become electrophilic, and can react with strong nucleophiles such as Grignard reagents.[81]

Quinolinium salts can also be hydrogenated to yield the tetrahydroquinoline skeleton. Further, methods have been recently developed for the formation of functionalized tetrahydro/dihydro-quinolines (Scheme 16).[82,83]

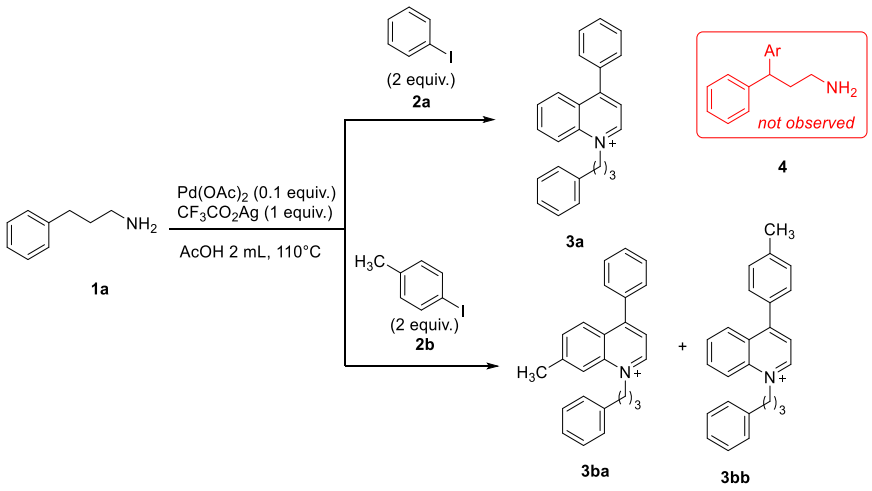


Scheme 16. Examples of possible reactions from quinolinium salts.

The aim of this project is to access to quinoline scaffolds from arylpropylamines, in one step. As the majority of synthetic routes to quinolines use aniline as starting material, our method offers an alternative approach to access their cyclic structure, forming the key Ar-N bond from open aliphatic amines. In addition, the control of the substitution pattern is important to provide a reliable transformation. The introduction of an alkyl quinolinium moiety offers diverse possibilities of further transformations.

II.2 Preliminary work and structure determination

Initially we reacted 3-phenylpropylamine with iodobenzene (**2a**) in the presence of a catalytic amount of palladium acetate and silver trifluoroacetate in acetic acid at 110 °C, with the intention of preparing diarylpropylamine derivatives (**4**). However, the formation of an unknown compound was observed (**3a**). A similar outcome was obtained when the reaction was run with iodotoluene (**2b**), obtaining a complex adduct (**3b**). In either case the arylated product **4** was not formed (Scheme 17).



Scheme 17. Early attempts on the arylation of aliphatic amines via C–H activation.

Products **3a** and **3b** were then isolated by preparative TLC and characterized. According to the starting materials used, the assumption was made that a limited number of nitrogen and oxygen atoms can be present on products **3a** and **3b**. The exact masses were fundamental to know the molecular formula of **3a** and **3b**, which, as expected, differ in one methyl group. With a measure of 324.1745 m/z for **3a**, its molecular formula was preliminary proposed to be $C_{24}H_{22}N$. For **3b**, a mass of 338.1900 m/z was measured, corresponding to $C_{25}H_{24}N$ (Figure 5). The error of the exact masses was below 3 ppm in both instances.

These formulas provided very useful pieces of information. For example, both **3a** and **3b** contained 14.5 unsaturations, so they contained potentially a polycyclic structure. The unsaturation figure is not an integer (14.5 unsaturations), and this could come from having the M+H detection. However, by ^{1}H NMR spectroscopy, 22 + 3 protons were obtained after integration of the signals, and a highly polar compound was detected by TLC. These data suggested the presence of a positive charge on the molecule, accompanied by an acetate moiety, possibly coming from the solvent. This is supported by a signal at around 1.9 ppm on the ^{1}H NMR spectrum, and at 181 ppm on the ^{13}C NMR spectrum.

The difference of mass and formula between **3a** and **3b** was equivalent to a methyl group, being the same difference between phenyl and tolyl starting materials, so it can be deduced that only one aryl group is involved in the reaction, as mentioned before.

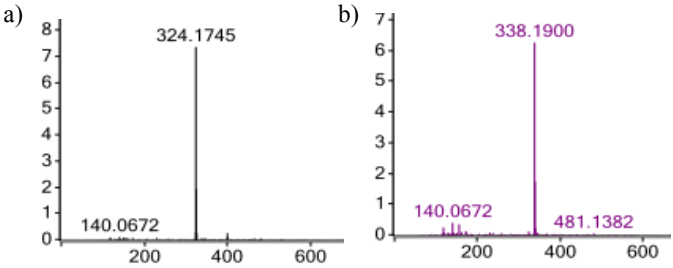


Figure 5. a) Exact mass of **3a**, b) Exact mass of **3b**.

From the ^{1}H NMR and COSY NMR spectra of compound **3a** independent coupling systems could be identified. A first one, with three signals from 2.5 to 5.0 ppm, each signal integrating for 2H, which can be assigned to a chain R-CH_2-CH_2-CH_2-R', associated with the propylamine moiety. Around 7.0 ppm, a multiplet signal for 5H, typical of a benzene ring with single substitution can be noticed. The same system for 5H, around 7.5 ppm, is also associated with a benzene ring, linked to a different part of the molecule. The next system contains two protons, one at 7.6 ppm, directly coupled with another at 9 ppm. The last coupling system bears four protons system, one of them at 7.8 ppm, coupled with two H at 8.1 ppm, which are coupled themselves with one proton at 8.3 ppm (Figures 6 and 7).

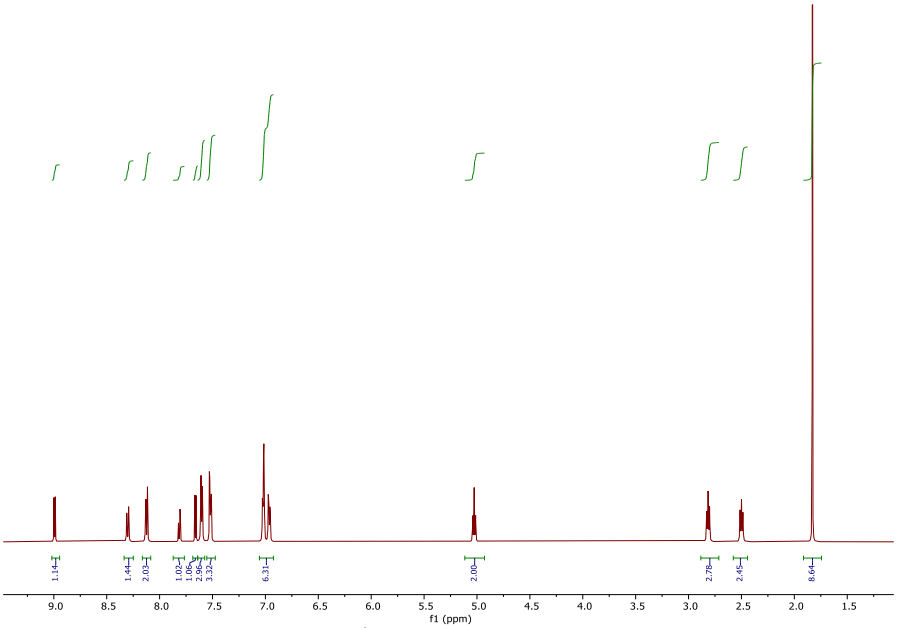
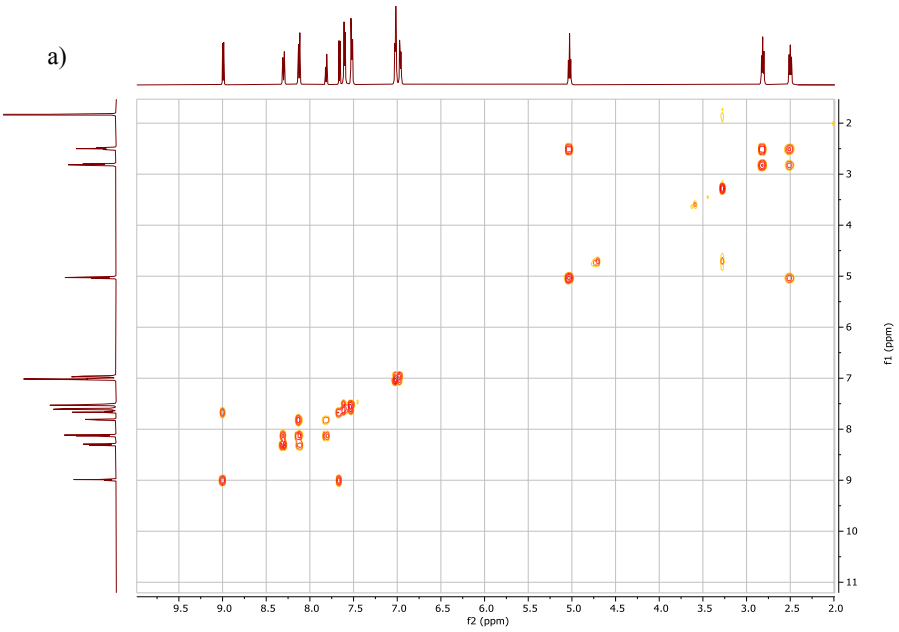


Figure 6. ^{1}H NMR in $CDCl_3$ of **3a**



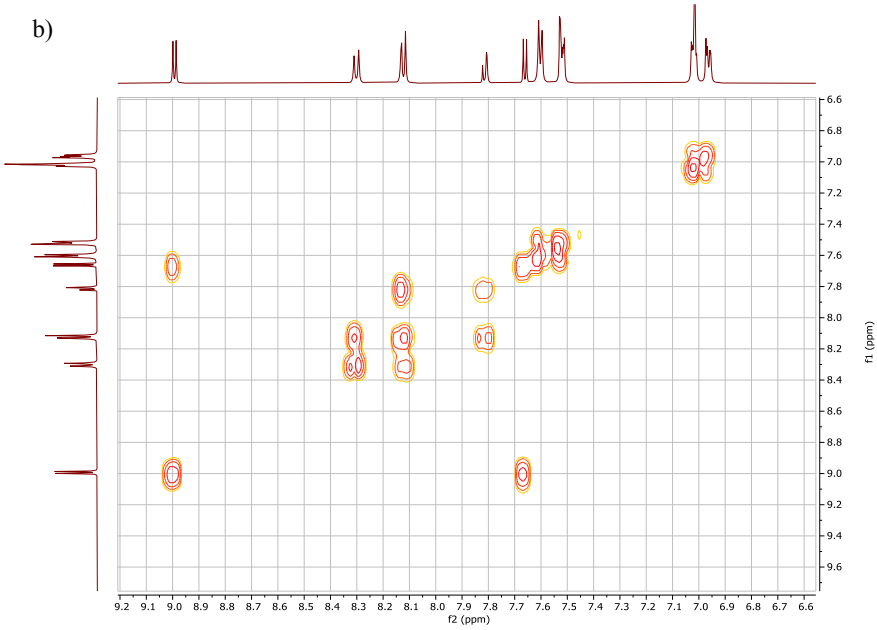


Figure 7. a) COSY ^{1}H NMR in $CDCl_3$ of **3a**, b) Enlargement of the COSY NMR.

When removing the number of carbons and protons, and the unsaturations related to the propyl chain and the two benzene rings from the formula of **3a**, the remainder counts for 9C, 6H, 1N and 7 unsaturations. This is typical of a substituted quinoline scaffold. Thus, it was proposed that the structure of **3a** agrees with that of quaternary quinolinium salt, with a 3-phenylpropyl alkyl chain, and a phenyl substituent on position 4 of the quinoline moiety (Figure 8). A NOE experiment was done on the signal at 5.1 ppm. This demonstrated an expected special proximity with the two other signals at 2.7 and 2.5 ppm, but also with those at 9.0 ppm and 8.4 ppm (Figure 9).

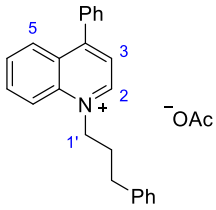


Figure 8. Proposed structure for **3a**.

