Deep Eutectic Solvents: À la Carte Solvents for Cross-Coupling Reactions

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PROLOGUE
Part of the results reported on this thesis have been already published.†


“Manganese oxide nanoparticles supported on graphene oxide as efficient nanocatalyst for the synthesis of 1,2,4-oxadiazoles from aldehydes” F. Saadati, B. Kaboudin, R. Hasanloei, Z. Namazifar, X. Marset, G. Guillena. Submitted.


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En la presente memoria se describe el uso de líquidos eutécticos sostenibles (DESs en inglés) como medios de reacción, empleando diferentes catalizadores metálicos para llevar a cabo la síntesis de compuestos orgánicos de interés en química orgánica.

En el Primer Capítulo se detalla el uso de un catalizador heterogéneo de cobre soportado sobre magnetita en el acoplamiento cruzado deshidrogenante de tetrahidroisoquinolinas en mezclas eutécticas.

En el Segundo Capítulo se pormenoriza sobre la síntesis de un complejo tipo pinza de paladio y su empleo en la reacción de acoplamiento cruzado de Hiyama, tanto en mezclas eutécticas como en glicerol, como medios sostenibles de reacción. Asimismo, y con el fin de mejorar la compatibilidad de los catalizadores de paladio en estos líquidos eutécticos, se detalla el diseño y la síntesis de fosfinas cationicas, las cuales han probado su efectividad como ligandos de paladio en reacciones típicas de acoplamiento cruzado (Suzuki, Heck y Sonogashira) en diferentes mezclas eutécticas.

Finalmente, en el Tercer Capítulo se describen reacciones multicomponente de acoplamiento cruzado para la formación de enlaces C-S. Por un lado, se ha desarrollado una metodología para la inserción de SO\textsubscript{2} catalizada por paladio a partir de ácidos borónicos y metabisulfito de sodio. Por otro lado, una variante de la metodología anterior permitió la síntesis de sulfonamidas sustituyendo los ácidos borónicos por compuestos de triarilbismuto y nitrocompuestos bajo catalís de cobre. En este último caso, una nueva mezcla eutéctica ha sido descrita y caracterizada, tanto físico-química como biológicamente.
This Thesis describes the use of Deep Eutectic Solvents (DESs) as reaction media, employing different metallic catalysts to synthesise valuable organic compounds.

In the First Chapter the use of a heterogeneous catalyst, based on copper oxide supported on magnetite, for the cross-dehydrogenative coupling of tetrahydroisoquinolines in DES is described.

In the Second Chapter the synthesis of a palladium pincer complex and its application in the Hiyama cross-coupling reaction is discussed, both in DESs and glycerol as sustainable reaction media. Moreover, trying to enhance the compatibility of the catalysts with the DES, cationic phosphine ligands are designed and synthesised, proving their applicability in typical cross-coupling reactions (Suzuki, Heck and Sonogashira) in different deep eutectic solvents.

Finally, in the Third Chapter multicomponent cross-coupling reactions for the C-S bond formation are described. A method for the SO$_2$ insertion catalysed by palladium from boronic acids and sodium metabisulfite is developed. Furthermore, a variation of the previous method has allowed the sulfonamide synthesis, changing the boronic acids for triarylbumuth reagents and nitrocompounds, under copper catalysis. In this case, a new DES is described and characterised, both physico-chemically and biologically.
En la present memòria es descriu l'ús de líquids eutèctics (DES en anglès) com a medis de reacció sostenibles, emprant diferents catalitzadors metàllics per a dur a terme la síntesi de compostos orgànics d’interès en química orgànica.

En el Primer Capítol es detalla l'ús d'un catalitzador heterogeni de coure suportat sobre magnetita en el acoplament creuat deshidrogenant de tetrahidroisoquinolines en DES.

En el Segon Capítol es detalla la síntesi d'un complex tipus pinça de pal·ladi i el seu ús en la reacció de acoplament creuat de Hiyama, tant en DESs com en glicerol com a medis de reacció. Així mateix, i a fi de millorar la compatibilitat dels catalitzadors de pal·ladi en DES, s’han dissenyat i sintetitzat fosfines catiòniques, les quals han provat la seua efectivitat com a lligants de pal·ladi en reaccions tipiques d'acoplament creuat (Suzuki, Heck i Sonogashira) en diferents mesclles eutèctiques.

Finalment, en el Tercer Capítol es descriuen reaccions multicomponent d'acoplament creuat per a la creació d'enllaços C-S. D'una banda, s’ha desenvolupat una metodologia per a la inserció de SO₂ catalitzada per pal·ladi a partir d'àcids borònics i metabisulfit de sodi. D'altra banda, una variant de la metodologia anterior va permetre la síntesi de sulfonamides substituint els àcids borònics per compostos de triarilbismut i nitrocompostos amb catalísis de coure. En este últim cas, un nou DES ha sigut descrit i caracteritzat, tant fisc-química com biològicament.
PREFACE
Over the last few years, the research at the Organic Chemistry Department of the University of Alicante has been focused on developing methodologies aligned with the Green Chemistry Principles.

Since the use of volatile organic solvents as reaction and work-up media is one of the main environmental concerns in Fine Organic Chemistry, our research has been focused on the search of alternative solvents, pursuing green methodologies of synthesis. In particular, Deep Eutectic Solvents (DESs) have been chosen as potential alternative for traditional organic solvents as reaction media.

Since their recent discovery at the beginning of this century, the application of these eutectic mixtures has been described in several Life Science areas. Nevertheless, their use in Organic Synthesis have not been much exploited. In particular, few reports of metal-catalysed processes that took place in these solvents were found in literature.

The use of DESs as reaction media could improve the sustainability of traditional organic transformations and lead the way for the discovery of novel methods for the synthesis of high added value molecules.

The present research work is inspired by this central idea and on this basis, heterogeneous and homogeneous catalysts have been synthesised and applied to different typical Organic Chemistry reactions in DES as reaction media.

The results and conclusions of this research work would be presented following this structure:

I. GENERAL INTRODUCTION

II. RESULTS
   CHAPTER I: “Cross-Dehydrogenative Coupling”
   CHAPTER II: “Palladium catalysed C-C Cross-Coupling Reactions”
   CHAPTER III: “C-S Cross Coupling Reactions”

III. EXPERIMENTAL PART
IV. CONCLUSIONS

V. BIOGRAPHY

VI. ACKNOWLEDGEMENTS

VII. INDEX

VIII. ABBREVIATION LIST

IX. EPILOGUE
GENERAL INTRODUCTION
1. SUSTAINABLE CHEMISTRY

Human history, from the Neolithic, has been characterised by the exploitation of natural resources for our own benefit. Since the Industrial Revolution in the XVIII Century, this exploitation has been increased, becoming unsustainable. Despite the short period of time that humanity have populated Earth, the consequences of human activity have been so deep that geologist even propose a new geological epoch, Anthropocene.¹

Despite the obvious benefits obtained from Industrial Revolution onwards, several problems are also bounded to this modern society model. For instance, the Great Smog caused by industries that affected London in 1952, left behind more than 4500 fatalities due to air pollution.² Other detrimental effects include the scarcity of natural resources, which was clearly manifested during the 1970s energy crisis.³ All these modifications of natural equilibrium do not have only localized consequences, but also global effects like Global Warming.

Taking all these facts into account, the society, specially in Occident, have become aware of the unsustainability of our industrial production. Over the last few years, sustainability has become a key factor in modern life. Society’s rapidly evolving needs cause an increase in industrial production, and thus, more environmental concerns. So that, production must be more efficient, not only in terms of productivity but also from an ecological point of view. This trend was reflected in 2015 by the United Nations when a development plan focused on sustainability was published under the title “Transforming Our World: The 2030 Agenda for Sustainable Development”.⁴ This trend is applicable to all aspects of Modern Society, including Chemistry.

In this matter, professor P. T. Anastas proposed the concept of Green Chemistry in 1991, which involves a mentality change from traditional efficiency (economical point of view focused mainly on chemical yields) to considering global sustainability (reduction of by-products and supressing the use of toxic or

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dangerous compounds, among others). This new trend was summed up in 12 basic principles that every chemical process should follow (Figure 1):\(^5\)

![Diagram of the 12 principles of Green Chemistry](image)

**Figure 1.** The 12 principles of Green Chemistry.

1. *Prevention*: avoiding waste formation instead of dealing with it once it is formed.
2. *Atom economy*: the incorporation of the starting materials into the final product must be maximised.
3. *Use of substances with less toxicity*: this aspect must be taken into account when planning a synthetic route, for starting materials and for any possible product formed during the reaction.
4. *Designing safer compounds*: chemicals must be designed attending to its function but also minimising its toxicity.
5. *Use of safer solvents and auxiliaries*: when possible, the use of auxiliary substances should be avoided, or at least, innocuous chemicals should be employed.

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6. Energy optimization: energy requirements must be considered, trying to use the mildest conditions possible.

7. Use of renewable feedstocks: avoiding, when possible, the use of depleting substances.

8. Reduce derivatives: avoid the use of additional steps, which generate more waste.

9. Catalysis: catalytic amounts should be used instead of stoichiometric when possible.

10. Biodegradability: avoid the persistence of substances in the environment at the end of their function.

11. Pollution prevention: new analytical methodologies that allow real-time analysis and control prior to generation of hazardous substances are needed.

12. Accident prevention: all the substances involved in a chemical process should be chosen to minimise potential accidents.

Following these principles when designing a chemical process, its sustainability would be greatly improved. Nevertheless, engaging all of them at the same time may become nearly an impossible task with the current knowledge. Some of these principles need to be more urgently addressed, especially the ones related to the use of renewable feedstocks.

When applying sustainable principles to Fine Chemistry, such as drug, cosmetics or agriculture industries, we rapidly identify the use of solvents as one of the major issues that should be addressed. Traditionally, volatile organic compounds (VOCs) have been employed as solvents. These compounds are usually petrol derivatives (not renewable, and therefore against 7th principle), most of them are flammable, very toxic to human and the environment, non-degradable, and their low boiling points make easier its accumulation in the atmosphere, having a very high carbon footprint.