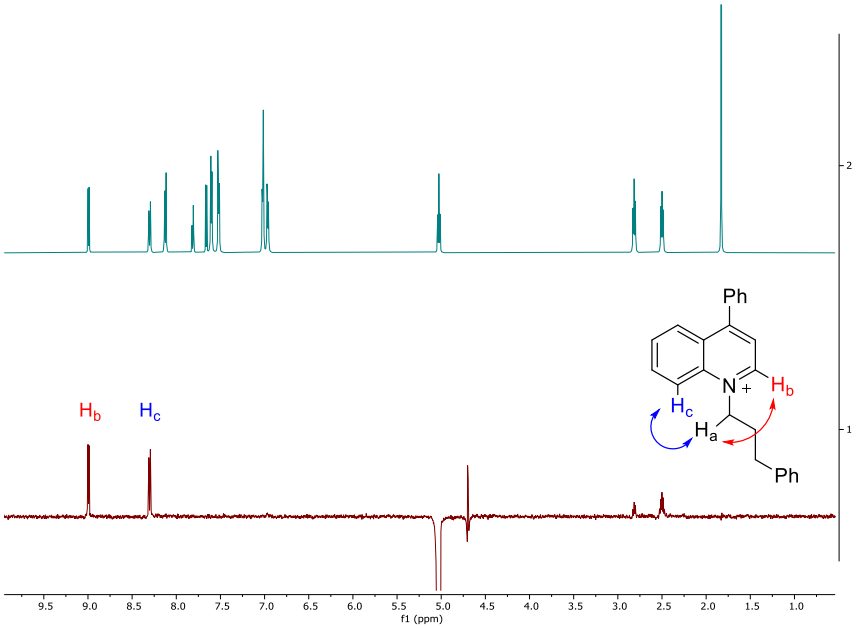
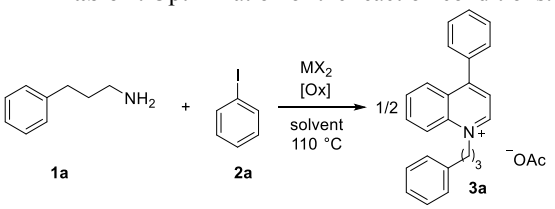


Figure 9. NOE experiment on the signal at 5.1 ppm of compound **3a**.

II.3 Optimization of the reaction conditions

With the structure identified, the optimization of the reaction conditions was carried out. By looking first for other active catalysts, different transition metal salts were tested (Table 1, entry 1). None of them, except palladium acetate (Table 1, entry 3), could afford the product. Other palladium sources like tetrakis(triphenylphosphine)palladium did not yield the product either (Table 1, entry 2). On the side of the oxidant, only silver salts such as silver oxide worked efficiently (Table 1, entries 3-4). Other oxidants[84] commonly used in connection with palladium-mediated transformation did not afford the product, such as nitric acid, oxygenated water or copper acetate (Table 1, entries 5-7). As reported by Bo,[44] silver could play a double role, as oxidant and also to capture the iodine atom during the oxidative addition / reductive elimination steps. Next, the focus was put on the possible solvents for the reaction (Table 1, entries 8-10). It was noticed from the beginning of our study that the presence of acetic acid is essential for the reaction to occur. Therefore, we decided to continue with pure acetic acid (Table 1, entry 4).

Table 1. Optimization of the reaction conditions.



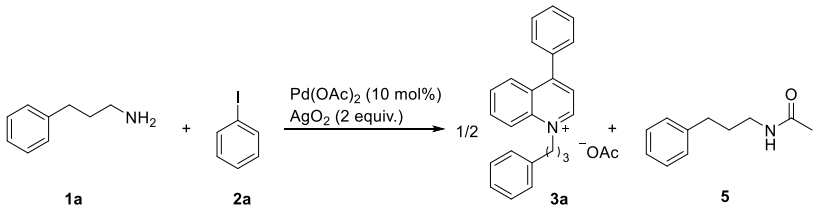
1a 2a 3a

Entry	Catalyst (10 mol%)	oxidant	Solvent	Yield (%)[a]
1[b]	$M(OAc)_2$	CF_3CO_2Ag (1.5 equiv.)	AcOH	0
2	$Pd(PPh_3)_4$	CF_3CO_2Ag (1.5 equiv.)	AcOH	0
3	$Pd(OAc)_2$	CF_3CO_2Ag (1.5 equiv.)	AcOH	16
4	$Pd(OAc)_2$	Ag_2O (2 equiv.)	AcOH	21
5	$Pd(OAc)_2$	HNO_3 (2 equiv.)	AcOH	0
6	$Pd(OAc)_2$	H_2O_2 (2 equiv.)	AcOH	0
7	$Pd(OAc)_2$	$CuOAc_2$ (2 equiv.)	AcOH	0
8	$Pd(OAc)_2$	Ag_2O (2 equiv.)	DMF	0
9	$Pd(OAc)_2$	Ag_2O (2 equiv.)	MeOH	0
10	$Pd(OAc)_2$	Ag_2O (2 equiv.)	Toluene	0

All reactions were performed with 2 equiv. of iodobenzene (**2a**), at 110 °C, overnight. [a]Yields by ^1H NMR spectroscopy with trimethoxybenzene as internal standard. [b]M: Cu, Mn, Co and Zn.

During the reaction, a by-product, acetamide **5**, was detected in the ^1H NMR spectrum of the crude mixtures. The next objective was therefore to reduce the amount of this undesired product. First, larger amounts of silver and iodobenzene (**2a**) substrates were tested in order to increase the rate of formation of the desired product **3a**, however, these changes did not succeed and no significant improvement of yields was observed (Table 2, entries 1-3). Increasing the temperature did not have the expected positive effect (Table 2, entry 4). The solution came with the idea that reducing the amount of acetic acid could decrease the speed of formation of amide **5** by-product. This can be done by using a mixture of acetic acid and water as the solvent mixture, as water was the only other compatible solvent. Different v/v ratios of AcOH and H_2O were investigated, and a 1:1 (v/v) ratio was found to give the best conversion into quinolinium product **3a** with a drastic reduction of amide **5** in the crude mixture. However, the reaction was incomplete at the standard times, so the reaction had to be prolonged for up to 60 h. Those conditions provided the best yields obtained so far (Table 2, entry 7). The number of equivalents of the different starting materials were also optimized, finding that decreasing silver or palladium quantities had a negative impact on the yield (Table 2, entries 8-9), whereas no impact was noted in the case of higher palladium and silver loadings (Table 2, entry 10). Reduction of temperature or time went together with a drop in the yields (Table 2).

Table 2. Optimization of the solvent.



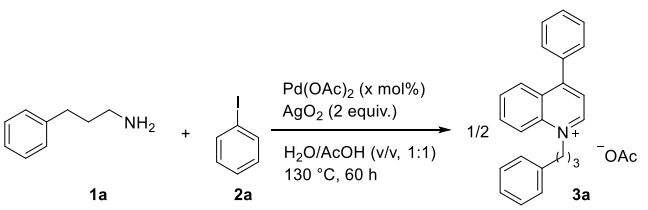
1a **2a** **3a** **5**

Entry	Ag_2O (equiv.)	PhI (**2a**) (equiv.)	Solvent (*v*/*v*)	Temperature (°C)	Yields (**3a** / **5**, %)[a]
1	2	2	AcOH	110	26 / 47
2	3	2	AcOH	110	31 / 46
3	2	3	AcOH	110	30 / 42
4	2	2	AcOH	130	28 / 49
5	2	2	AcOH/H_2O (1:1)	110	21 / 0
6	2	2	AcOH/H_2O (1:1)	130	35 / 2
7[b]	2	2	AcOH/H_2O (1:1)	130	77 / 4
8[c]	2	2	AcOH/H_2O (1:1)	130	15 / 35
9	1	2	AcOH/H_2O (1:1)	130	22 / 29
10[d]	5	2	AcOH/H_2O (1:1)	130	73 / 3

Reactions were run overnight. [a]Yields by ^{1}H NMR spectroscopy with trimethoxybenzene as internal standard [b]Reaction time was 60 h. [c]Palladium acetate 2 mol%. [d]Palladium acetate 25 mol%.

After optimization, control experiments were done to confirm that in the absence of palladium or iodobenzene (**2a**), the reaction did not occur (Table 3, entries 1 and 3). Meanwhile, it was highlighted that the reaction can proceed in the absence of silver (Table 3, entry 2), although in this case, stoichiometric amounts of palladium are needed (Table 3, entry 4).

Table 3. Control experiments of the reaction.



1a **2a** **3a**

Entry	$Pd(OAc)_2$ (mol%)	Ag_2O (equiv.)	**2a** (equiv.)	Yields (%)[a]
1	0	2	2	0
2	10	0	2	7
3	10	2	0	0
4	100	0	2	42

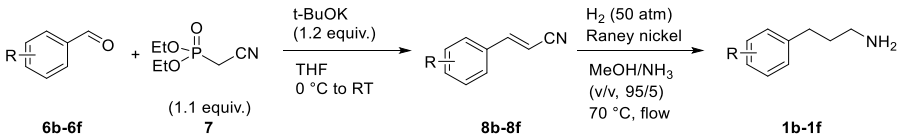
Conditions: AcOH/H_2O (v/v = 1:1), 130 °C, 60 h. [a]Yields by ^{1}H NMR spectroscopy with trimethoxybenzene as internal standard.

II.4 Scope

II.4.1 Substrate scope:

For the study of the synthetic scope, 3-aryl propylamines were prepared as follows. Starting from aldehydes **7a-7d**, the corresponding acrylonitriles **9a-9e** were prepared by Horner–Wadsworth–Emmons reactions. For the reduction of the double bond and CN group in **9a-9e** to alkyl amines **10a-10e**, several conditions were proven to be unsuccessful. Only Raney Nickel, utilizing flow reactor at high pressure and temperature was able to provide the product without degradation. However, to avoid formation of secondary or tertiary amines, ammonia was added (Table 4).

Table 4. Synthesis of propyl amines.



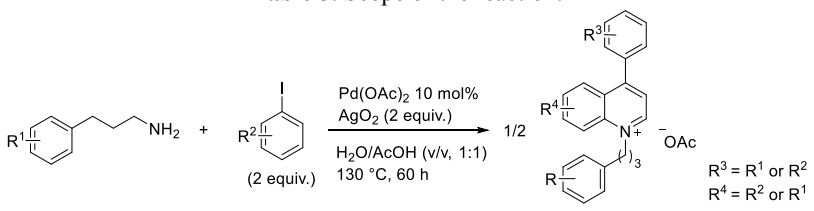
Entry	R	**1** (%)[a]
1	4-CH_3 (**1b**)	75
2	4-F (**1c**)	68
3	4-Cl (**1d**)	72
4	4-OMe (**1e**)	65
5	2,6-F (**1f**)	71

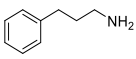
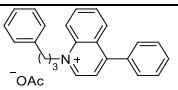
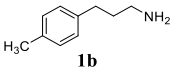
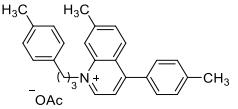
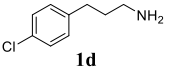
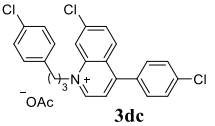
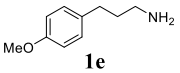
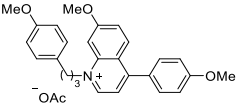
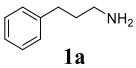
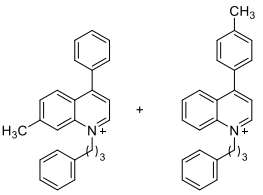
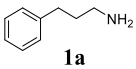
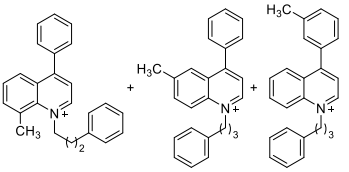
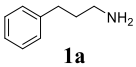
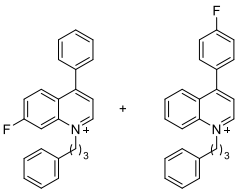
[a]Yields of isolated products.