According to recent reports, solvents constitute from 80 to 90% of non-aqueous mass employed when synthesising an active pharmaceutical ingredient (API). Owing these facts, finding alternative solvents is crucial in order to improve the sustainability of these industries.

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1.1. ALTERNATIVE SOLVENTS

The selection of an alternative green solvent depends on many factors, such as chemical efficiency, human and environmental toxicity, manipulation safety or industrial limitations. For these reasons, there is not a perfect solvent, and the best choice depends on the specific application. Taking this into account, several alternative solvents have been proposed over the last few years, all of them having several advantages and drawbacks.

Following sustainability standards, the best possible solvent is “no solvent” at all. Nevertheless, solvents have generally a crucial role in the reaction outcome. Solvents allow heat and mass transference over the reaction bulk, they may stabilise transition states or modify their reactivity. For instance, an appropriate solvent can increase a reaction chemo- or regio-selectivity. For these reasons, the use of solvent is not always avoidable, and some alternatives to VOC solvents have been tested. Nevertheless, finding a liquid that could be defined as a sustainable solvent is a difficult task.

When thinking about alternative solvents, the use of water may seem an obvious choice. Water fulfil most of the requirements to be considered a good solvent, since it is very cheap, biorenewable, non-flammable, and non-toxic for humans or environment. Despite its advantages, the use of water in organic reactions also involves major drawbacks, as low solubility of organic reagents, instability of some catalyst, the incompatibility of several organic functionalities that can be hydrolysed or the work-up process which relies in the use of VOC solvents.

Supercritical fluids have also been considered as an alternative, specially CO$_2$ and water. Again, they are cheap and renewable substances, but the solubility of most organic compounds in them is very low. Also, CO$_2$ can react easily with nucleophiles. Nevertheless, the major drawback of these solvents is the

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12 A. Chanda, V. V. Fokin, Chem. Rev. 2009, 109, 725-748.
high cost of the equipment necessary to achieve supercritical conditions. Because of that, supercritical fluids can be very interesting for specific industrial applications, but not as solvents for general use.

*Fluorinated solvents* are also an interesting choice, since they are reported to be non-toxic, stable and non-flammable.\textsuperscript{15-16} However, these compounds decompose when heated at high temperatures, releasing substances which persist in the atmosphere, which added to the fact that its price is quite high, reduces its attractiveness as sustainable solvent.

Taking the bio-renewability factor into account, *biomass-derived solvents* seem an excellent choice. Ethanol, γ-valerolactone,\textsuperscript{17} limonene, glycerol,\textsuperscript{18,19,20} ethyl lactate\textsuperscript{21-22} or 2-methyltetrahydrofuran\textsuperscript{23} are some of the solvents which have attracted interest in Sustainable Chemistry recently. In this case, the solubility of organic compounds is quite good, they are usually cheap and safe to use, although its flammability is comparable to VOC solvents. Probably, the major drawback of these solvents is that all of them have similar properties, limiting their use for a wide range of different reactions. Therefore, the incapability of solvent modulation hampers the applicability of these solvents.

More recently, *ionic liquids* (ILs) were proposed as the best alternative to VOC solvents. ILs are fluids composed exclusively by ions with a melting point below 100 °C. They are usually composed by an organic cation, such as an imidazolium or pyridinium moiety, and a poor coordinating anion, such as BF\textsubscript{4} or PF\textsubscript{6}.\textsuperscript{24-25} One of the most interesting features of these solvents is their absence of vapor pressure, which make them safe to handle. ILs are usually stable even at high temperatures, are immiscible with most of organic solvents and can have catalytic activity by their own. Moreover, they afford the opportunity for solvent design,
with fine tuning properties for each designed process. On the other hand, some of their properties are incompatible with Sustainable Chemistry standards. When Ionic Liquids were discovered, they were proposed to be non-toxic. However, when ILs became more relevant, their toxicity was underestimated. They have been found to be quite toxic and poorly biodegradable recently.\textsuperscript{26} In fact, it has been stated that most of ILs are acutely toxic, being the negligible vapor pressure the only advantage form a environmental point of view.\textsuperscript{27} Also, their water stability is rather low, and their economic cost is very high, since they must be synthetized usually through several steps, showing a low atom economy. Finally, their origin from petrol made their sustainability low at long term.

Last decade, a new kind of solvent emerged. Deep Eutectic Solvents (DESs) were proposed by Abbott at the beginning of this century, featuring most of the advantages of ILs but minimizing their drawbacks.\textsuperscript{28}

1.1.1. Deep Eutectic Solvents

Deep Eutectic Solvents are defined as systems formed from a eutectic mixture of two or more components, usually Lewis or Bronsted acids and bases which can contain a variety of anionic and/or cationic species.\textsuperscript{29} The term eutectic, from Greek $\varepsilon\upnu\tau\epsilon\kappa\alpha\varsigma$, melting,\textsuperscript{30} was employed for the first time by Frederick Guthrie in 1884 to describe homogeneous systems which melt at a single temperature lower than the melting point of either of their components.\textsuperscript{31} The constituents of the DES interact via intermolecular forces (being hydrogen bonding one of the most important ones) but no covalent or ionic bonds are involved in the eutectic formation. These interactions decrease the lattice energy, explaining the drop in melting point compared with their components (Figure 2). The components of DES mixtures are usually a quaternary ammonium salt complexed with a

\textsuperscript{27} T. P. T. Pham, C.-W. Cho, Y.-S. Yun, Water Res. \textbf{2010}, \textit{44}, 352-372.
hydrogen bond donor (HBD) or a metal salt.\textsuperscript{29} Attending this definition, four types of DESs have been proposed:

- **Type 1** (Cat\textsuperscript{X} zMCl\textsubscript{x}): formed from a quaternary ammonium salt and a metal chloride. Due to the use of anhydrous metal halides in their preparation, they are usually more expensive and toxic compared to the other types of DES, which limits its general use as a green solvent.

- **Type 2** (Cat\textsuperscript{X} zMCl\textsubscript{x} yH\textsubscript{2}O): differ from type 1 for having hydrated metal halides instead of nonhydrated ones. The number of type 2 DESs is much bigger due to the higher availability and stability of hydrated metal salts, affording mixtures which are usually liquid at lower temperatures.

- **Type 3** (Cat\textsuperscript{X} zRZ): formed from a quaternary ammonium salt and hydrogen bond donors (HBDs). This is the most interesting type from a sustainable point of view, since both, the ammonium salt and the HDB can be natural products (e.g. alcohols, aminoacids or amides). In those cases, DESs are also called NADESs (i.e. natural deep eutectic solvents).\textsuperscript{32}

- **Type 4** (MCl\textsubscript{x} +RZ=MCl\textsubscript{x-1}RZ+ MCl\textsubscript{x+1}): formed from transition metal salts and HBDs. They have been utilised mainly in the electrodeposition of metals.

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{figure2.png}
\caption{Phase diagram of a DES.}
\end{figure}

Eutectic mixtures do share some characteristics with ILs, as the negligible vapor pressure, but they offer some advantages over the formers. First of all, the synthesis of DESs only involves mixing their components on an appropriate ratio and heating it slightly until a melt is formed. The atom economy of the process is complete, and no by-products are formed, which is also an important aspect for achieving sustainability. Although, since its first report, the definition of DESs as non-toxic media have become a constant, generalization about the non-toxicity of DESs should be avoided. Attending the previous classification, types I, III and IV of DESs cannot be considered non-toxic, since are formed by metal salts, which are toxic for humans and environment.

The sustainability of DESs can only be related to type III, formed by an organic salt and a hydrogen bond donor. Again, toxicity depends on the components of each DESs, with first studies reporting very low toxicities for this type of mixtures.\(^{33}\)

Another advantage is the possibility of using highly available and/or natural products as components of DESs, decreasing their potential toxicity and assuring good biodegradability properties. Some of the most common DES hydrogen bond acceptors are depicted in Figure 3.

![Figure 3. Hydrogen bond acceptors.](image)

In fact, the most commonly used salt to form DES is choline chloride (ChCl), which is an important compound in the animal feedstuff industry with 160000 tons being produced every year. Furthermore, it has an atom efficient synthesis from

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trimethylamine, ethylene oxide and hydrochloric acid in a continuous, single-stream process (Scheme 1).\textsuperscript{34}

\[
\begin{align*}
\text{Me}_3\text{N}^+ & + \text{HCl} + \underset{\text{H}}{\text{OH}} \\
\rightarrow & \text{Me}_3\text{N}^+\text{Cl} \underset{\text{OH}}{\underset{\text{H}}{\text{OH}}} \\
\end{align*}
\]

\textbf{Scheme 1.} Choline chloride synthesis.

About the hydrogen bond donors, there are countless options to form a eutectic mixture, including naturally occurring substances as glucose, citric acid or urea, among others (Figure 4).

\textbf{Figure 4.} Hydrogen bond donors.

Despite the fact that eutectic mixtures have been known for decades, only recently its use as solvents started to become popular. For this reason, there is still a lot to be discovered about this field, but since it is attracting interest of all kinds of scientists, a global understanding of DES is being developed. For instance, it was stated that the driving force of the DES formation was the charge delocalization between the anion and the HBD through hydrogen bond interactions, but only NMR, IR and conductivity experiments supported this fact. Recently, an atomistic modelling from neutron diffraction from ChCl:urea (1:2) was proposed, being the first experimental technique applied to DESs to confirm the phenomena after the DESs formation.\textsuperscript{35} This technique evaluates mixture of hydrogenated and deuterated components of DES using a small angle neutron diffractometer for amorphous and liquid samples (SANDALS).


The analysis reported several structural conformations that are preferable, but on average, each chloride, is solvated by two urea molecules, hydrogen bonded at a distance of 2.2 Å. At the same time, every urea molecule is associated via hydrogen bonding with several other urea molecules. Each chloride is strongly associated with the hydroxyl group of one choline molecule. Furthermore, there is a shell of 7 other choline molecules oriented in opposite directions solvating each choline (Figure 5).

**Figure 5.** Spatial density functions showing probabilistic 3D structures of the components of ChCl:urea (1:2). Yellow surfaces depict choline cations, purple surfaces represent urea molecules and green show chloride anions.

In general, it can be said that urea and choline work synergistically to sandwich the chloride anion via hydrogen bonding forces, while maximizing its interaction with one another. Thus, the hypothesis that hydrogen-bonding was the driving force of DESs formation was confirmed experimentally.

The same group has also studied the effect of water upon DESs nanostructure. This fact is extremely important due to the hygroscopic character of most of the salts and some HBD used in eutectic mixtures. This can lead to poor reproducibility due to different amounts of water present in the DESs. Some physical properties of the eutectic mixtures can be tuned by the addition of water, like reducing the viscosity. Nevertheless, the limit between DES/water mixture and an aqueous solution of the DES needed to be clarified. The mixture of

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ChCl:urea (1:2) containing a wide range of water was studied by neutron total scattering. The results showed that for low amounts of water, ChCl:urea:water (1:2:1), water contributed to the hydrogen-bonding network and enhances the choline-urea interaction. For higher concentration of water, between 1:2 and 1:10 (DES:water molar ratio), there exist DES clusters separated by the diluent. Starting in 1:15 molar ratio (DES:water) the system is described as an aqueous solution of DES at the molecular level.37

1.1.2. Applications of DESs

Since the first report about DESs, many applications have been found for these neoteric solvents. For instance, taking advantage of its solubilising properties, they have been successfully applied to metal processing, including metal extraction, processing of metal oxides, electrodeposition and electropolishing.39 Separation science has also used the unique properties of DESs,40 including Analytical Chemistry where the stabilisation skills and their extraction power of DESs open the door for the development of new techniques.41

With these precedents, DESs were fast considered to be used as reaction mediums in organic transformations. One of the first applications in this regard was the synthesis of biodiesel, where DESs can act both as co-solvent and as catalyst for transesterification reaction.42 Biocatalysis is another research area where eutectic mixtures have been employed as solvents, since they are able to solubilise and stabilise some proteins.43 The growing popularity of DESs (Figure 6), motivated researchers to develop new synthetic methodologies based on the use of these neoteric solvents.

Taking into account the special properties of DESs, compared to traditional VOC solvents (including its ionic nature and presence of strong hydrogen-bonding), the possibilities of interacting with reagents are higher. Therefore, they

can have a further role beyond the solubilisation of the starting materials. Attending to this fact, reactions performed in DESs can be differentiated between reactions in which DESs act as catalysts or reagents from those in which they have a less active role and act as innocent reaction media.

1.1.3. DES-catalysed reactions

DESs types I, II and IV contain a metal halide in their structure, having a Lewis acidic character. Thus, these DESs can act both as solvent and as catalyst for several organic transformations. The mixture of ChCl:ZnCl\(_2\) (1:2) have been applied to several organic transformations.\(^{44}\) One of the earliest reports about the use of this DES in an organic transformation was the Fischer indole synthesis, where DES act as stoichiometric Lewis-acid reagent (1-3 eq. were used).\(^{45}\) Specially interesting is the fact that the product could be isolated easily by sublimation, since the vapour pressure of the DES is negligible (Scheme 2).

![Scheme 2. Fischer indole reaction in ChCl:ZnCl\(_2\) (1:2).](image)

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Another classic reaction that has been reported in DESs is the esterification reaction. Despite the difficulties typically found using longer than C10 carboxylic acids or alcohols as substrates, the esterification of acids between C8-C22 using ChCl:ZnCl₂ (1:2) as catalyst has been accomplished. Furthermore, the catalyst could be recycled up to six times without a significant drop in the yield (Scheme 3). A similar reaction was reported for the O-acetylation of cellulose and monosaccharides.

![Scheme 3. Esterification of long chain acids in DES.](image)

The synthesis of amides from aldehydes has also been reported using this Lewis-acid eutectic mixture. The methodology involves the reaction with hydroxylamine, which undergoes a dehydration to yield a nitrile. This nitrile reacts then with the in situ generated water to afford a primary amide. The reaction was also tested starting directly with aromatic nitriles, obtaining excellent yields in both cases (Scheme 4).

![Scheme 4. Synthesis of amides in ChCl:ZnCl₂ (1:2).](image)

Other organic transformations performed in ChCl:ZnCl₂ (1:2) include Diels-Alder reaction, Biginelli reaction, Kabachnik–Fields reaction.

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multicomponent synthesis of substituted imidazoles,\textsuperscript{52} Friedel-Craft alkylation\textsuperscript{53} and acylation,\textsuperscript{54} Mannich reaction\textsuperscript{55} or A³-coupling,\textsuperscript{56} among others.

Nevertheless, the presence of a metal salt is not mandatory for the DESs to have an active role in the reaction. In some cases, DES components can act as reagents. For instance, the Biginelli reaction to synthesize dihydropyrimidinones from aldehydes, keto esters and dimethyl urea (DMU) has been reported. In this case, DMU act as a component of a eutectic mixture with tartaric acid but also as a reagent which is incorporated into the final product of this multicomponent reaction (Scheme 5).\textsuperscript{57}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\begin{array}{c}
R^1 \text{H} \quad \text{O} \\
R^2 \text{R}^3
\end{array}
\end{align*}
\]

\[
\text{L-}(\pm)-\text{tartaric acid DMU (7:3) 70 °C 14 examples 70-99 \%}
\]

Scheme 5. Synthesis of 3,4-dihydropyrimidin-2-ones.

A similar reaction was reported in 2015 for the synthesis of bisamides, using an aldehyde in ChCl:urea as reaction media. In this case, the aldehyde reacted with urea, being the large-scale reaction feasible and without the need of chromatographic purification, since filtering the solution and washing with water afforded the pure product.\textsuperscript{58}

Non-containing metal DESs can also act as organocatalysts due to their basic/acidic properties. The archetypal ChCl:urea (1:2) has been reported to act as a base catalyst for several reactions, such as condensation like Knoevenagel,\textsuperscript{59} Perkins reaction\textsuperscript{60} or Paul-Knorr synthesis.\textsuperscript{61} The multicomponent synthesis of pyran derivatives has also been reported in ChCl:urea (1:2), with a proposed

\textsuperscript{56} M. Obst, A. Srivastava, S. Baskaran, B. König, \textit{Synlett} \textbf{2018}, \textit{29}, 185-188.
mechanism in which urea activates the starting materials being proposed (Scheme 6).\textsuperscript{62}

\[
\begin{align*}
\text{O} & \quad + \text{N}\text{C} = \text{CN} + \text{O} = \text{C} = \text{O} \quad \xrightarrow{\text{ChCl:urea (1:2)}} \quad \text{O} \quad \text{Ar} \quad \text{CN} \\
\text{Ar} & \quad \text{R}^1 \quad \text{R}^2 \\
80{\degree}\text{C} & \\
17 \text{ examples} & \\
75-95\% & 
\end{align*}
\]

\textbf{Scheme 6.} Synthesis of pyran and benzopyran derivatives in DES.

\subsection*{1.1.4. DESs as innocent reaction media}

Despite the fact that solvents can have a critical effect in the reaction outcome, in some cases the role of DES has not been clearly identified, but it cannot be described as acid/base catalyst or reagent. Within this type of reactions, ChCl:urea (1:2) is again one of the most commonly employed DES found in recent literature.

Among these examples of DESs as innocent media, bromination of substituted 1-amino-anthra-9,10-quinones was reported.\textsuperscript{63} In this report, the use of strong acids or VOC solvents is replaced by DES. Furthermore, products were easily recovered by filtration after adding water to the DESs, and the reaction media was reused five times by evaporating the water.

A thia-Michael addition in ChCl:urea (1:2) was also reported. Unsymmetrical dialkylsulfides were obtained from alkyl halides, thiourea and acenes. In this case, NaOH was used as a base and thiourea served as a sulphur source, being an odourless approach. Furthermore, the major by-product of this reaction was urea, which could be incorporated into the solvent structure.\textsuperscript{64}

Another reaction involving C-S bond formation in DES is the synthesis of dithiocarbamates from epoxides, amines and carbon disulphide (Scheme 7).\textsuperscript{65} The solvent of this multicomponent reaction was recovered and reused 4 times without a significant decrease in the reaction yield.

\textsuperscript{63} S. B. Phadare, G. S. Shankarling, Green Chem. 2010, 12, 458-462.
\textsuperscript{65} N. Azizi, E. Ghelibegio, RSC Adv. 2012, 2, 7413-7416.
The same DES has also been used in the regioselective reduction of epoxides, aldehydes and ketones using NaBH\textsubscript{4} as reducing agent (Scheme 8).\textsuperscript{66} A similar procedure was also reported for the reducing amination of aldehydes and ketones to afford secondary amines. In this case, authors claim that DES can act as catalyst, activating the carbonyl through hydrogen-bonding.\textsuperscript{67}

Despite the sensitivity of organometallic reagents, some examples of the use of organomagnesium and organolithium compounds in DES have been reported so far.\textsuperscript{69} Normally, this kind of reagents should be only used employing dry solvents and under inert atmosphere and low temperatures, since they react vigorously with water and carbon dioxide. Eutectic mixtures based on ammonium salts are normally highly hygroscopic, and therefore they do not seem to be a good solvent for these reactions. Surprisingly, the addition of Grignard and organolithium reagents to ketones in ChCl:glycerol (1:2) was reported in 2014 under air atmosphere at room temperature (Scheme 9).\textsuperscript{70} Authors proposed a kinetic activation of alkylation reagents by an ate complex formation, favouring the nucleophilic addition over hydrolysis.\textsuperscript{71}

Scheme 9. Addition of organometallic reagents to ketones.

Also interesting is the ortho-lithiation of diaryltetrahydrofurans, followed by reaction with an electrophile. In this case, the reaction between t-BuLi and the aromatic ring took place at 0 °C using cyclopentylmethyl ether as solvent. Then, the solution of the corresponding organolithium compound was added to an electrophile-containing DES solution, where the alkylation took place in an atmosphere-opened vessel. Later, the same research group reported that o-tolyl-substituted tetrahydrofuran derivatives could be lithiated at the benzylic position, followed by an alkylative ring-opening using 2 eq. of organolithium reagent (Scheme 10).

Scheme 10. Alkylative ring opening of tetrahydrofurans in deep eutectic solvents.