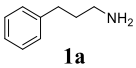
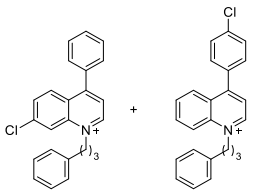
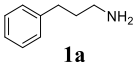
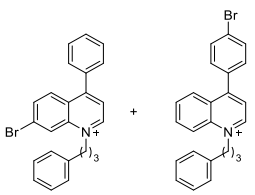
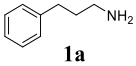
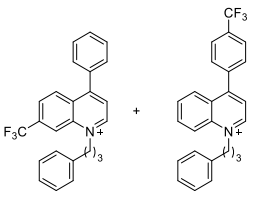
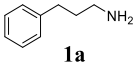
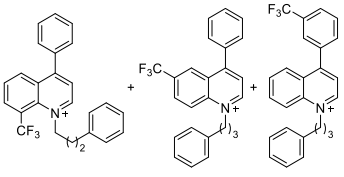
II.4.2 Scope of the reaction

First the reaction between arylated amines **1a-1e** and iodoaryls **2a-2i** was investigated under the optimized conditions (Table 5). When both substrates had the same substitution pattern on the corresponding benzene rings, the products were formed as single isomers (Table 5, entries 1-3) in yields varying from moderate to good, and where fully characterized after isolation. When the substituents on the amine and iodoaryl partners are different, multiple products are obtained in a non-separable mixture. None of the isomers from these mixtures were isolated, and the ratio of the different isomers for each mixture was determined by ^{1}H and ^{19}F NMR, when possible. In the case of *para* substitutions on the iodoaryls, only two isomers are formed (Table 5, entries 5, 7-10), in yields ranging from 31 to 72%. No selectivity was observed, and the method tends to yield equal amounts of both products. With *ortho* substituted iodobenzene derivatives **2e** and **2i**, three isomers were obtained (Table 5, entries 6 and 11). The ratios are, in the case of **3aia-3aic**, not equivalent for all of them (1:6:4).

Table 5. Scope of the reaction.



Entry	Amine (**1a-1e**)	Iodoaryl (**2**)	Product	Yields (%)[a]
1	 **1a**	**2a**	 **3a**	55 (77)
2	 **1b**	4-CH_3 (**2b**)	 **3bb**	45 (52)
3	 **1d**	4-Cl (**2c**)	 **3dc**	0 (48)
4	 **1e**	4-OMe (**2d**)	 **3ed**	29 (40)
5	 **1a**	4-CH_3 (**2b**)	 **3ba** 1:4.3 **3bb**	72 (88)
6	 **1a**	3-CH_3 (**5e**)	 **3aea** **3aeb** **3aec**	47 (65)
7	 **1a**	4-F (**2f**)	 **3afa** 1:1.2 **3afb**	54 (61)

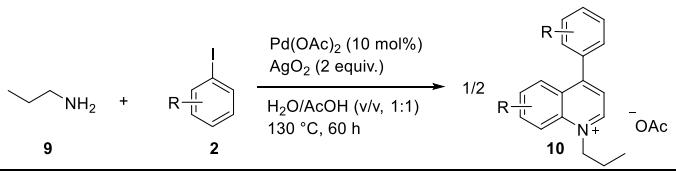
8	 **1a**	4-Cl (**2c**)	 **3aca** + **3acb**	43 (54)
9	 **1a**	4-Br (**2g**)	 **3aga** + **3agb**	39 (48)
10	 **1a**	4-CF_3 (**2h**)	 **3aha** 1:1.2 **3ahb**	31 (38)
11	 **1a**	3-CF_3 (**2i**)	 **3aia** **3aib** **3aic** 1:6:4	26 (34)

a) Isolated yields (NMR yields with trimethoxybenzene as internal standard). Ratio was determined by ^{1}H or ^{19}F NMR spectroscopy, if possible.

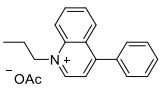
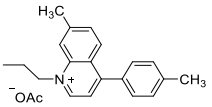
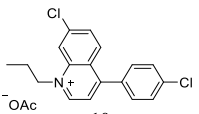
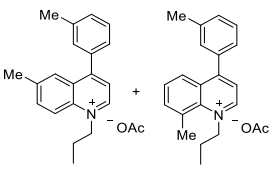
II.4.3 Propylamine as substrate:

Propylamine (**9**) is a challenging substrate towards C–H activation.[85] However, to our surprise, our conditions can be applied to this simple aliphatic amine to afford the quinolinium adducts by introduction of two equivalents of the aryl iodides (**2a**). As only one single aryl iodide is used in this reaction, the two aryl units introduced in the molecule will be the same on each part of the quinolinium core (Table 6). The yields are significantly lower than previously noted in Tables 4 and 5, ranging now from 16% to 38%. The drawback is counterbalanced by the easiness of using propylamine as substrate, instead of the synthetically more complex phenyl propylamines. Noteworthy, the method allows to functionalize the otherwise very unreactive propylamine (**9**). Also, the increase in complexity from **9** to the final quinolinium product structures in a single reaction is remarkable (Table 6).

Table 6. Synthesis of quinolonium structures from propylamine **9**.



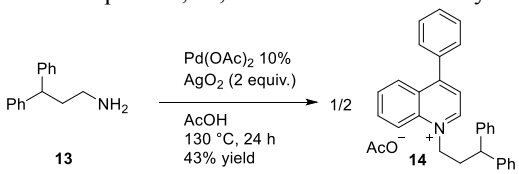
9 **2** **10**

Entry	Aryl iodide (R')	Quinolonium	Yields (%)[a]
1	**2a**	 **10a**	32 (38)
2	4-CH_3 (**2b**)	 **10b**	38 (43)
3	4-Cl (**2c**)	 **10c**	16 (23)
4	3-CH_3 (**2h**)		0 (39)

[a]Isolated yields. In parenthesis yields determined by ^{1}H NMR spectroscopy with trimethoxybenzene as internal standard.

II.5 Mechanistic investigation

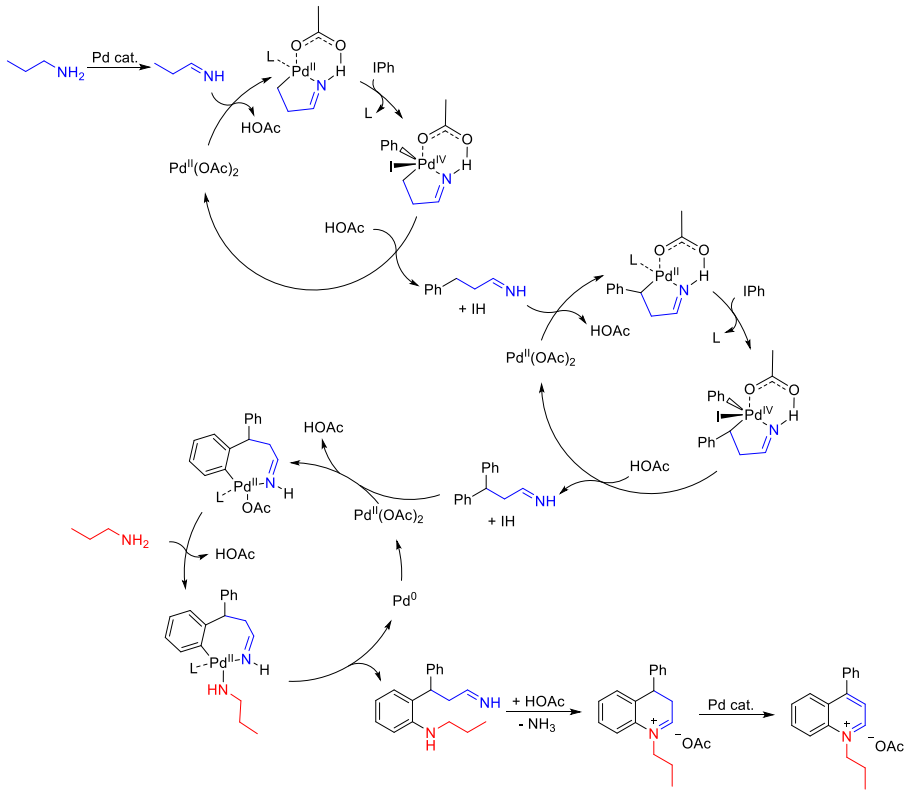
For the investigation of the mechanism, the initial literature search suggested a reaction based on multiple Pd-catalyzed activations of C_{sp^3}–H and C_{sp^2}–H bonds. We, thus, hypothesized the participation of a number of singular steps in the mechanism, in an unknown order. These steps were the double arylation of propylamine, C_{sp^2}–H activation and C_{sp^2}–N bond formation on one of the aromatic rings, a cyclization, and a final oxidation of the product to yield the quinolinium form. Based on this assumption, questions remained about the sequence of the different steps. A simple experiment was conducted to know if the amination/cyclization and oxidation can proceed on 3,3-diphenylpropylamine **13**. The product, **14**, was obtained with 43% yield (Scheme 18).



Scheme 18. Reaction from 3,3-diphenylpropylamine **26** as the starting material.

Note that the reaction was conducted in the absence of aryl iodide. Thus, the reaction with iodine containing reagents, like a Hofmann-type elimination was discarded as potential elementary step. In addition, an order for the different steps can be proposed for the case of the propylamine, starting with a double arylation via C_{sp^3}–H activations The reaction needs a directing group, a role that the amine can hardly play, since amines can strongly bind palladium, inhibiting any further reaction.[86] Alternatively, the oxidation of the primary amine to imine by palladium can occur at the outset of the reaction, offering a better directing group for the reaction.

Following our hypothesis, the mechanism in Scheme 19 can be proposed, starting with the oxidation of the amine by the palladium acetate. Then, the first C–H activation occurs, followed by classical oxidative addition/reductive elimination of iodobenzene with Pd^{II}/Pd^{IV} catalytic cycle. The recent literature is in agreement with the possibility of forming Pd^{IV} complex by oxidative addition. Gaunt and co-workers successfully isolated a palladacycle intermediate after oxidative additions.[87,88] Starting from 3-phenylpropylimine, a second identical catalytic cycle could occur. Then, a C_{sp^2}–H activation can follow to complete the first amination of the aromatic ring. When the Aryl-N intermediate is formed, a cyclization to the heterocycle might take place, accompanied by the elimination of ammonia. Finally, the product is obtained after oxidation by palladium of the 3,4-hydroquinolinium to the quaternary quinolinium salt.



Scheme 19. Proposed mechanism for the reaction.

The different parts of the proposed mechanism were studied by DFT,[89–92] using B97D/6-311g**+SDD (Pd and I) for geometry optimization and M06/DEF2TZVPP for the energy refinements.[93] The final free energies were the result of the thermal correction from B97D/6-311g**/SDD added to the electronic energy from the single point refinement with M06/DEF2TZVPP. As the reaction also works with the palladium complex alone, in dry acetic acid, this solvent has been used for the calculations, and therefore silver was not considered.

The oxidation study starts with the coordination of the palladium to the amine and formation of an N-Pd bond by H transfer to one of the acetates (**I** to **II**), with a downhill energy of –14.4 kcal/mol (Figure 10). Then, the amine / imine transformation occurs through a classical β-hydride elimination reaction, like in **TS1**, with an overall activation energy of 10.2 kcal/mol. If the reference for the energy is the complex **II** (obtained from IRC calculation of the TS), the energy barrier is 24.6 kcal/mol. The energies involved in this transformation, are reasonable and in agreement with the temperature of the experimental conditions. The formation of the imine is uphill from the amide N-Pd complex, but favourable from the separate reactants (amine + $Pd(OAc)_2$), showing an energy of -6.5 kcal/mol for **III**, a complex that evolves by release of the free imine, Pd(0) and two molecules of acetic acid.

The ability of the amine in **I** to function as directing group for the C-H activation was also computed. From **I** to **TS1'**, an activation of 11.0 kcal/mol was found for the C-H cleavage, 1.0 kcal/mol higher than the oxidation step in **TS1**, and therefore, the amine

oxidation to imine is slightly favoured. In any case, these data do not allow us to completely discard that the C-H activation occurs first, followed by the amine/imine oxidation. On the other hand, Pd(0) is formed at the end of Figure 1, which has to be re-oxidized to Pd(II) to continue the process.

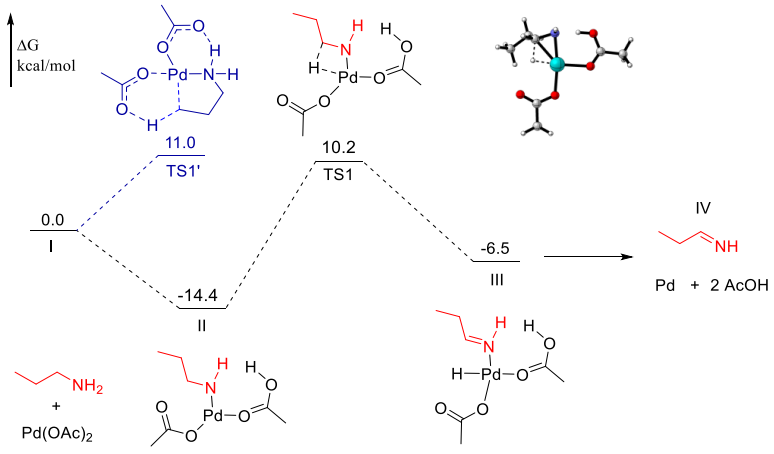


Figure 10. Energetic profile of the oxidation transformation and comparison with amine as directing group of the C-H activation.