Organolithium reagents have also been added to imines in DES media, yielding secondary amines in excellent yields. The reaction employed ChCl:glycerol (1:2) as reaction media, 1.4 equivalents of organolithium reagent and took only 3 seconds at room temperature to be completed. This procedure was also effective for synthetizing 2-substituted dihydroquinolines from the corresponding quinolines.

Even more interesting was the one-pot synthesis of tertiary alcohols from allylic alcohols. In this report, a ruthenium-catalysed isomerization of allylic alcohols is followed by addition of organolithium or Grignard reagents to the \textit{in situ} generated ketone (Scheme 11).\textsuperscript{75}

\begin{center}
\begin{align*}
\text{PhCH}-\text{CH(OH)Ph} & \xrightarrow{\text{RuCl}_2(12); 50-75^\circ\text{C}}} \text{PhCH} & \text{-COCHPh} \\
\text{PhCH}-\text{CH(OH)Ph}(5 \text{ mol\%}) & \xrightarrow{\text{R-M} \ (M=\text{Li or MgX})} \text{PhCH} & \text{-COCHPh} \\
\end{align*}
\end{center}

\textbf{Scheme 11.} Ru-catalysed alcohol isomerisation followed by organometallic addition.

The addition of organolithium reagents to nitriles has also been reported in DES. Two equivalents of organometallic reagent were used to transform the nitriles into the corresponding primary ketimines, which were subsequently hydrolyzed affording the corresponding ketones.\textsuperscript{76} Although this reaction was reported in DES, better yields were obtained in water or neat glycerol as reaction media. All these reports suggest a bright future for the main-group organometallic chemistry in air and moisture compatible organic synthesis.\textsuperscript{77}

1.1.5. \textbf{Metal-catalysed reaction in DES as reaction media}

It is widely known that metallic complexes are able to catalyse stoichiometric organic transformations employing milder reaction conditions. But these complexes can also open the gates for new reactions which cannot be performed otherwise. Metallic complexes catalysts are traditionally related to homogeneous catalysis, being usually designed to be employed in organic solvents. Due to its undeniable interest and the problematic with VOC solvents discussed above, the development of metal-catalysed organic transformations in DESs is an interesting topic to be studied. When the project of the present doctoral thesis started, only a few examples of the use of metallic catalysts were reported in DESs.


As was depicted in Scheme 11, a ruthenium catalysed isomerization of secondary alcohols into saturated carbonyl compounds was reported in ChCl:glycerol (1:2) at 75 °C. Only 10 examples were reported with yields ranging from 36 to 99% with varying catalyst loadings, down to 0.2 mol%. The same catalyst was previously reported in ILs, observing a dramatic increase in activity when the reaction was performed in DESs due to hydrogen bond interactions between DESs and catalyst, according to authors. Furthermore, the use of DES as reaction media allowed the recyclability of the catalyst for four consecutive cycles, although longer reaction times were needed for achieving the same yield.

Cycloisomerization of γ-alkynoic acids has also been performed in ChCl:urea employing an iminophosphorane-Au(I) complex. Again, the catalyst was recycled four times in a reaction carried out under air atmosphere (Scheme 12). A similar system was used for the cycloisomerization of Z-enynols to yield the corresponding furane, which was then submitted to a Diels-Alder reaction with activated alkynes.

![Scheme 12. Cycloisomerization of γ-alkynoic acids catalysed by gold(I) in DES.](image)

Other metallic catalysed processes in DES include the Diels-Alder reaction promoted by scandium triflate in L-carnitine:urea as reaction media in a pioneering work by B. König. In this paper, two examples of palladium-catalysed cross-couplings (Heck and Sonogashira) were also reported, and they will be further

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discussed. Moreover, an example of click-chemistry catalysed by copper iodide was also presented, employing a tertiary mixture D-sorbitol:urea:NH₄Cl (Scheme 13).

\[
\text{Ph}^\text{Br} + \text{Ph} + \text{NaN}_3 \xrightarrow{\text{D-sorbitol:urea:NH}_4\text{Cl}} \text{Ph} \quad \text{Cul (5 mol%) at } 85^\circ\text{C}, 5 \text{ h}
\]

Scheme 13. One pot synthesis of 1,4-substituted 1,2,3-triazoles.

Regarding palladium-catalysed processes, Stille reaction between aryl halides and organotin reagents catalysed by [Pd₂(dba)₃·CHCl₃] was performed in different melts formed by ammonium chloride, N,N’-dimethylurea and different sugars (lactose, sorbitol, mannitol or maltose). In this case, AsPh₃ was required as ligand for the reaction to work in good yields. The Tsuji-Trost reaction has been performed in a low melting mixture (LMM) composed by methylated β-cyclodextrine and N,N’-dimethylurea. Pd(OAc)₂ was used as palladium source with P[m-(NaSO₂)C₆H₄]₃ (TPPTS) as ligand (Scheme 14). The need of using this type of ligand confirms the special requirements of this medium regarding ligand design.

\[
\text{O} \quad \text{Pd(OAc)}_2 \quad 1 \text{ mol%}
\]
\[
\text{TPPTS (9 mol%)}
\]
\[
\text{Methylated β-CD:DMU at } 70^\circ\text{C}
\]

Scheme 14. Tsuji-Trost reaction.

Another interesting reaction is the oxidation of toluene to benzaldehyde, with important industrial applications. This reaction has been employed employing FeCl₃ as catalyst and H₂O₂ as oxidant, although the reaction did not take place completely in DES, since a biphasic mixture of ChCl:ethylene glycol (1:2) and toluene was used. Another reaction with potential industrial application is the dehydration of xylan and xylose to afford furfural using metal chlorides as catalyst.
(FeCl₃, AlCl₃ and CrCl₃). This reaction has been carried out in ChCl:citric acid and ChCl:oxalic acid obtaining moderate yields in both cases.⁸⁶

A multicomponent synthesis of imidazo[1,2-α]pyridines from arylacetylenes, aldehydes and 2-aminopyridines, catalysed by CuFeO₂ was also reported.⁸⁸ Due to the superparamagnetic properties of the catalyst, an easy recovery of the catalyst was possible, being recycled up to five times without a significant decrease in the catalytic activity (Scheme 15).

Scheme 15. Synthesis of imidazo[1,2-α]pyridines using CuFeO₂ in citric acid:DMU.

Hydrogenations have been explored in this neoteric medium as well. The first report in this matter employed Wilkinson’s catalyst used under 1 atm of H₂ in citric acid:DMU to hydrogenate methyl α-cinnamate in quantitative yields.⁸⁹

Scheme 16. Rh-catalysed hydrogenation in DES.

Finally, Rh(acac)(CO)₂ was used as catalyst for the hydroformilation of 1-decene, using TPPTS as ligand and a eutectic mixture based on DMU and methylated β-CD under a pressure of 50 bar (H₂:CO, 1:1).⁸⁴

More recently, while this thesis project was ongoing, more examples of metal-catalysed processes in DESs have been reported, proving the growing interest in this field.

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⁸⁶ L. Zhang, H. Yu, BioResources 2013, 8, 6014-6025.
Magnetite nanoparticles were reported to catalyse the synthesis of carbanates and monosubstituted ureas from urea and alcohols or amines. Reactions were performed in ChCl:ZnCl$_2$ at 130 °C for 6 h, employing 10 mol% of catalyst. This methodology is compatible with aromatic and aliphatic alcohols and amines, affording moderate to excellent yields. Moreover, the catalyst showed an excellent performance when reused in five consecutive cycles (Scheme 17).\(^\text{90}\)

\[\text{R}-\text{N}^+\text{NH}_2 \quad \xrightarrow{\text{Fe}_2\text{O}_3 (10 \text{ mol\%})} \quad \text{CHCl}_2\text{ZnCl}_2 (1:1) \quad 130 ^{\circ} \text{C}, 6 \text{ h} \quad \text{NHRR}^+ \quad \xrightarrow{\text{R}-\text{OH}} \quad \text{CHCl}_2\text{ZnCl}_2 (1:1) \quad 130 ^{\circ} \text{C}, 6 \text{ h} \quad \text{H}_2\text{N}^+\text{NH}_2 \quad \xrightarrow{\text{Fe}_2\text{O}_3 (10 \text{ mol\%})} \quad \text{CHCl}_2\text{ZnCl}_2 (1:1) \quad 130 ^{\circ} \text{C}, 6 \text{ h} \quad \text{H}_2\text{N}^+\text{OR} \]

**Scheme 17.** Synthesis of monosubstituted ureas and carbanates.

Recent palladium-based catalysis include the aminocarbonylation of aryl iodides has been carried out in ChCl:urea (1:2) and ChCl:glycerol (1:2) using 5 mol% of Pd(OAc)$_2$ as catalyst. This coupling was achieved by using aryl iodides, amines (6 eq.), K$_2$CO$_3$ (3 eq.) under 27 atm of CO. 13 examples were reported, with yields ranging from 15 to 95%. Furthermore, the catalyst was recycled up to four times observing only partial decrease in the reaction yield (Scheme 18).\(^\text{91}\)

\[\text{R}^1\text{I} \quad + \quad \text{R}^2\text{N}^+\text{H}_2 \quad \xrightarrow{\text{Pd(OAc)}_2 (5 \text{ mol\%})} \quad \text{CO (27 atm)} \quad \text{DES} \quad 60 ^{\circ} \text{C}, 12 \text{ h} \quad \text{R}^1\text{I} \quad + \quad \text{R}^2\text{N}^+\text{OR} \]

**Scheme 18.** Aminocarbonylation of aryl iodides in DES.

Other recent Pd-catalysed processes in DESs include the Suzuki coupling between aryltrifluoroborates and aryl halides in ChCl:glycerol (1:2). This procedure uses Pd(OAc)$_2$ as catalyst and is compatible with aryl iodides, bromides and chlorides (increasing the temperature for the latest).\(^\text{92}\) Chiral biaryl alcohols have also been obtained by combining Suzuki coupling in DES and biocatalysis in a one-pot fashion. In this case, PdCl$_2$ and a water-soluble phosphine ligand were employed to carry out the coupling between an aryl halide and a boronic acid, any


of the formers carrying a ketone as a substituent. A mixture of ChCl:glycerol (1:2) and a buffer aqueous solution was employed as solvent. Once the Suzuki coupling was completed, a ketoreductase was added, obtaining the corresponding chiral alcohol with excellent enantioselectivities (Scheme 19).

Scheme 19. Cascade Suzuki coupling + biocatalysed reduction in DES.

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RESULTS

Universitat d’Alacant
Universidad de Alicante
CHAPTER I

Cross-Dehydrogenative Coupling
1. GENERAL INTRODUCTION

Among the reactions that have attracted most interest in organic synthesis over the last years, C-H activation clearly stands out.\textsuperscript{94-95} In fact, C-C bond formation \textit{via} C-H activation is one of the most challenging reactions in organic synthesis. The main advantage of this strategy is to avoid a pre-functionalization step, which reduces the number of steps required to synthesize a molecule, increasing the atom economy. Due to this fact, transition-metal-catalysed C-H bond activations are considered environmentally friendly processes.\textsuperscript{96}

Among this kind of reactions, the C(sp\textsuperscript{3})-H bond activation at the α-position of nitrogen compounds has been broadly studied owing the great importance of the achieved derivatives in pharmaceutical industry. More specifically, a scaffold that have attracted loads of interest is tetrahydroisoquinoline (THIQ), since this heterocyclic motif is widely present in nature.\textsuperscript{97} The synthesis of substituted THIQs is therefore of great significance due to the presence of this moiety in anticancer,\textsuperscript{98-99} anticonvulsant agents,\textsuperscript{100} enzyme inhibitors,\textsuperscript{101} ligand receptors,\textsuperscript{102-103} and different types of therapeutic agents.\textsuperscript{104}

C-H activation in THIQ systems is based on the generation of an iminium intermediate, assisted by nitrogen lone pair via a single-electron transfer (SET)

\textsuperscript{94} H. Nakamura, \textit{Synlett} \textbf{2015}, 26, 1649-1664.
mechanism. The cationic iminium moiety generated in situ is an excellent electrophile to be coupled with different nucleophiles, generating new C-C bonds.

Therefore, in this reaction two different C-H bonds form a new C-C bond under oxidative conditions. This general strategy, known as cross-dehydrogenative coupling (CDC) has become an excellent tool for the amine functionalisation.

To achieve this transformation, several methods have been developed over the last years. Among the reported methodologies, there are a few metal-free protocols published. Nevertheless, since the typical CDC reaction proceeds via radical species, these methodologies rely on the use of organic radical promoters, which major drawback is the production of toxic waste by-products.

On the other hand, metal-catalysed protocols are well established. In the last decade, a great variety of metals have been successfully applied to CDC reaction, including metals such as iron, rhodium, iridium, gold, vanadium or palladium, among others.

Most of the reported results are based in metal catalyst derived from copper,\textsuperscript{124-137} and ruthenium.\textsuperscript{138-145} In all cases, high catalyst loadings (5-20 mol\%) were needed, and no recyclability of the catalytic system was reported. The aforementioned protocols needed a highly reactive oxidising agent, such as peroxides. Although in some cases oxygen was reported to be the oxidant, high pressures of oxygen atmosphere were needed. All these facts reduce the sustainability of the process and hamper the applicability of these protocols, especially for a large chemical production.

With these precedents we decided to develop an heterogenous-catalyst based methodology for the C-C bond formation via C-H functionalisation in DES as reaction medium. This approach was expected to be a more sustainable methodology. For that purpose, we decided to use metallic oxides supported on magnetite as catalyst. This type of catalysts are easy and cheap to prepare and can be recovered after the reaction.

\begin{thebibliography}{99}
\bibitem{129} D. Sureshkumar, A. Sud, M. Klusmman, \textit{Synlett} \textbf{2009}, 1558-1561.
\end{thebibliography}
1.1. MAGNETITE

Homogeneous catalysts have been broadly employed in organic synthesis with excellent results. Nevertheless, recovering the catalyst after the reaction is nearly impossible and the thermal stability of the catalytic system is often lower compared to heterogeneous catalyst. On the other hand, homogeneous catalysts often show better selectivity and can be easily modified to achieve a better performance. However, the barrier between homogeneous and heterogeneous catalysis has diminished thanks to the development of catalysts based on nanoparticles (NPs). Increasing the surface/volume ratio, the catalytic activity is usually improved, while as for homogeneous catalysts other properties could be also modified.

In order to recycle the nanoparticles easily, several methods for supporting them onto different materials have been developed. One of these materials is magnetite. It is a mixed iron oxide (II, III) with a molecular formula Fe₃O₄, which shows a superparamagnetic behaviour. This property allows the easy recover of the catalyst by means of a magnet or a magnetic field (magnetic decantation).

For this reason, magnetite has been employed as support for different metallic species, based on three different strategies. The first of these strategies involves the use of an organic linker between magnetite surface and the other metallic catalytic center. The main drawback of this method is the difficulty of magnetite surface functionalisation. On the other hand, a co-precipitation method is also known. In this case, magnetite is formed from iron salts at the same time that the corresponding metal oxide. Several catalysts have been synthesised following this strategy, including palladium, silver or nickel among others. Due to this fact, the metal species is distributed over the surface and the core of the material. This fact decreases the optimal activity of the catalyst since most catalytic processes take place on its surface.

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To avoid this problem, a superficial adsorption of the active specie can be performed. In this case, magnetite is pre-formed and then, the corresponding metal oxide is precipitated in aqueous solution from a metal salt. The resulting metal species are known as impregnated oxides in magnetite.

Our research group have large experience in this kind of impregnated catalysts,\textsuperscript{151} including palladium, ruthenium, platinum, iridium, osmium, cobalt or copper.

This last metal oxide has proven to be useful for a plethora of organic transformations, including Mannich reaction,\textsuperscript{152} addition of diboronic esters to double bonds,\textsuperscript{153} Sonogashira reaction followed by cyclisation to afford benzofurans and indoles,\textsuperscript{154} imine formation from alcohols and nitroarenes or amines,\textsuperscript{155} Glaser-Hay reaction\textsuperscript{156} or dipolar cycloadditions.\textsuperscript{157}

In view of these precedents, we decided to test the CDC process employing copper oxide impregnated on magnetite and DES as reaction media.

2. RESULTS

In order to start the study, the coupling between 2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (1a) and phenylacetylene (2a) was selected as the model reaction for the optimisation of the conditions. Copper impregnated on magnetite was chosen as the initial catalyst for the starting tests, in view of the good results previously reported in literature for this transformation with different copper sources. The results of this optimisation process are summarised in Table 1, showing conversions to the desired product (3a) and the oxidised by-product (4a).

First of all, different DESs were tested (entries 1-6), with the best results being obtained with ChCl:ethylene glycol (1:2; entry 4). Then, catalyst loading was evaluated, obtaining similar results when the loading was decreased (entry 7). However, a further decrease of catalyst loading down to 0.37 mol\% (entry 8) led

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\textsuperscript{154} R. Cano, M. Yus, D. J. Ramón, \textit{Tetrahedron} 2012, 68, 1393-1400.
\textsuperscript{156} J. M. Pérez, R. Cano, M. Yus, D. J. Ramón, \textit{Synthesis} 2013, 45, 1373-1379.
\textsuperscript{157} J. M. Pérez, R. Cano, D. J. Ramón, \textit{RSC Adv.} 2014, 4, 23943-23951.
to a significant drop in reaction yield. On the other hand, increasing the amount of copper to 3.64 mol% (entry 9), the yield was improved. It should be pointed out that even this high amount of copper catalyst is one of the lowest metal catalyst loadings reported in literature for this type of coupling. The use of only one equivalent of alkyne led to the decrease of the reaction yield (entry 10), while the addition of a large excess of alkyne did not improve it (entry 11).

**Table 1. Optimization of the reaction conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>DES (molar ratio)</th>
<th>T (°C)</th>
<th>3a (%)</th>
<th>4a (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CuO-FeO₄ (1.82)</td>
<td>CHCl:urea (1:2)</td>
<td>50</td>
<td>55</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>CuO-FeO₄ (1.82)</td>
<td>CHCl:urea (1:2)</td>
<td>50</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>CuO-FeO₄ (1.82)</td>
<td>CHCl:glycerol (1:2)</td>
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<td>11</td>
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<td>4</td>
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<td>CHCl:ethylene glycol (1:2)</td>
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<td>CuO-FeO₄ (0.91)</td>
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<td>18</td>
<td>CuO-FeO₄ (3.64)</td>
<td>Ethylene glycol</td>
<td>50</td>
<td>40</td>
<td>9</td>
</tr>
</tbody>
</table>

*Reaction carried out using compounds 1a (0.5 mmol) and 2a (1 mmol) in 1 mL of DES.

*Conversion determined by ¹H NMR. †Reaction carried out using compounds 1a (0.5 mmol) and 2a (0.5 mmol) in 1 mL of DES. ‡Reaction carried out using 1a (0.5 mmol) and 2a (2.5 mmol) in 1 mL of DES. §99% of conversion after 7 days of reaction. ¶Reaction carried out in argon atmosphere. ©Reaction carried out using visible LED light irradiation. •Reaction carried out under microwave irradiation during 10 h at 80 W. ††Reaction carried out under ultrasound bath during 8 h.
The temperature of the reaction was evaluated as well, obtaining full conversion of the starting material at room temperature after seven days (entry 12). Increasing the temperature up to 100 °C, decreased the conversion (entry 13). Despite the good conversion obtained at room temperature, the longer reaction time required pushed us to decide the use of 50 °C as the optimal temperature.

The reaction was also carried out under an argon atmosphere (entry 14) obtaining very low conversion. This fact highlights the capital role of oxygen in the air as the final oxidizing agent. In view of the aforementioned literature reports of photocatalysed CDC processes, the model reaction was tested under LED irradiation, as well as under non-conventional irradiation sources (microwave and an ultrasound bath) (entries 15–17), but the yield was lower in all cases. Finally, since one of the components of the chosen DES, ethylene glycol is liquid at room temperature, the reaction was tested in neat ethylene glycol obtaining a modest result (entry 18).