Next, the previously formed propylimine coordinates with $Pd(OAc)_2$ in **V**. As this complex is in a different oxidation state from the final adducts in Figure 10, we took **V** as relative G=0 to study the next steps of the reaction. From complex **V**, the following elementary step is the C–H activation in position 3 of the propyl chain, promoted by one of the acetate ligands (Figure 11). The computed energy for **TS2** is 8.7 kcal/mol higher than the palladacycle, while the product **VI** is at –10.0 kcal/mol. After a slight decrease of energy due to the ligand exchange and acetate release from **VI** to **VII**, the oxidative addition to PhI happens with a barrier of 17.4 kcal/mol, affording Pd(IV) complex **VIII**. Then, an easy reductive elimination was computed in **TS4** with only 5.5 kcal/mol over **VIII** kcal/mol activation barrier to provide the formation of the Ph-C bond. Propylimine **IX** is favoured compared to the starting materials, being at an energy of -34.1 kcal/mol.

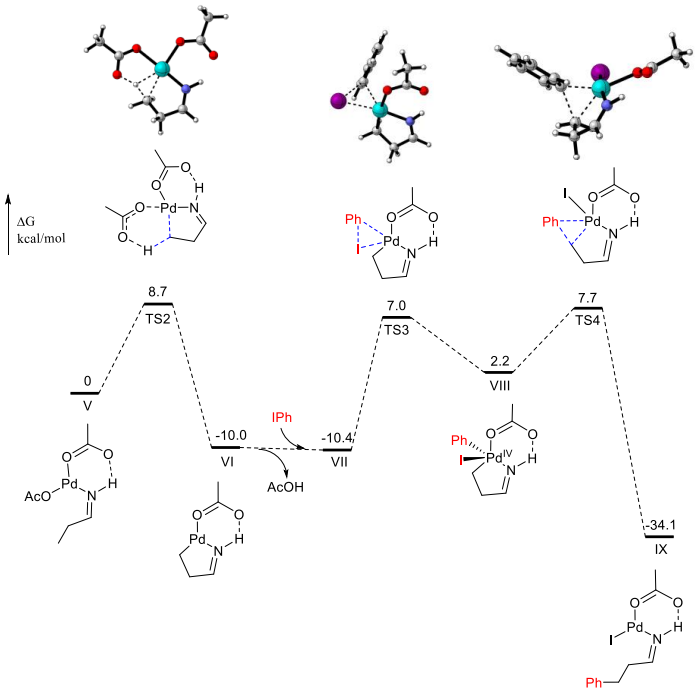


Figure 11. DFT computed energy profile of the arylation of propylamine.

We also studied the feasibility of a second C-H activation and formation of another Ph-C bond in the same position (Figure 12). This step is especially important in the case of substrate **1a**, which already contains a phenyl group, as in **IX**, and must be able to incorporate the second one. Initially, the iodide present in **IX** must be replaced by an acetate ligand. Acetic acid and/or eventually silver salts can participate in this anion exchange, which is difficult to be accurately described. In any case, complex **X** is prone to suffer a similar process as mentioned before for **V**, and in principle Figures 12 and 11 should show similar results. The main difference related to the absence/presence of the phenyl group at C-3 is the general increase of the activation energies due to the larger steric hindrance. For example, the barrier for the C-H activation is quite larger in the presence of the phenyl group (19.3 kcal/mol in **TS5** *vs* 8.7 kcal/mol in **TS2**). A similar trend occurs also during the oxidative addition to PhI (30.0 kcal/mol in **TS6** *vs* 17.4 kcal/mol in **TS3**), and for the final reductive elimination (10.0 kcal/mol in **TS7** *vs* 5.5 kcal/mol in **TS4**). However, the overall pictures stays unaltered, pointing to the oxidative addition to form the Pd(IV) complex as the slowest step.

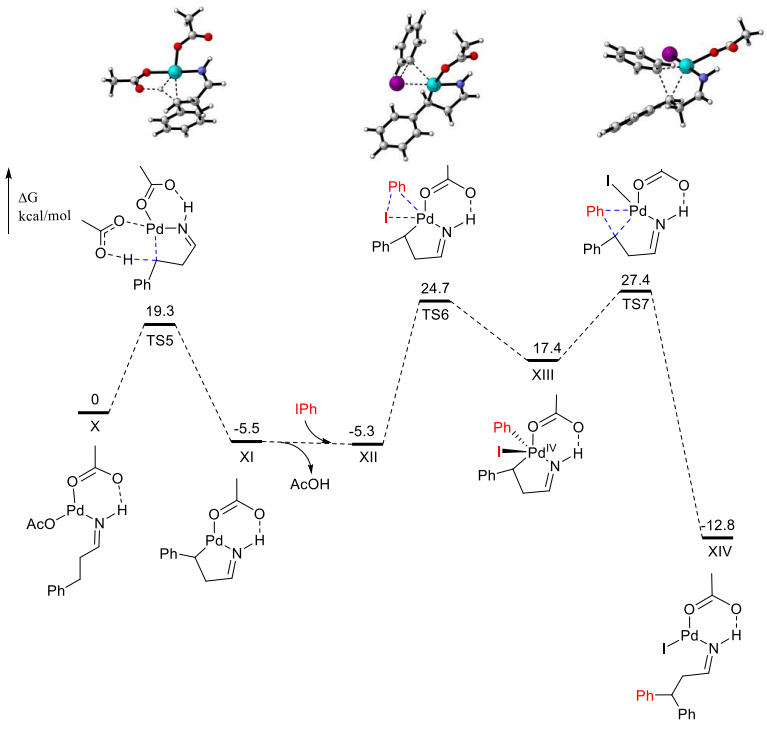


Figure 12. DFT computed energy profile of the arylation of 3-phenyl substituted substrate.

The last steps of the mechanism were also assessed, although we could not locate all structures involved, because of the existing uncertainties about the coordination pattern around palladium in most species. However, we can offer some hints about a few individual steps that might happen to complete the process. For example, after formation of a **XV**-type complex, one of the aromatic rings has to be activated by palladium through a C-H cleavage / Ar-Pd bond formation, like in **TS8** (Figure 13). Our calculation shows

that this process is completely feasible, spite the fact that the resulting complex **XVI** is a 7-membered ring palladacycle. Later, the formation of an amide-Pd bond in **XVII** might trigger a Buchwald-Hartwig aryl amination. The computed transition state **TS9** presents a low energy value, leading to an amine-imine adduct **XVIII**, which contains all the atoms and disposition needed for the formation of the final adducts. The hypothetical sequence could probably occur through cyclization to **XIX** and aromatization of **XX**, steps which do not really need the aid of palladium.

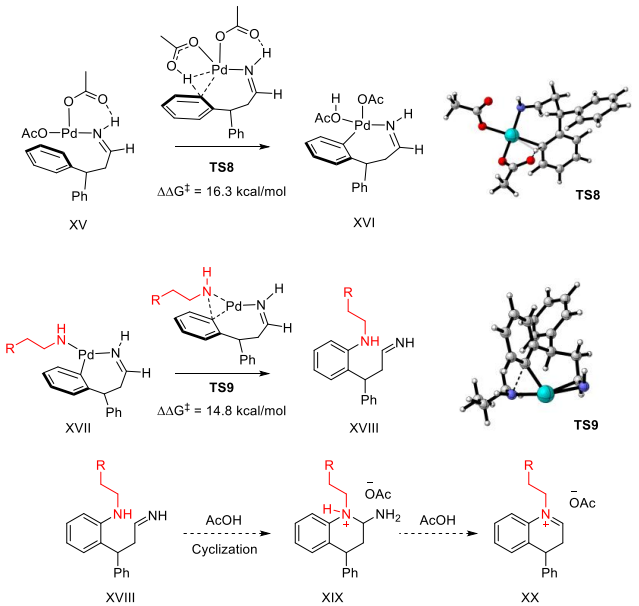


Figure 13. Last steps of the reaction, including calculated aryl CH-activation and aryl amination

Overall, the computed energies for the steps of the process are compatible with the temperature of the reaction, usually at 130 °C. All energies are below 30 kcal/mol, with the maximum at the oxidative addition of **XII** in **TS6**. Noteworthy, we did not locate any intermediate with a significantly lower energy than the rest, and thus, none of them represent a global minimum in the energy surface that could be experimentally isolable.

Those DFT results can explained that the formation of **4** is not observed, as the amine is oxidized to imine quickly. On the other hand, the imine becomes a good directing group for further transformations.

These calculations offer one of the possible pathways that explains some of the experimental observations, and at least shed some light on part of the transition states and intermediates that take place in this intricate transformation. Obviously, more experimental evidence is needed to confirm the different parts of the mechanism. The necessity of the acetic acid as solvent is not fully explained. KIE measurements on deuterated propylamine could confirm that C–H activation is not the rate limiting step. Since two equivalents of amine are needed to complete the reaction, a well designed experiment with ^{15}N labelled amines could be useful to ascertain the amine source of the quinolinium nitrogen. Also, the role of the silver is not taken into account in these mechanistic studies. A recent work[94] shows the important role of the metal for the C–H

activation, therefore, investigation of potential ease of the reaction by silver is interesting.[44]

II.6 Conclusion

In this chapter, a successful and innovative synthesis of quartenary quinolinium salts from propylamines and its derivates is reported, catalyzed by palladium acetate. Aryl-proylamines have been transformed into the desired products, with moderate to good yields. Moreover, the method can be used with propylamine, in a process that involves the activation of two aliphatic C–H bonds.

The mechanism for the reaction has been studied by computational means, and compared with the experimental results and literature precedents. In the case of propylamine, the proposed mechanism starts with the oxidation to imine, then a double C_{sp^3}–H activation/arylation. Then a C_{sp^2}–H bond is activated, followed by a C–N bond formation. The intermediate is cyclized and oxidized to yield the final products.

The interests of the method are, the possibility offered to form quinolines scaffold from simple starting material and to have multiple C–H activations, and creating multiple C–C bonds and a C–N bond, in a single reaction.

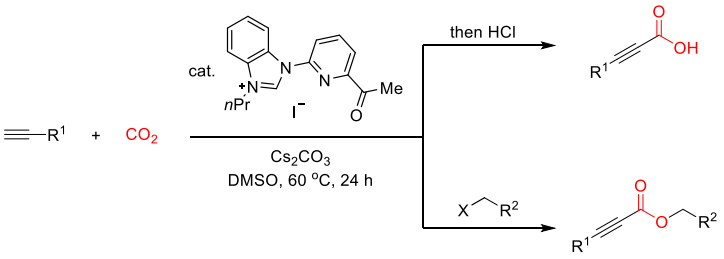
III NHC-catalyzed synthesis of propargylic esters with CO_2 capture (Paper II)

III.1 Introduction

Propargylic esters are present in wide range of compounds. From intermediates for total synthesis of natural products, Diphylin, Justicine B or Tawainin C,[95] to bioactive compounds such as Oxybutynin for the treatment of bladder cancer.[96] Their synthesis can be achieved *via* the esterification of the corresponding carboxylic acid,[97,98] which needs to be prepared before. The group of Prof. Vougioukalakis developed the methodology for the synthesis of the propargylic esters, and the experimental results used for the DFT studies were performed by his group. They reported a method that uses commercially available starting materials and CO_2 for a one-step synthesis of propargylic esters. Because CO_2 is one of the major greenhouse gases and at the same time a cheap and safe reagent, methods using CO_2 as reagent have in general a great interest economically and for the society. A similar reaction to this work has been developed, showing the interest for new routes of synthesis using CO_2.[99]

In the recent literature of CO_2 fixation on terminal alkyls, organocatalyzed by NHC, two methods of synthesis were reported by two different groups.