![Conversion of model reaction in different solvents.](image)

**Figure 7.** Conversion of model reaction in different solvents.

To further prove the essential role of DES, other VOC solvents were tested as reaction medium (Figure 7). In most cases, lower conversions were obtained, with low selectivity between products 3a and 4a. In the case of using 1,4-dioxane as
solvent, the oxidised by-product was the main product. In view of these results, the use of DES did not only lead to better conversions, but also minimised the lactam formation.

It is worth to mention that an unexpected trend was observed during the DES optimisation. It seemed to be a correlation between the DES conductivity and the yield of the desired product, in such a way that a higher conductivity of the DES affords a better yield (Figure 8).

![Figure 8. Correlation between solvent conductivity and 3a yield.](image)

This trend may be explained owing the fact that an iminium intermediate is generated during the reaction course. A higher conductivity value could be related to a better ion movement, which could explain the increase in the reaction yield. However, the correlation between obtained yields and conductivities of VOC solvents or water did not fit with the aforementioned plot. For instance, when the reaction was performed using the ternary mixtures ChCl:1,2-propanediol:water (1:1:1; conductivity 12.09 mS cm⁻¹) or ChCl:glycerol:water (1:2:1; conductivity 13.78 mS cm⁻¹) the yield of product 3a was 46 and 53%, respectively. In those cases, the highly nucleophile character of water may change the direct correlation between yield and conductivity observed with non-water containing DES, even if the conductivity of these ternary mixtures was higher.

With the optimal conditions determined, the reaction was evaluated with a variety of metal oxides impregnated on magnetite (Table 2).\(^\text{158}\) It should be pointed

out that a poor yield was obtained without catalyst (entry 2). Moreover, the activity of the support was evaluated using magnetite, both in micro- and nano-particles sizes (entries 3 and 4).

**Table 2. Optimization of the catalyst.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>3a (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>4a (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>CuO-Fe₃O₄ (3.64)</td>
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<td>3</td>
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<td>2</td>
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<td>6</td>
<td>20</td>
</tr>
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<td>3</td>
<td>Nano-Fe₃O₄ (259.15)</td>
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<td>Micro-Fe₃O₄ (259.15)</td>
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<td>Co₃O₄ (2.83)</td>
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<td>31</td>
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<td>NiO-Fe₃O₄ (2.06)</td>
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<tr>
<td>7</td>
<td>Ru₂O₃-Fe₃O₄ (2.64)</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>Rh₂O₃-Fe₃O₄ (0.84)</td>
<td>0</td>
<td>45</td>
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<tr>
<td>9</td>
<td>PdO-Fe₃O₄ (2.43)</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>Ag₂O-Fe₃O₄ (2.5)</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>OsO₂-Fe₃O₄ (1.03)</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>IrO₂-Fe₃O₄ (0.26)</td>
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<td>47</td>
</tr>
<tr>
<td>13</td>
<td>PtO/PtO₂-Fe₃O₄ (1.08)</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>Au₂O₃-Fe₃O₄ (0.28)</td>
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<td>4</td>
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<tr>
<td>15</td>
<td>PdO/Cu-Fe₃O₄ (3.05/1.79)</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>16</td>
<td>NiO/Cu-Fe₃O₄ (1.82/1.76)</td>
<td>78</td>
<td>2</td>
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<td>17</td>
<td>W₂O₅-Fe₃O₄ (1.13)</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>18</td>
<td>CuCl₂ (8.5)</td>
<td>88</td>
<td>5</td>
</tr>
<tr>
<td>19</td>
<td>CuO (4.04)</td>
<td>46</td>
<td>10</td>
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<tr>
<td>20</td>
<td>CuO (3.64)</td>
<td>80</td>
<td>6</td>
</tr>
<tr>
<td>21</td>
<td>CuO (3.64) + Fe₃O₄ (255.26)</td>
<td>51</td>
<td>9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction carried out using compounds 1a (0.5 mmol) and 2a (1 mmol) in 1 mL of DES.

<sup>b</sup> Conversion determined by ¹H NMR, conversion of oxidised compound 4a in parenthesis.

In both cases, the inactivity of the support was proven, observing low or no conversion to 3a and moderate conversion to by-product 4a. Once the activity of
the support was tested, different metal oxides impregnated on magnetite (entries 5–17) were evaluated as catalysts, observing that none of them gave better results than the copper catalyst (entry 1). Finally, and taking advantage of the high solubility of metallic salts in DES, different copper sources were also tested in a homogeneous version of the reaction (entries 18–20). In all those cases, moderate to good results were obtained, but poorer than the one obtained by the heterogeneous catalyst (entry 1). The synergic effect between the copper oxide and the support was proven by carrying out the reaction employing an heterogeneous mixture of CuO and Fe₃O₄ (entry 21). In that case, a decrease in the conversion compared to the impregnated catalyst was observed.

With the optimal conditions established, the scope of the reaction was evaluated. First of all, different N-substituted tetrahydroisoquinolines were submitted to the cross-dehydrogenative coupling with phenylacetylene (Table 3).

Excellent results were obtained with 4-substituted aryl group, regardless its electronic nature (entries 1 and 3). In the case of using an unsubstituted phenyl ring, the yield was moderated. Nevertheless, when the reaction was carried out with the unsubstituted THIQ or bearing a strong electron-withdrawing group such as tosyl group, the starting material was recovered unchanged (entries 4–5).

Table 3. Scope of the reaction with N-substituted THIQs. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-FC₆H₄</td>
<td>3a</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>3b</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>4-MeOC₆H₄</td>
<td>3c</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Ts</td>
<td>3d</td>
<td>0/0 c</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>3e</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reaction carried out using compounds 1a (0.5 mmol) and 2a (1 mmol) in 1 mL of DES. b Isolated yield after distillation. c Yield obtained after 7 days of reaction at room temperature.
Then, the scope of pro-nucleophiles was evaluated, starting by the coupling between 1a and different terminal alkynes (Table 4). When aryl-substituted alkynes were employed, the substituents of the aryl ring did not seem to have effect on the reaction outcome, obtaining moderate to good yields (entries 1–5) in all cases. Not only aryl substituents were tested, but also olefinic and aliphatic ones (entries 6–9) and the reaction still worked smoothly. It has to be pointed out that, in the case of using a dialkyne, the reaction was selective in such a way that only one of the two alkynes groups reacted (entry 8).

Table 4. Scope of the reaction using different alkynes.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeOC₆H₄</td>
<td>3f</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>4-BrC₆H₄</td>
<td>3g</td>
<td>61</td>
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<tr>
<td>3</td>
<td>4-CF₃C₆H₄</td>
<td>3h</td>
<td>68</td>
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<tr>
<td>4</td>
<td>3-ClC₆H₄</td>
<td>3i</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>2-BrC₆H₄</td>
<td>3j</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>1-C₆H₉</td>
<td>3k</td>
<td>37</td>
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<tr>
<td>7</td>
<td>C₆H₁₁</td>
<td>3l</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>HC=CC₆H₉</td>
<td>3m</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>THPOCH₂c</td>
<td>3n</td>
<td>65</td>
</tr>
</tbody>
</table>

a Reaction carried out using compounds 1a (0.5 mmol) and 2a (1 mmol) in 1mL of DES.
b Isolated yield after distillation. c THPO stands for 2-(tetrahydro-2H-pyran-2-yl)oxy.

Once the study of alkynes was conducted, we decided to expand the scope to other types of reagents. In this regard, the CDC between 1a and a variety of pro-nucleophiles was tested (Table 5). Excellent yields were obtained using nitromethane (entry 1), as well as 1-methylindole, which reacted at the 3-position in an 84% yield (entry 2). C-P bond formation was also accomplished by using diethyl phosphite as pro-nucleophile (entry 3). The use of 1-(trimethylsiloxy)cyclohexene and ciclohexanolone lead to the same product 3r, although with different diastereomeric ratios (entries 4-5). When 3-buten-2-one was used the coupling reaction took place by the methyl group (entry 6). Finally, a trifluoroborate derivative was also used (entry 7). All these reactions proved the
wide applicability of the process, not being limited to a single type of nucleophilic reagents.

It should be noticed that when low yields were obtained, only the starting material alongside a small amount of by-product 4a were detected from the crude material.

**Table 5. Scope of the reaction with different pro-nucleophiles.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nu-H</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeNO₂</td>
<td>3o</td>
<td>95/15&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>MeCO₂</td>
<td>3p</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>EtO-P-OEt</td>
<td>3q</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>OTMS</td>
<td>3r</td>
<td>50&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>3r</td>
<td>38&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>BF₃-K</td>
<td>3s</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>3t</td>
<td>51</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction carried out using compounds 1a (0.5 mmol) and pro-nucleophile (1 mmol) in 1mL of DES. <sup>b</sup> Isolated yield after distillation. <sup>c</sup> Yield after 7 days at rt. <sup>d</sup> Mixture of isomers syn:anti (1:1.25).<sup>e</sup> Mixture of isomers syn:anti (1.4:1).

The main advantage of using a heterogeneous catalyst is the easiness to recover it after the reaction. For this reason, and taking advantage of the magnetic properties of the catalyst, a study of the possible reusability of the catalyst and solvent was performed (Figure 9).
The reaction between THIQ 1a and nitromethane (see Table 5, entry 1) was repeated under standard conditions. Once the reaction was completed and cooled to room temperature, cyclopentyl methyl ether (recently reported as a potential green alternative solvent)\textsuperscript{159} was added to the reaction vessel. The mixture was stirred, and the upper organic phase was removed by decantation. By doing so, reaction product, and any possible starting material or by-product, were removed from the DES phase, while the catalyst remained in the eutectic phase, ready for another cycle. Then, fresh starting materials were added, and the reaction was performed again under the same conditions, without adding neither new catalyst, nor solvent. The mixture of DES and copper impregnated on magnetite could be recycled up to ten times without any significant drop in the reaction yield.

Alternatively, the recycling process was tested by dissolving the DES in water after the reaction was completed. Then, the catalyst was isolated by magnetic decantation and employed again in a new reaction with fresh starting materials and solvent. In that case, the reaction yield showed a sharp drop after the fourth cycle. Trying to understand better this fact, the initial crude solution of the reaction was submitted to an ICP-MS analysis, which confirmed that a small leaching process

was taking place (14.2 ppm, 3.6% of the initial copper amount was found in solution, but only 0.30 ppm, 0.001% of the initial iron loading).

The solubilities of magnetite and copper oxide in ChCl:ethylene glycol (1:2) were previously reported in literature\(^{160}\) (2.68 ppm for CuO and 10.85 ppm for Fe\(_3\)O\(_4\)), which clearly differs from our own findings. The higher solubility of the copper species from our supported catalyst in DES may indicate that the heterogeneous catalyst is only a reservoir of highly active copper clusters.

Further tests were performed to shed some light over the true nature of the catalyst. The standard reaction was set up as usual and the catalyst was removed by magnetic decantation, when the conversion to product 3a was estimated to be 40% by GC-MS. The mixture was heated again for additional 36 h and analysed after the usual work-up. The conversion to product 3a increased to 65%, although 25% of oxidised by-product 4a was also obtained.

Concurrently, another reaction was set up under optimised conditions. Once the reaction was completed, the catalyst was removed, and the organics extracted with cyclopentyl methyl ether, obtaining a 93% yield of compound 3a. Then, fresh reagents were added, without the addition of new catalyst, and the mixture was allowed to stir at 50 °C for three days. After this second cycle, product 3a was obtained in 52% yield (29% of by-product 4a).

These two experiments showed that the partial leaching of active species was, in fact, capable of performing the oxidative step. However, these leached species seemed to be less effective to catalyse the final nucleophilic addition, since the amount of oxidised by-product was greatly increased when compared to standard conditions.

The effect of the reaction medium on the heterogeneous catalyst was also evaluated. First of all, the nanoparticle size distribution was analysed by transition electron microscopy (TEM) after one reaction cycle and compared with the fresh catalyst (Figure 10). For the recycled catalyst, a uniform size distribution was found, with 60% of nanoparticles having an average size between 2-4 nm. In the fresh catalyst, 63% of nanoparticles have an average size between 2-6 nm (Figure

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11). This slight difference shows a small overall decrease in the particle size after the reaction, which is in concordance with the process of partial solubilization–reabsorption of copper species over the support.

![Figure 10. TEM images of CuO-Fe$_3$O$_4$: a) before and b) after the reaction.](image)

![Figure 11. Particle size distribution of fresh and recycled catalyst.](image)

Fresh and reused samples of catalyst were also analysed by X-ray photoelectron spectroscopy (XPS) and Auger Electron Spectroscopy (AES). With these techniques, it was observed that the initial Cu(0) present in the fresh catalyst
was transformed onto the corresponding copper(I) oxide and Cu(OH)$_2$ in the recycled catalyst (Fig. 5), while CuO remained as the main species in both cases. Nevertheless, these small changes in particle size as well as the initial oxidation state did not seem to affect the activity of the catalyst, since it could be reused ten times without losing its activity.

**Figure 12.** a) XPS of the recycled catalyst. b) AES of the recycled catalyst.
CHAPTER II

Palladium-catalysed C-C Cross-Coupling Reactions
1. GENERAL INTRODUCTION

Nowadays, C-C bond formation is one of the process that attracts most interest among organic chemists. Thus, cross-coupling reactions have become an essential tool in organic synthesis that provide access to compounds of great value for different areas; such as materials, pharmaceuticals or fine chemicals, since they permit the synthesis of relatively complex molecules in a simple way.161 The importance and high applicability of this kind of reactions was proven with the award of several Nobel Prizes in this area over the last years.162

Cross-coupling reactions are usually performed with the aid of metallic catalysts, the most used metals being: Pd,163 Cu,164-165 Fe,166-167 Ni168-169 or Zn.170 These metals have been proven to be active catalysts for several transformations, being the most well-known the Suzuki–Miyaura,171-172 Heck,173-175 Negishi,176-177 Stille,178-179 Kumada,180-181 Hiyama,182-183 or Sonogashira reactions.184-185

Considering the aforementioned reactions, the metal that has been more extensively used is Pd, due to its high selectivity, reactivity and tolerance to a broad

185 M. Bakherad, Appl. Organomet. Chem. 2013, 27, 125-140.
scope of functional groups.\textsuperscript{186} As a result of its enormous popularity, in most cases the mechanism of these reaction is also well established. Reactions such as the Suzuki, Heck or Sonogashira couplings often take place under classical Pd(0)/Pd(II) catalytic cycle,\textsuperscript{187} although there are some reports regarding the involvement of Pd(II)/Pd(IV) species.\textsuperscript{188}

Since these reactions have become so important, being largely applied in industry and academia, to find sustainable methodologies to carry them out is a matter that has to be urgently addressed. For instance, all the aforementioned approaches are typically performed in volatile organic solvents (VOC), and their replacement by greener media should be considered. For these reasons, we decided to develop more sustainable cross-coupling methodologies employing deep eutectic solvents (DESs) as reaction medium.

It is worth to mention that when the present project started, very few reports of palladium chemistry in DES were known. As it was anticipated in the introduction, Suzuki reaction was carried out using Pd(OAc)$_2$ (10 mol\%) in a ternary mixture of mannitol, dimethyl urea and ammonium chloride as DES combination.\textsuperscript{89} Regarding Sonogashira coupling, the synthesis of only two products have been published in DES medium (D-mannose/DMU), while the Heck cross-coupling reaction has been performed in D-mannose-dimethyl urea (DMU) as reaction media.\textsuperscript{82}

2. NCN Pd PINCER AS CATALYST IN HIYAMA REACTION

2.1. INTRODUCTION

Not only solvents are an important issue to consider a methodology as sustainable. According to Green Chemistry third principle, less hazardous chemicals should be used when preparing a synthetic plan. In this matter, Hiyama reaction stands out among other cross-coupling reactions, since it is based in the use of organosilicon reagents. This kind of chemicals are usually very stable against air and moisture, they are non-toxic, environmentally-friendly and are commercially available at low cost or easily prepared. However, their reactivity is usually lower when compared to reagents used for similar transformations.\textsuperscript{189} Due

to these facts, we decided to develop a methodology to carry out the Hiyama reaction in deep eutectic solvents. This type of C-C coupling process was not previously reported in DES.

Although the Hiyama coupling was not previously described in DES, a few methodologies of this cross-coupling reaction in neoteric solvents were reported. These include the use of water as reaction medium, usually under reflux conditions, using phase transfer catalyst or with highly activated starting materials, such as diazonium salts.\textsuperscript{190-194}

Ionic liquids, which share some of the properties of DES, have also been investigated recently as reaction medium for this transformation. A Hiyama-type reaction in ionic liquids was described, using 10 mol\% of a Pd precursor, 20 mol\% of a complex ligand and 4 equivalents of a fluoride salt.\textsuperscript{195} Another report in this kind of solvent employed 4 mol\% of Pd without any additives, but required instead the use of an expensive ionic liquid containing fluoride anions. Also, MeCN was used as co-solvent, being the problematic of the use of VOC as solvent not avoided.\textsuperscript{196}

It should be pointed out that there is an increasing interest in recent years in the use of biorenewable solvents as neoteric reaction media.\textsuperscript{76,197-198} Hiyama coupling have been performed in γ-valerolactone,\textsuperscript{199} and more recently in glycerol, although to the best of our knowledge only one report of this coupling reaction have been published in this medium so far.\textsuperscript{200} In that case, 2 mol\% of Pd(0) nanoparticles (preformed from Pd(OAc)\textsubscript{2} and a phosphine ligand), were used as catalyst for the

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reaction. Only 6 biaryl products were obtained, showing uncontrolled selectivity towards homocoupling by-products, which are difficult to separate from the corresponding cross-coupling products, having a negative impact on the applicability of the whole process.

One of the most interesting aspects of using neoteric solvents is the possibility of immobilizing the catalyst, which allows the recyclability of the system. Nevertheless, this recycling process have not been described for the Hiyama-type reaction in the aforementioned reports.

2.2. RESULTS

It was expected that the unusual properties of DESs would let the immobilisation of the catalyst in it, allowing to reuse the catalytic system without the need of supporting the active species into inorganic supports.

With these precedents, our aim was to develop a recyclable catalytic system based on a Pd complex able to perform the Hiyama reaction. This goal could be achieved taking advantage of the solubilising properties of neoteric solvents such as DES. For this purpose, we thought that a highly stable pincer-type palladium complex might be a good candidate to be considered as catalyst. Catalyst 9a was synthetized following a literature procedure (Scheme 20).\textsuperscript{201}

\begin{equation}
\begin{array}{c}
\text{Scheme 20. Synthetic pathway to Pincer 9a.}
\end{array}
\end{equation}

A study to determine the optimal reaction conditions was performed, employing organometallic complex 9a as catalyst for the reaction between 4'-bromoacetophenone (10a) and trimethoxyphenylsilane (11). First, ChCl:glycerol (1:2) was chosen as solvent and K$_2$CO$_3$ as base, testing the reaction at different temperatures, obtaining the best results at 100 °C (Table 6, entries 1-4). Then, several organic and inorganic bases were tested (entries 5-13). Unfortunately, results were not improved by the use of a base different from K$_2$CO$_3$, although the amount of base equivalents have an important effect on the reaction outcome (entries 14-16). With the base and temperature optimised, several eutectic mixtures were tested (entries 17-31). The reaction failed in most of the employed DES, as well as in water (entry 32).

As the best obtained results were 70% yield in ChCl:glycerol (1:2) and 25% yield in ChCl:ethylene glycol (1:2), the reaction was also tested in neat ethylene glycol and glycerol, obtaining yields of 72% and 89%, respectively (entries 34-35). Toluene, a traditional VOC solvent, was also employed as reaction media, as well as neat conditions, obtaining low conversions in both cases (entries 36-37). This fact highlights the role of neoteric solvent, enhancing the catalytic activity of the system.