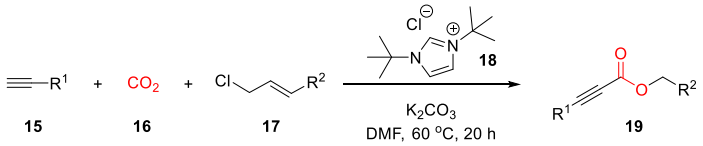
The first one, by Liu *et al.*,[100] were able to react terminal alkynes with CO2 to form the propargyl carboxylic acid. Then, the treatment with HCl in the presence of alkyl halides led to the corresponding esters.The reaction is carried ut at 60ºC in DMSO, catalyzed by in situ generated NHC (Scheme 20). The mechanism proposed is similar to our proposal[101] and rely on the formation of the NHC-CO_2 adduct.



Scheme 20. Synthesis of propargylic acid and esters catalyzed by NHC.

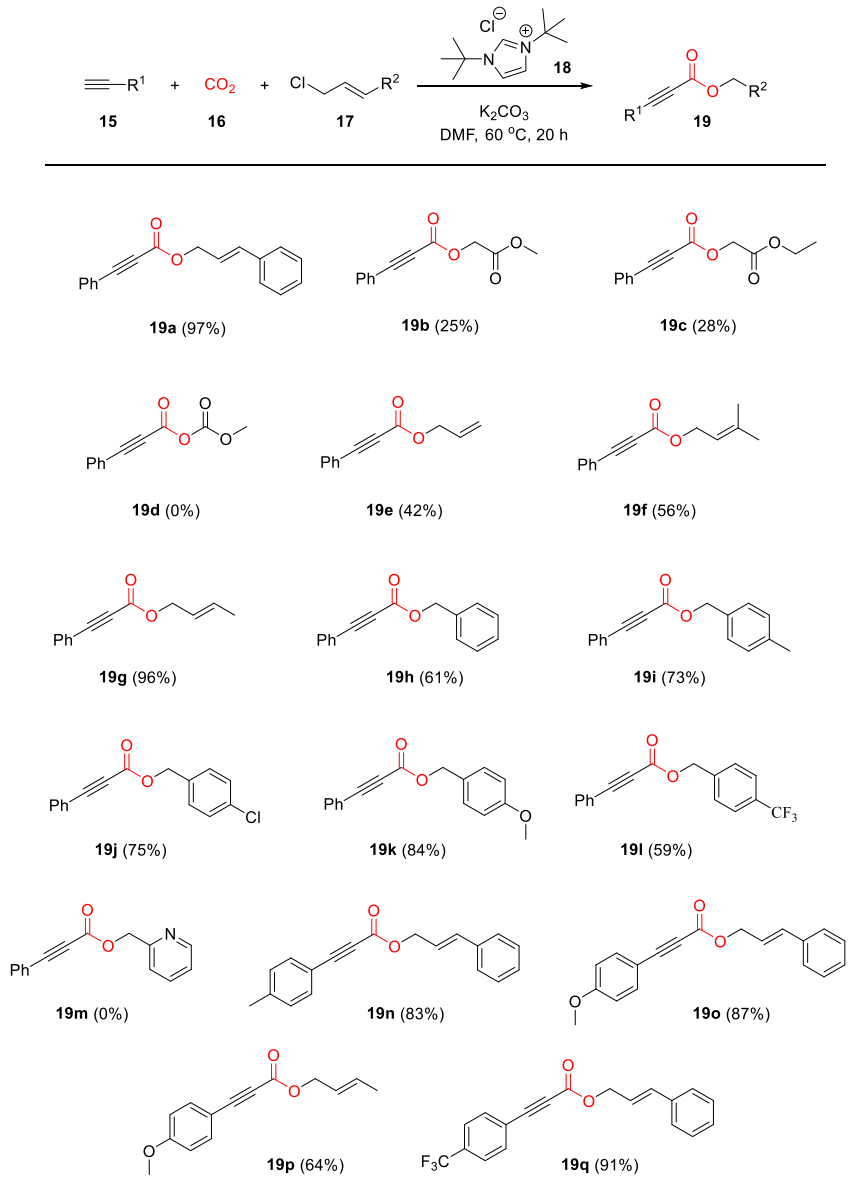
III.2 Experimental results and scope of the reaction

For the synthesis of propargylic esters, three common reagents are involved: terminal alkynes (**15**), allylic chlorides (**16**) and CO_2. The reaction is catalyzed by NHC **18** (Scheme 21). The experimental results presented in this section (II.2) have been performed by the group of Prof. Vougioukalakis.



Scheme 21. Three-component reaction for the synthesis of propargylic esters.

After optimization of the reaction conditions, the substrate scope was extended. Aromatic propargylic reagents, with different substituents on the aromatic ring, gave good results (Scheme 22). It was also possible to use different allylic chloride reagents, with various functional groups, such as ester, cinnamyl, benzyl, carbonate or even olefins (Scheme 22). On the other hand, when using 2-picolyl chloride the expected product was not formed (**19m**).



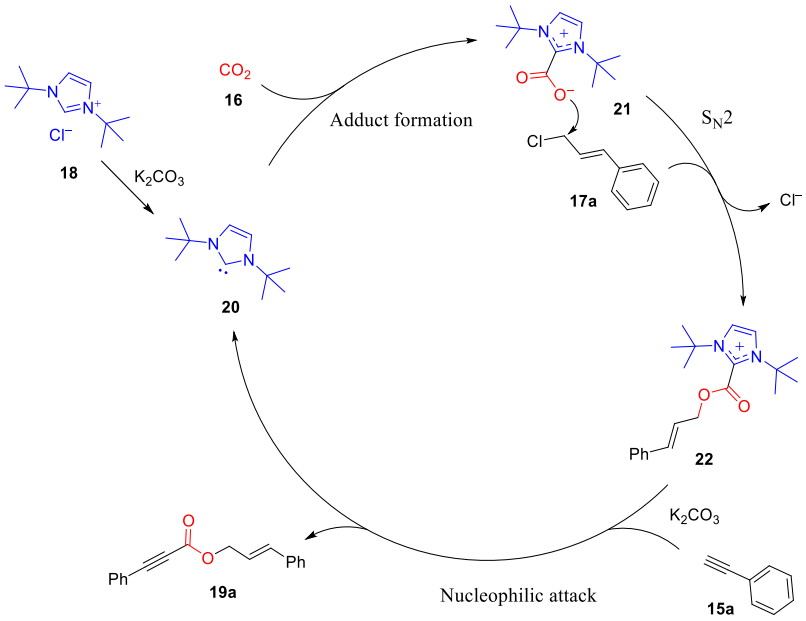
Scheme 22. Scope and limitations of the reaction studied by the group of Prof. Vougioukalakis.

III.3 Mechanistic studies

III.3.1 Proposed mechanism

First, we wanted to identify the rate limiting step of the reaction. Second, we wanted to understand the reactivity trend. In particular, the goal was to understand why aromatic allylic halides (i.e. **17h - 17l**) were active substrates, whilst picolyl chloride **17m** did not react under the reaction conditions (Scheme 22).

Tentatively, a mechanism was proposed, consisting of an initial attack of the NHC catalyst to CO_2. Then, the zwitterionic intermediate formed (**21**) reacts with the allylic chloride (**17a**) through an S_N2 reaction yielding **22**. Next, the deprotonated propargylic moiety (**15a**) reacts with **22** through an addition-elimination mechanism, releasing the NHC catalyst and producing the final ester **19a** (Scheme 23).



Scheme 23. Proposed mechanism.

III.3.2 Methodology for computational investigations

We used DFT methods to confirm or discard the previously shown mechanism, to identify the possible rate-determining step and to explain the different reactivity of certain chloride substrates. As a model of the reaction, the most reactive substrates, cinnamyl chloride and phenyl acetylene (**17a** and **15a**, respectively), were selected. The calculations were done using Gaussian 16, with M06-2X[102] for the functional and 6-311G(s,p)[103] as the basis sets for the geometry optimization and energies.[104] The solvent model used is IEFPCM with DMF.

III.3.3 Results and discussion

As first step of the proposed mechanism, we investigated the attack of the NHC catalyst to CO_2. An activation energy of 10.9 kcal/mol was found for **TS1** (Figure 14). This low value shows that the first reaction is an easy step and agrees with previous results.[105] The intermediate obtained (**II**) is stable due to its low energy (–2.7 kcal/mol). As the energy of the NHC–CO_2 complex is lower than that of the two reagents (**I** and CO_2), it is possible to isolate it. This is why the intermediate is already reported and is involved in different NHC-catalyzed reactions as a catalyst precursor.[106] The next step is the S_N2 reaction between **II** and allylic chloride **30a**. The computed energy of activation for this step was $\Delta\Delta G^{\ddagger}$ = 22.1 kcal/mol. Even if this step is more energy demanding, it is affordable at the experimental conditions. The 3D structure of **TS2** shows a typical S_N2 nucleophilic attack (Figure 16). The step yields a more stable intermediate (**III**, –4.2 kcal/mol). Then, the deprotonated alkyne attacks the carbonyl group in **III** (**TS3**, $\Delta\Delta G^{\ddagger}$ = 20.9 kcal/mol). A fairly stable tetrahedral intermediate is formed (**IV**), quickly followed by the release of the NHC catalyst, yielding the product **19a** (**TS4**, $\Delta\Delta G^{\ddagger}$ = 5.1 kcal/mol).

From this point, we have a global view of the energy profile of the reaction. We can highlight that the rate-limiting step is the nucleophilic substitution (**TS2**) of the chloride by the NHC–CO_2 adduct. And, as there are significant differences of reactivity concerning the electrophile, we next focused our attention on this transition state to explain those differences.

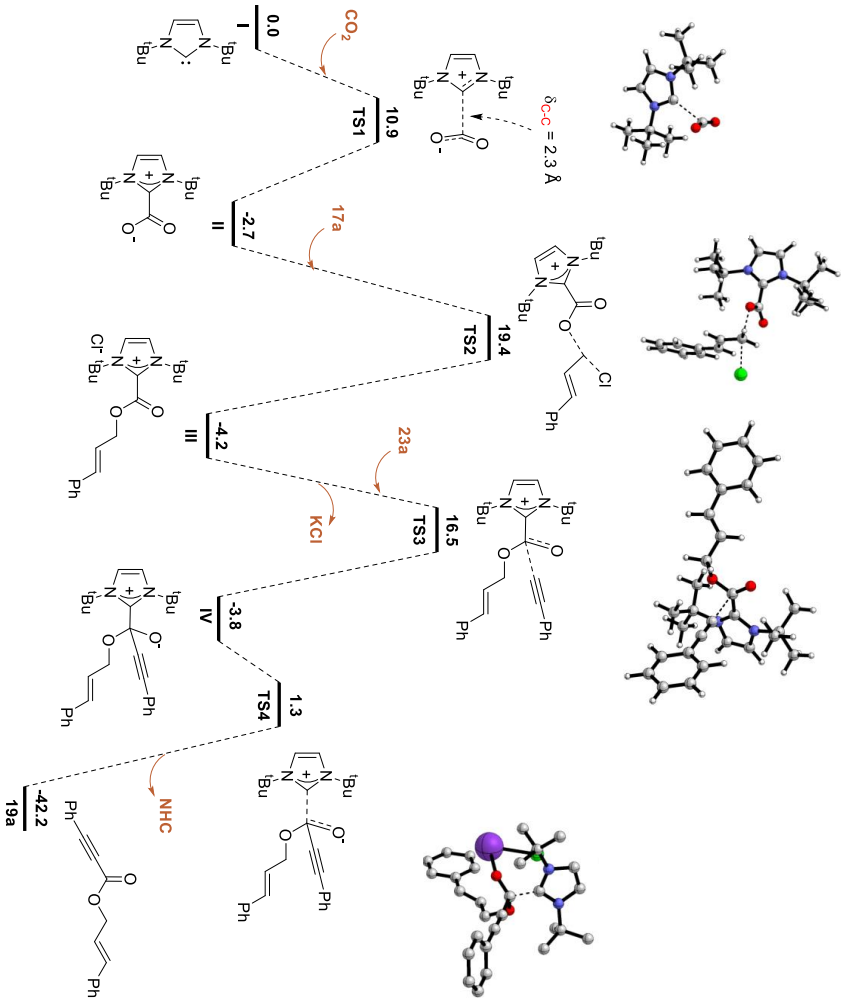


Figure 14. Energy pathway for the reaction.

We were able to locate the transition state for the problematic chlorides, which are benzyl chloride (**17h**) due to its low reactivity, and 2-picolyl chloride (**17m**) for its complete absence of reactivity. The energy of activation of **TS2** in the model reaction (from cinnamyl chloride, **17a**) is $\Delta\Delta G^{\ddagger}$ = 22.1 kcal/mol, and was set as the reference for the study. In the case of benzyl chloride (**17h**, 61% yield), we obtained an energy of 23.0 kcal/mol for the corresponding **TS2**. From the Eyring equation, with transmission coefficient set to 1 and a temperature of 333.15 K, we can calculate the half-life times of both intermediates and compare them. For the cinnamyl chloride, we obtained a half-life time of 26.5 s, and for benzyl chloride, of 121.8 s. Those values can give an approximation to the difference of reactivity between the two substrates (97% vs 61%). In the case of

the 2-picolyl chloride, **17m**, we obtained an activation energy of 24.7 kcal/mol for the corresponding **TS2-mi**, indicating a half-life time of 25 min. The difference with the previous compounds is significant, but it is not able to explain an absolute absence of reactivity for this substrate. We thought that other factors associated with the pyridine moiety itself could play a crucial inhibiting role in the reaction. To further check this hypothesis experimentally, a control reaction was carried out. Pyridine (1 equiv.) was added to the reaction mixture with cinnamyl chloride (**17h**) and **15a** as substrates, applying the same reaction conditions as before. The expected product was not detected; thus, pyridine inhibits the reaction.

From the three different **TS2** previously found, we can also look at the bond distances. The C–O bonds lengths of the TSs from **17a**, **17h** and **17m** are 2.09 Å, 2.04 Å and 2.00 Å, respectively. And the C–Cl are 2.44 Å, 2.38 Å and 2.34 Å, respectively (Figure 15). Thus, the reactivity increases with increasing bond lengths in the TSs. It seems that the carbon has to be as electropositive as possible, according to the difference between **17k** (84%) and **17i** (59%): The formation of product with pyridine moiety could not be achieved. The calculated energy for the **TS2-m** suggests that the time of reaction should be longer compare to others substrate. But this higher energy level does not correspond with the absence of product, 24.7 kcal/mol of energy of activation is compatible with the experimental conditions.

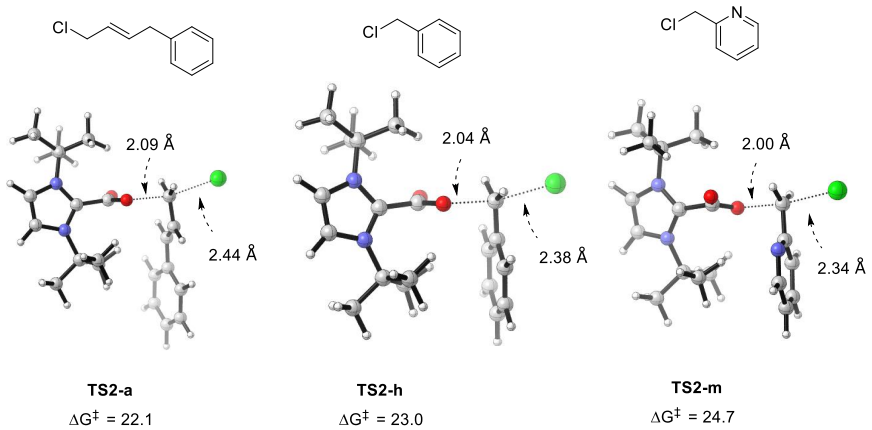


Figure 15. Comparison of energies in kcal/mol with different chains for **TS2**.

III.4 Conclusion

The mechanism of a novel organocatalytic protocol for the multicomponent carboxylative coupling of terminal alkynes with organochlorides and CO_2, catalyzed by an *in situ* generated NHC was studied in collaboration with the group of Prof. Vougioukalakis. The DFT calculations on the mechanism of this transformation indicate that the reaction is initiated with the addition of the carbene to a molecule of CO_2, forming an NHC-carboxylate. This species is nucleophilic enough to react with chlorides, even though the high activation energy of this step suggests that it is the rate-limiting step. This fact explains well the large difference in reactivity of the different allyl and benzyl chlorides and the effect of the substituents. The reaction with substrates with a pyridine moiety could not be formed, which is due to the pyridine acting as inhibitor of the reaction.

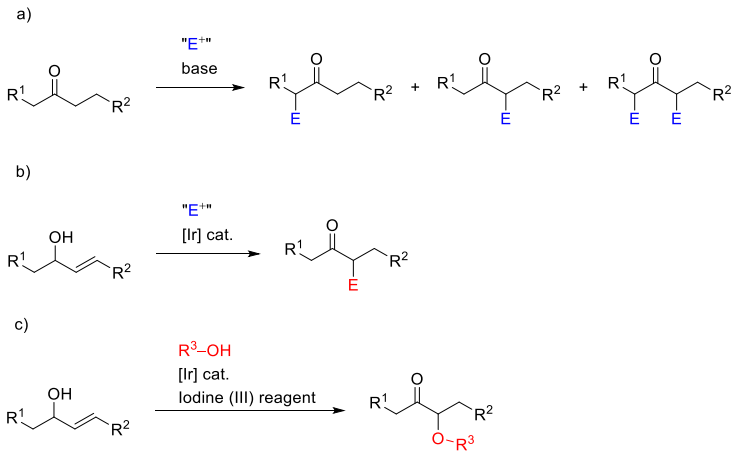
IV Reaction of Catalytic Enols with Nucleophiles (Paper III)

IV.1 Introduction

Functionalization of the Cα of carbonyl moieties using electrophiles is well-known. Ketones can tautomerize to enols or form enolate ions in the presence of base, and then behave as nucleophiles. If the ketone has two enolizable positions that are similar electronically and sterically, both Cα can be functionalized upon reaction with electrophiles (Scheme 24a). To avoid formation of regioisomeric α-functionalized carbonyl compounds, an alternative is to use allylic alcohols as starting materials, and combine a 1,3-hydrogen shift mediated by transition metal catalysts with a functionalization reaction using electrophilic reagents. This approach has been used by us[107–110] and others[111,112] (Scheme 24b). The reaction relies on the formation of enol(ate) intermediates after the isomerization (1,3-hydrogen shift) of the allylic alcohol. This type of reactivity allows the regiospecific formation of α–substituted ketones, and avoids the use of a strong base.

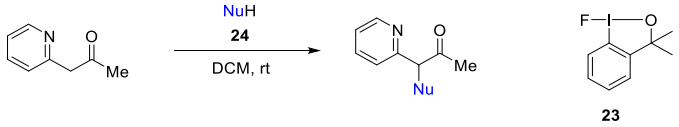
The functionalization of enols or enolates with nucleophiles requires to apply umpolung strategies. Different approaches can be used, employing for example Lewis acid,[113] transition metals[114] or, as in the method developed here, hypervalent iodine reagents.[108,115–118]

In this chapter our work on the use of an umpolung strategy in the stereospecific transformation of allylic alcohols into α-functionalized carbonyl compounds is presented. The electrophilic reagents have been exchanged by nucleophilic ones, (i.e. MeOH). The umpolung is achieved by performing the reaction in the presence of a hypervalent iodine reagent (**24**) (Scheme 24c).[117]



Scheme 24. "E^+" = electrophile, a) Classical method for α-functionalization of ketones. b) Regiospecific reaction of allylic alcohols with electrophiles catalyzed by iridium. c) This work: umpolung approach for the synthesis of α-functionalized carbonyls upon reaction of allylic alcohols with nucleophiles.

A recent methodology was developed by Kielf and Gulder,[119] for α-functionalization by nucleophiles of α-pyridyl-ketones with hypervalent reagent. With the same umpolung strategy, they succeeded to form, regioselectively, C–O, C–N and C–S bonds with no enol ether pre-formation needed. The selectivity is driven by the pyridyl group, coordinating weakly but sufficiently with iodine atom. Therefore, the nucleophile reacts only on one side of the ketone (Scheme 25).

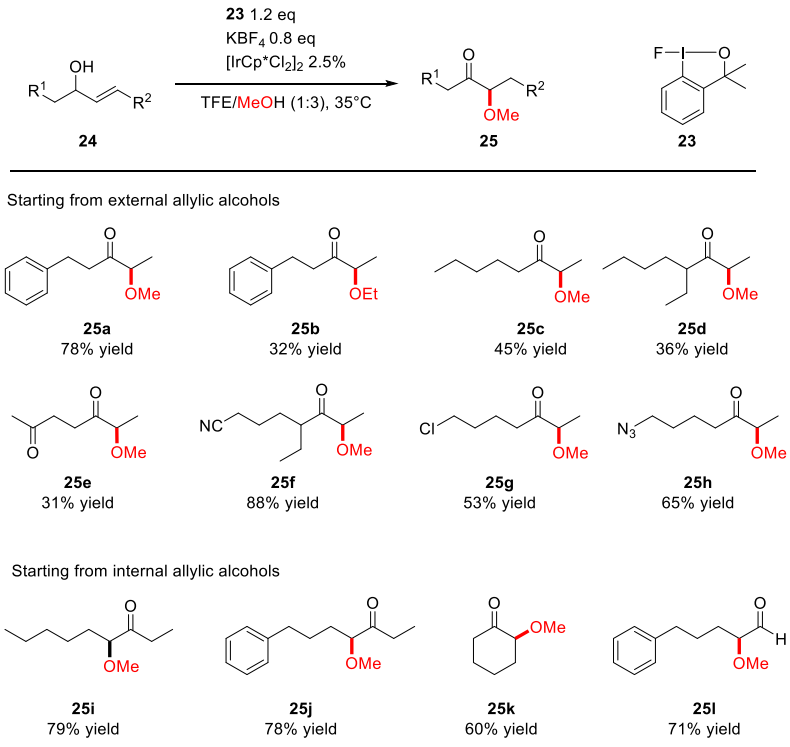


Scheme 25. Functionalization of pyridyl ketone with hypervalent iodine.

IV.2 Experimental results and scope of the reaction

The experimental protocol uses the iridium dimer $[Cp^*IrCl_2]_2$ as the catalysts for the isomerization of the allylic alcohol. A small excess of the hypervalent iodine reagent **23** is needed (1.2 equiv.), to provide good yields. Importantly, the yields were improved in the presence of 80 mol% of KBF_4 as an additive. Methanol is one of the solvents in the mixture used (TFE, 1:3, TFE/MeOH v/v), as well as being the source of the methoxy group (nucleophile). The best yields were obtained at 35 °C.

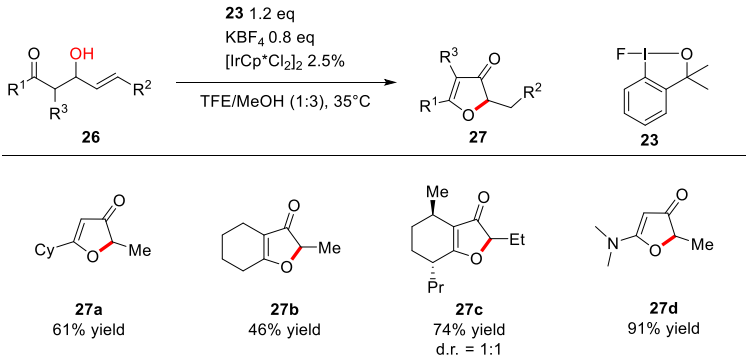
The method was successfully applied to a wide range of allylic alcohols (Scheme 26). First, allylic alcohols with terminal double bonds gave moderate to quantitative yields of methoxy ketones **25a-25h**. The reaction afforded the products without any detectable byproduct when the allylic alcohols contained functional groups such as nitrile, ketone, halogen, or even azide (**25e-25h**). It was possible to obtain the ethoxy product using ethanol as the solvent (**25b**), although in lower yields. Allylic alcohols with internal double bonds also afforded the corresponding α-methoxy ketones (**25i-25l**) in good yields, ranging from 60 to 79%.



Scheme 26. Scope for the synthesis of α-methoxy ketones from allylic alcohols.Isolated yields*

For the case of allylic alcohol with a ketone in γ position, different products were obtained. The reaction yielded five membered-rings, 3-furanones, **27a-27c** in yields ranging from 46% to 91%. Interestingly, 5-amino-3-furanone **27d** was obtained from the corresponding amide.

*Experimental results were obtained by Dr. A. Sanz-Marco and Dr. S. Martinez-Erro.



Scheme 27. Scope of the reaction affording 3-furanones.*

IV.3 Mechanistic studies

IV.3.1 Method and model selection

To study the mechanism we performed DFT calculations with the help of Gaussian 16 software suit and with M06[102] as functional and 6-31G(d,p)[120] as basis set (SDD for I).[121,122] Different mechanistic pathways were considered. First, we considered a mechanism occurring in two independent stages; first the iridium-mediated isomerization of the allylic alcohol to an enol or enolate, followed by its reaction with the hypervalent iodine reagent **23** and methanol, to yield the product. A more complex mechanism, where all parts (iridium complex, iodine(III) reagent **23** and MeOH) react in a concerted fashion could also be envisioned. The second proposal was evaluated, but the energies obtained were much higher than those expected from the experimental conditions.

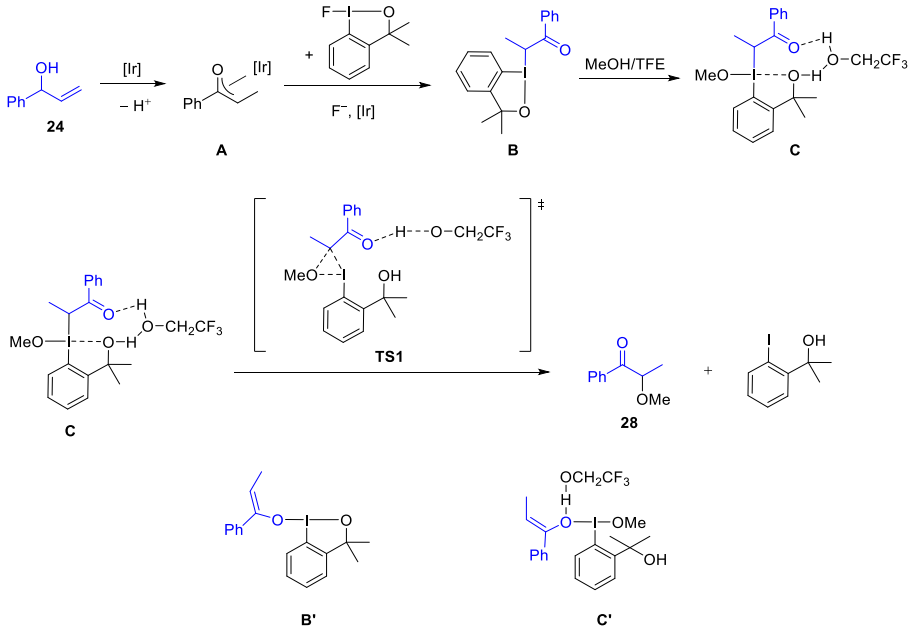
An experiment with an isolated silyl enolate reacting under the same conditions of the method yielded the expected product. This result points in the direction of the first mechanism considered. In addition, the possible presence of radical intermediates was tested with radical scavengers such as TEMPO or 2-diphenylethylene and product **27a** was obtained in high yields. Thus, the reaction does not seem to pass through radical intermediates.

From these results, we can hypothesize that the isomerization by iridium and the reaction of the resulting enolate with iodine(III) reagent **23** and methanol are two independent parts of the mechanism. We focused our study here on the second part of the reaction. The mechanism of the isomerization of the allylic alcohol catalyzed by iridium has been in studied in detail by our group recently.[123] The mechanism goes through complex multiple steps, starting with coordination, followed by oxidation of the alcohol, and insertion of an iridium hydride to form an iridium enolate moiety.

*Experimental results were obtained by Dr. A. Sanz-Marco and Dr. S. Martinez-Erro.

IV.3.2 Intermolecular reactivity mechanism

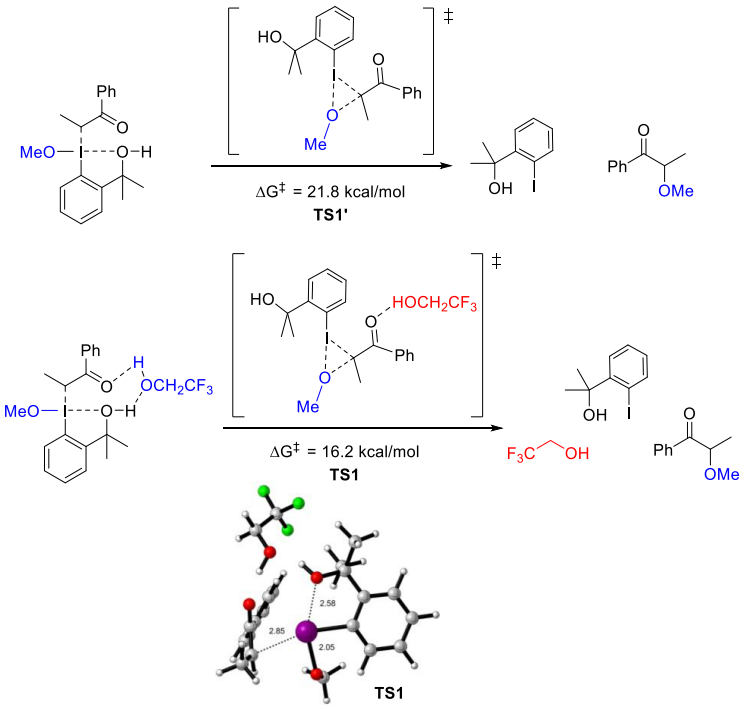
First, we investigated the mechanism of the reaction using MeOH as the nucleophile (i.e. the intermolecular reaction). The proposed mechanism (Scheme 28) starts with the reaction of enolate **A** and the iodine(III) species **23** to form an enolonium intermediate (**B**). This one reacts with MeOH to render intermediate **C**. A reductive ligand coupling forms the final product **28**. A transition state (**TS1**) was found, showing an activation energy of 16.2 kcal/mol, which is a value that fits well with the experimental conditions.



Scheme 28. Proposed mechanism for intermolecular reactivity.

During the calculations, we hypothesized that the addition of a molecule of TFE would activate the carbonyl group of the enolonium through hydrogen bonding. Without this molecule of TFE, the TS1' had an activation energy of 21.8 kcal/mol. These findings illustrate the positive effect of TFE by reducing the electron density of intermediate **C**, what facilitates the ligand coupling. A model with two molecules of TFE was also computed, affording higher activation energy (20 kcal/mol). This effect can be explained by a less significant reduction of the electron density of the complex by the second TFE molecule and an increase of the entropic effect as the structure contains multiple "free" molecules.

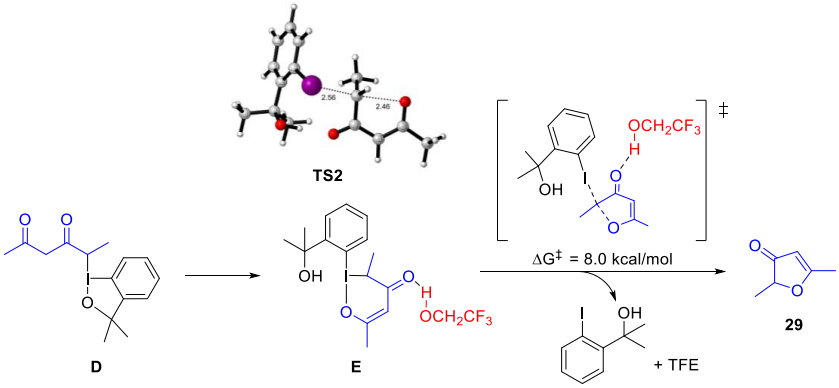
Different tautomers have been considered, like the enolonium **B'** and **C'** with I-O bonding. Similar enoloniums have been considered before in the reaction of enolates with non-cyclic iodine(III) reagents.[115] Both structures have significantly higher energies than those of **B** and **C**. Specifically, $\Delta G = 14.1$ kcal/mol higher for **B'** compared to **B**, and $\Delta G = 5.3$ kcal/mol higher for **C'** compared to **C**. A TS starting from **C'** could not be found. For those reasons, **B'** and **C'** have not been considered as possible intermediates of the reaction (Scheme 29).



Scheme 29. Proposed mechanism for intermolecular reactivity

IV.3.3 Intramolecular reactivity mechanism

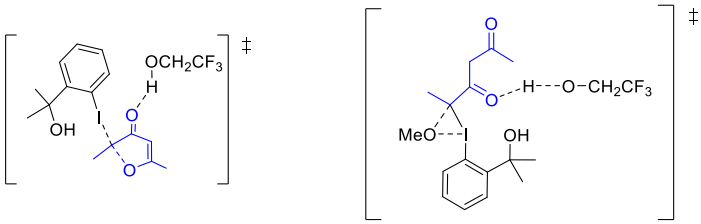
We then turned our attention to the mechanism of the intramolecular reaction, where the nucleophile is the oxygen of a carbonyl or of a carboxylic acid derivative. Similar to the previous part, enolonium **D** renders the most stable species (**E**, $\Delta G^{\ddagger} = -11.7$ kcal/mol, Scheme 30). This intramolecular rearrangement corresponds to a nucleophilic-addition/tautomerization. As in the intermolecular reaction, the product is obtained *via* a reductive ligand coupling. The energy of activation of **TS2** is 8.0 kcal/mol, resulting in a much faster reaction than the intermolecular reaction.



Scheme 30. Proposed mechanism for intramolecular reactivity.

IV.3.4 Competitive reactions

In order to explain why only the cyclic product was obtained when both reactions can happen, we computed both TSs for the same substrate. In the case of the first reaction, with the molecule of methanol reacting, the energy of activation is $\Delta G^{\ddagger} = 18.3$ kcal/mol (**TS3**). In addition, for the cyclization, only $\Delta G^{\ddagger} = 8$ kcal/mol were predicted (**TS2**). With a difference of 10 Kcal/mol, we can easily explain the absence of the product derived from the intermolecular reaction with MeOH.



Scheme 31. Key elementary steps for competitive reactions from carbonyl-functionalized allylic alcohols.

IV.4 Conclusion

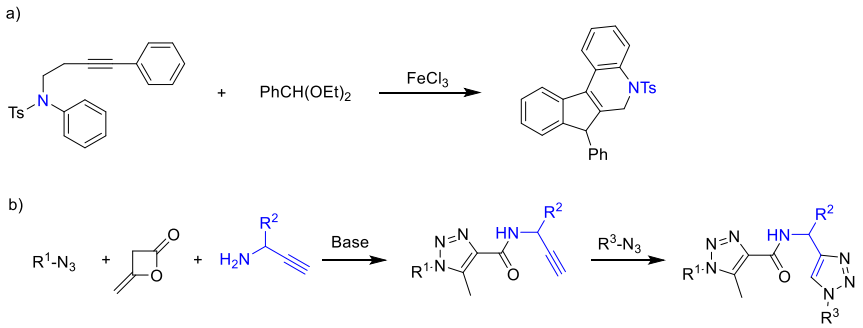
The mechanism for the synthesis of α-methoxyketones and of 3(2*H*)-furanones from allylic alcohols has been studied by computational means. The iridium catalyst seems to be involved only in the isomerization of the allylic alcohol. The resulting enolate reacts then with the hypervalent iodine reagent. The key step is a ligand coupling, promoted by trifluormethyl ethanol, which allows the formation of a new C–O bond *via* an overall umpolung strategy. Further, we have also concluded that the selectivity of the reaction resulting in formation of 3(2*H*)-furanones as sole products from carbonyl-functionalized allylic alcohols is due to a lower activation energy for the cyclization step than that of the alternative intermolecular reaction with the solvent MeOH.

V Theoretical study of manganese-catalyzed synthesis of propargylamines (Paper IV)

V.1 Introduction

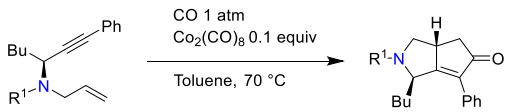
Propargylamines are common building blocks for the synthesis of N-containing organic molecules.[124] The fact that propargylamines contain multiple functional group allows to use a variety of synthetic tools to transform them. Examples include the synthesis of different heterocycles, such as pyridine,[125] quinoline,[126] hydroquinoline or even oxazolidinones.[127] For example, Yu and coworkers,[126] reported the synthesis of hydroquinolines from *N*-substituted propargyl amines and aldehyde acetals mediated by iron halides salts (Scheme 32a).[126]

The triple bond in propargyl amines can undergo click reactions upon reaction with azides.[128] Cai and coworkers developed a multicomponent one-pot reaction to quickly generate numerous bioactives compounds from a set of azides (Scheme 32b). They used first a metal free triazole synthesis from azide, ketene and the propargylanime, with DBU as base, follow by a classical, copper catalyzed click reaction with a second azide.



Scheme 32. a) Hydroquinoline synthesis from propargylamine. b) Sequential triazoles formation with propargylamines as intermediate.

Chiral propargylamines can be used for the synthesis of optically active compounds. Innocenti and co-workers used enantioenriched propargylamines to synthetize bicyclic compounds as a single diastereoisomer through a cobalt-mediated Pauson-Khand reaction (Scheme 33).[129]



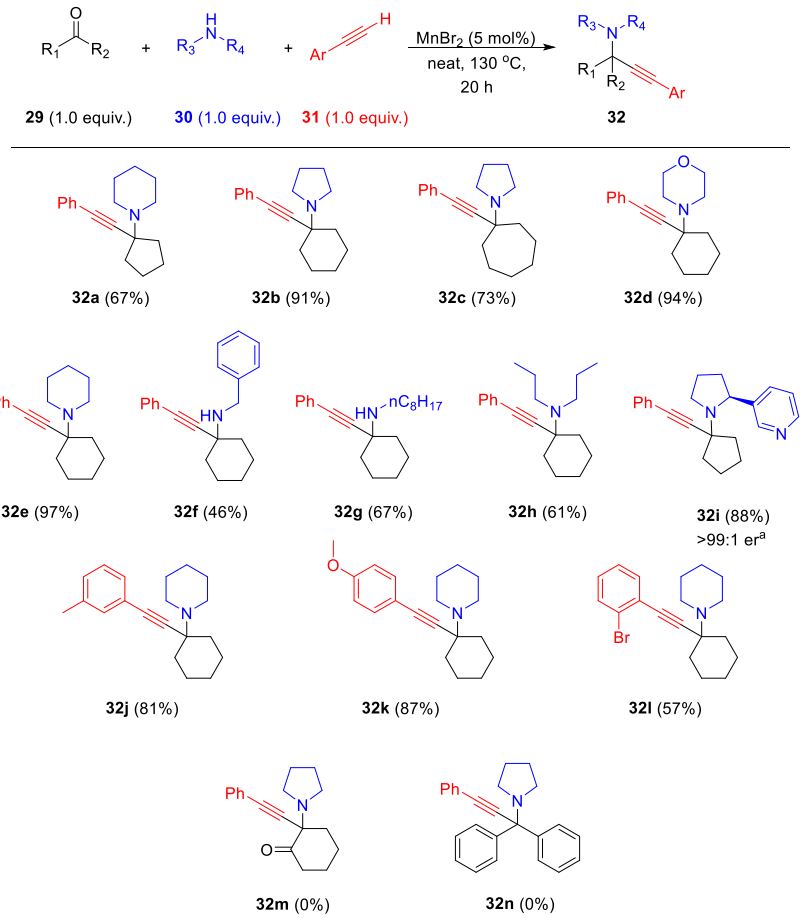
Scheme 33. Pauson-Khand reaction from chiral propargylamines.

In this chapter, the KA^2 reaction has been mediated by manganese catalysts.[130] As an abundant metal, the development of new catalytic methods mediated by manganese are of interest to the industry.[131] Manganese complexes has been used to catalyzed C–H activation reactions with concomitant C–C bond formations,[132] cross-coupling reactions[133] or hydrogenation.[134]

V.2 Scope of reaction

The KA^2 reaction studied in this chapter was experimentally developed by our collaborators, the group of Prof. Vougioukalakis.[101] In this reaction, primary or secondary amines (**30**), terminal alkynes (**31**), and ketones (**29**) are reacted using manganese bromide as catalyst. The reactions are run neat, at 130 °C for 20 h (Scheme 34).

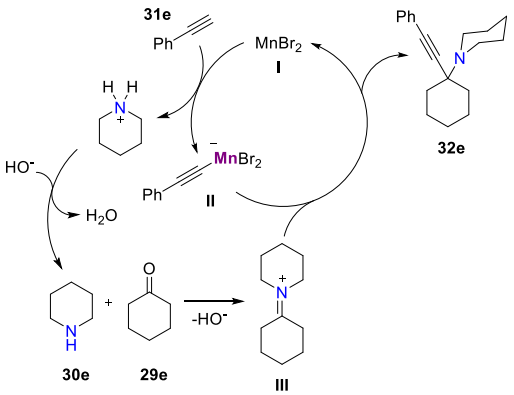
Cyclic amines such as piperidine **30a**, pyrroline **30b**, morpholine **30d** or nornicotine **30i** gave the corresponding propargyl amines (**32a**, **32b**, **32d**, **32i)** in excellent yields. With the latter amine, **32i** was obtained as a single diastereoisomer. In addition, aliphatic, primary or secondary amines afforded their corresponding products, **32g** and **32h**, respectively, in good yields. Regarding the scope of the ketones (**29**), cyclopentanone, cyclohexanone and cycloheptanone could be used successfully, as well as non-cyclic aliphatic ketones. Phenylacetylene derivatives were used in all instances. The reaction was not successful when using 1,2-cyclohexanedione nor with benzophenone.



Scheme 34. Scope of the $MnBr_2$-catalyzed KA^2 coupling. [a] enantiomeric ratio determined by ^{1}H NMR spectroscopy.

V.3 Mechanism study

Lee and co-workers proposed a mechanism for the A^3 reaction that we took as the starting point for the mechanistic investigations of the KA^2 coupling.[135] We selected cyclohexyl amine (**30e**), phenyl acetylene (**31e**) and cyclohexanone (**29e**) as the reagents. Condensation of **30e** with **29e** forms iminium **III**. In parallel, acetylene **31e** is deprotonated *in situ by* piperidine **30e**, with the assistance of the manganese salt **I**, forming Mn phenyl acetylide **II**. This intermediate reacts then with iminium **III** affording propargylic amine **32e**, and releasing $MnBr_2$ (Scheme 35).



Scheme 35. Proposed mechanism for the KA^2 reaction catalyzed by $MnBr_2$.

There only exist a few computational studies on the mechanism KA^2 reactions.[56] We therefore started the DFT calculations on the model substrates. The experimental reaction is performed in neat conditions, and as solvation is important for accurate calculations, cyclohexanone was used for solvation model for the DFT studies. Since iminium salts can be formed at temperatures lower than 130 °C, their formation was not calculated. We used the B97-D functional for the structure optimizations, together with the 6-31G(d,p) basis sets for all the atoms.

At first, we noticed that the manganese species involved in the catalytic reaction were lower in energy at quartet state instead of doublet state, with an average difference of 10 kcal/mol. This means that the metal complex holds three unpaired electrons during the reaction pathway. As the proposal for the mechanism, phenylacetylene is first deprotonated by a base, being the strongest one in the system piperidine. The triple bond coordinates to $MnBr_2$, leading to an increase acidity of the acetylenic proton. This proton is then removed by piperidine (**30e**), yielding to an ionic pair. The product was found less stable that the starting materials (4.2 kcal/mol higher). This means that the concentration of this species is low in the reaction media (Figure 16a).

The second part of the mechanism is the formation of the imminium salt **III**, by reaction of the ketone and the amine. **III** reacts then with the manganese phenyl acetylide (**II**), generating the product. The energy involved in the transition state, **TS1**, is 23.9 kcal/mol. This energy needs to be added to the energy of the previous complex, leading to a transition state at 28.9 kcal/mol, a reasonable number taking into account the experimental conditions, i.e. a temperature of 130 °C. The product consists then of the expected product (**32e**) coordinated to manganese. The energy of this complex is –1.7

kcal/mol compared to that of the starting materials. Thus, the reaction is driven by the stability of this final compound (**IV**, Figure 16b).

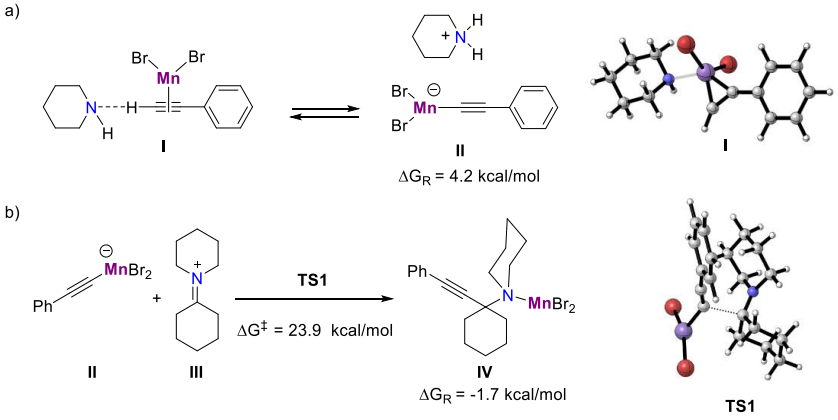


Figure 16. DFT results for: a) the deprotonation of the acetylene, b) Nucleophilic attack of the manganese complex onto the ketamine.

V.4 Conclusion

The mechanism of a manganese-catalyzed KA^2 coupling has been investigated by DFT. It was shown that upon coordination of $MnBr_2$ to the terminal alkyne substrate, a facile deprotonation takes place, forming an anionic manganese phenylacetylide complex. This species reacts with the iminium species. The moderate activation energy of the C–C bond-forming step, together with the low concentration of the manganese phenylacetylide makes this step rate-limiting, and agrees with the need for high temperatures in the experiments. With appropriate ligands on Mn that enables stabilization of the generated anionic Mn acetylide species, its concentration may be increased, which may result in reasonable reaction rates at lower temperatures.

VI Concluding remarks

The work presently reported in this thesis has the aim of studying new methods of C–C, C–N and C–O bond formations. The experimental and mechanistic aspects of those methods have been investigated with a focus on the utilization of DFT tools.

In the first project, the readily available propylamine and its derivatives demonstrated their capacity to be transformed into quaternary quinolinium salts by a multicomponent process. This reaction, catalyzed by palladium salts, allows to access substituted quinolinium salts in just one step, with a specific substitution pattern. The mechanism proposed for the reaction involves multiple C–H activations, and formation of two new C–C and one C–N bond, in a single transformation.

The second project concerns the study of the mechanism for the NHC-catalyzed formation of propargylic esters from terminal alkynes, allylic chlorides and CO_2. We could propose a mechanism for this new reaction by DFT calculations, consisting on an initial formation of an NHC/CO_2 adduct. Then, this adduct reacts with the allylic chloride reagent, to form an ester as intermediate, before the formation of the product by nucleophilic attack of the alkyne. The experimental limitations found in the scope of the reaction were also investigated.

In the third chapter, the mechanism of an umpolung reaction was studied. The transformation consists on the reaction of catalytic enolates with alcohol nucleophiles. The mechanism through which the final product is formed from the enolate was investigated, which occurs *via* enolonium intermediates. These species render the final products through a reductive elimination. Our studies also explain the selectivity obtained when there exist two competing nucleophiles.

In the last project, the mechanism of a multicomponent reaction for the synthesis of propargylamines was computationally studied by DFT. A mechanism was proposed, which indicates how the reaction may be improved in future experimental investigations.

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Appendix A. Author contribution:

PAPER I:
-Bibliography search of existing reactions, literature of C–H activation of aliphatic amine.
-All experimental results
-Bibliography search of existing mechanisms, optimal basis set and functional.
-All computational results
-Wrote the article
- Wrote the supporting information.

PAPER II:
-Bibliography search of existing mechanisms, optimal basis set and functional.
-Computation of the intermediates and transition states with DFT.
-Wrote the mechanistic part of the paper,
-Wrote of the supporting information for DFT part.

PAPER III:
-Bibliography search of existing mechanisms, optimal basis set and functional.
-Proposition of different models, computation of the intermediates and transition states with DFT.
-Wrote the DFT part of the paper,
- Wrote the supporting information for DFT part.

PAPER IV:
-Bibliography search of existing mechanisms, optimal basis set and functional.
-Proposition of different models, computation of the intermediates and transition states with DFT.
-Wrote the DFT part of the paper,
- Wrote the supporting information for DFT part.

Appendix B. Reprint Permissions

Permissions to reprint the following publications were obtained from their respective publishers:

II. Argyro T. Papastavrou, Martin Pauze, Enrique Gómez-Bengoa and Georgios C. Vougioukalakis. *ChemCatChem***2019**, *11*, 5379.

III. Amparo Sanz-Marco, Samuel Martinez-Erro, Martin Pauze, Enrique Gómez-Bengoa and Belén Martín-Matute. *Nature Communications* **2019**, *10*, 5244.

IV. Stavros P Neofotistos, Nikolaos V Tzouras, Martin Pauze, Enrique Gómez-Bengoa, Georgios C Vougioukalakis. *Advanced Synthesis & Catalysis* **2020**, *362*, 3872-3885.

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