Better results were obtained in neat glycerol, with the presence of ChCl seeming to be detrimental for the reaction outcome. Nevertheless, both DES and glycerol were employed to analyse the scope of the reaction in order to shed some light on the role of choline chloride in the reaction outcome. Thus, after optimising the reaction conditions, the scope of the reaction was analysed with different aryl halides. (Table 7). In the case of using ChCl:glycerol (1:2) as reaction media, moderate to low yields were obtained for aryl halides bearing electron-withdrawing groups (Table 7, entries 1-3) or electron-neutral aryl halides (entries 4, 8), while the reaction yields were slightly lower with electron-rich aryl halides (entries 5-7).

The scope of aryl halides was analysed again using neat glycerol. In this case, moderate to excellent yields were obtained for aryl bromides and iodides bearing both, electron-withdrawing and electron-donating groups (Table 7). It is worth to mention that no homocoupling by-products were observed under the optimized reaction conditions, neither in DES nor in glycerol, as solvent.
Table 6. Optimisation of Hiyama reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (eq.)</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃(3)</td>
<td>100</td>
<td>ChCl:glycerol (1:2)</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃(3)</td>
<td>50</td>
<td>ChCl:glycerol (1:2)</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃(3)</td>
<td>80</td>
<td>ChCl:glycerol (1:2)</td>
<td>3</td>
</tr>
<tr>
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<td>K₂CO₃(3)</td>
<td>120</td>
<td>ChCl:glycerol (1:2)</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>Et₃N (3)</td>
<td>100</td>
<td>ChCl:glycerol (1:2)</td>
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</tr>
<tr>
<td>6</td>
<td>Pr₂NH (3)</td>
<td>100</td>
<td>ChCl:glycerol (1:2)</td>
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</tr>
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<td>7</td>
<td>NaOH (3)</td>
<td>100</td>
<td>ChCl:glycerol (1:2)</td>
<td>23</td>
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<tr>
<td>8</td>
<td>NaOAc(3)</td>
<td>100</td>
<td>ChCl:glycerol (1:2)</td>
<td>3</td>
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<tr>
<td>9</td>
<td>KOH (3)</td>
<td>100</td>
<td>ChCl:glycerol (1:2)</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>K₃PO₄(3)</td>
<td>100</td>
<td>ChCl:glycerol (1:2)</td>
<td>16</td>
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<tr>
<td>11</td>
<td>NaF(3)</td>
<td>100</td>
<td>ChCl:glycerol (1:2)</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>Na₂CO₃(3)</td>
<td>100</td>
<td>ChCl:glycerol (1:2)</td>
<td>9</td>
</tr>
<tr>
<td>13</td>
<td>- (1)</td>
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<td>ChCl:glycerol (1:2)</td>
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<td>ChCl:urea (1:2)</td>
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<td>ChCl:ethylene glycol (1:2)</td>
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<td>100</td>
<td>CHCl:glucose·H₂O (1:1:1)</td>
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<td>Glucose:malic acid (1:1)</td>
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<td>CHCl:oxalic acid (1:1)</td>
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<td>CHCl:sorbitol (1:2)</td>
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<td>DecA:menthol (1:2)</td>
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<td>DecA:lidocaine (2:1)</td>
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<td>K₂CO₃(2)</td>
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<td>CHCl:guanidine·H₂O (1:2:1)</td>
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<tr>
<td>31</td>
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<td>100</td>
<td>Urea:acetamide (1:2)</td>
<td>0</td>
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<td>H₂O</td>
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<td>CHCl:urea:glycerol (1:2:1)</td>
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<tr>
<td>34</td>
<td>K₂CO₃(2)</td>
<td>100</td>
<td>Glycerol</td>
<td>89</td>
</tr>
<tr>
<td>35</td>
<td>K₂CO₃(2)</td>
<td>100</td>
<td>Ethylene glycol</td>
<td>72</td>
</tr>
<tr>
<td>36</td>
<td>K₂CO₃(2)</td>
<td>100</td>
<td>Neat conditions</td>
<td>12</td>
</tr>
<tr>
<td>37</td>
<td>K₂CO₃(2)</td>
<td>100</td>
<td>Toluene</td>
<td>23</td>
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</tbody>
</table>

<sup>a</sup> Yield determined by GC using tridecane as internal standard.
Table 7. Scope of aryl halides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>X</th>
<th>Yield in DES (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield in glycerol (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>12a</td>
<td>70</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td></td>
<td>19</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>12b</td>
<td>11</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td></td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>12c</td>
<td>35</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>12d</td>
<td>85</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>I</td>
<td></td>
<td>69</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>12e</td>
<td>27</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>I</td>
<td></td>
<td>58</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>Br</td>
<td>12f</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>I</td>
<td></td>
<td>36</td>
<td>83</td>
</tr>
<tr>
<td>12</td>
<td>I</td>
<td>12g</td>
<td>58</td>
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<td>13</td>
<td>Br</td>
<td>12h</td>
<td>77</td>
<td>80</td>
</tr>
<tr>
<td>14</td>
<td>I</td>
<td></td>
<td>63</td>
<td>99</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: Aryl halide (1 mmol), PhSi(OMe)<sub>3</sub> (1.5 mmol), K<sub>2</sub>CO<sub>3</sub> (2 mmol), catalyst 9a (0.01 mmol) in 2 mL of solvent. <sup>b</sup>DES stands for ChCl:glycerol (1:2/molar ratio). <sup>c</sup>Isolated Yield.

Then, the vinylation reaction of aryl halides employing trimethoxyvinylsilane (13) was tested. In this case, the reaction worked with good to excellent yields for aryl iodides and bromides bearing electron-withdrawing functional groups, and in moderate yields with aryl iodides with electron-donating groups, including electron-rich heterocycles (Table 8, entries 11-12). The same range of yields were obtained using glycerol and ChCl:glycerol (1:2) as solvent. The reaction products, vinylbenzenes, sometimes suffer from a second Pd-catalysed Heck-type reaction with the aryl halide to yield a 1,2-disubstituted ethene.
derivative (15).\textsuperscript{202} The selectivity to these products could not be controlled, as it depends on the nature of the starting material, obtaining only the Hiyama-type product (entries 1-5) or the Heck reaction product in some cases (entries 6, 11-12). The use of additives, such as KF, did not improve the reaction yield.

Table 8. Synthesis of vinylarene derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>X</th>
<th>Product 14</th>
<th>Yield 14 (%)\textsuperscript{b,c}</th>
<th>Product 15</th>
<th>Yield 15 (%)\textsuperscript{b,c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeCOC\textsubscript{6}H\textsubscript{4}</td>
<td>Br</td>
<td>14a</td>
<td>27 (60)</td>
<td>15a</td>
<td>&lt;1% (&lt;1%)</td>
</tr>
<tr>
<td>2</td>
<td>4-MeCOC\textsubscript{6}H\textsubscript{4}</td>
<td>I</td>
<td>14a</td>
<td>69 (75)</td>
<td>15a</td>
<td>&lt;1% (&lt;1%)</td>
</tr>
<tr>
<td>3</td>
<td>4-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>Br</td>
<td>14b</td>
<td>51 (98)</td>
<td>15b</td>
<td>&lt;(-)</td>
</tr>
<tr>
<td>4</td>
<td>4-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>I</td>
<td>14b</td>
<td>89 (91)</td>
<td>15b</td>
<td>&lt;(-)</td>
</tr>
<tr>
<td>5</td>
<td>3-pyridil</td>
<td>Br</td>
<td>14c</td>
<td>77 (52)</td>
<td>15c</td>
<td>&lt;(-1%)</td>
</tr>
<tr>
<td>6</td>
<td>4-FC\textsubscript{6}H\textsubscript{4}</td>
<td>I</td>
<td>14d</td>
<td>&lt;(-)</td>
<td>15d</td>
<td>65 (23)</td>
</tr>
<tr>
<td>7</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>Br</td>
<td>14e</td>
<td>63 (55)</td>
<td>15e</td>
<td>&lt;(-1%)</td>
</tr>
<tr>
<td>8</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>I</td>
<td>14e</td>
<td>54 (64)</td>
<td>15e</td>
<td>&lt;1% (&lt;1%)</td>
</tr>
<tr>
<td>9</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>Br</td>
<td>14f</td>
<td>56 (-)</td>
<td>15f</td>
<td>30 (34)</td>
</tr>
<tr>
<td>10</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>I</td>
<td>14f</td>
<td>26 (-)</td>
<td>15f</td>
<td>52 (74)</td>
</tr>
<tr>
<td>11</td>
<td>2-thieryl</td>
<td>Br</td>
<td>14g</td>
<td>&lt;(-)</td>
<td>15g</td>
<td>44 (8)</td>
</tr>
<tr>
<td>12</td>
<td>2-thieryl</td>
<td>I</td>
<td>14g</td>
<td>&lt;(-)</td>
<td>15g</td>
<td>32 (55)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: Aryl halide (1 mmol), H\textsubscript{2}C=CH-Si(OMe)\textsubscript{3} (1.5 mmol), K\textsubscript{2}CO\textsubscript{3} (2 mmol), catalyst 9a (0.01 mmol) in 2 mL of glycerol. \textsuperscript{b}Isolated yields. \textsuperscript{c}Yields obtained using CHCl\textsubscript{3}:glycerol (1:2; 0.50 M) as solvent in parenthesis.

The reaction was tested also with allyltrimethoxysilane (16) under the same reaction conditions as before. In this case, a mixture of products was obtained. The coupling reaction took place to introduce the allyl moiety, achieving a \textit{sp}^2-\textit{sp}^1 C-C coupling. Nevertheless, an isomerization also occurred, obtaining a mixture of the three possible isomers, with the more stable internal \textit{trans} double bond being the major one (Scheme 21). Reaction between benzyl bromide and

phenyltrimethoxysilane was also tested, obtaining only traces of product diphenylmethane.

\[
\begin{align*}
16 & \quad \text{Si(OMe)}_3 \\
10b & \quad \text{phenyltrimethoxysilane} \\
9a & \quad (1 \text{ mol\%}) \\
glycerol & \quad (0.5 \text{ M}) \\
K_2CO_3 & \quad (2 \text{ eq.}) \\
100^\circ\text{C}, 24 \text{ h} & \\
17a & \quad 16\% \\
17b & \quad 1\% \\
17c & \quad 83\%
\end{align*}
\]

**Scheme 21.** Hiyama-type coupling with allyltrimethoxysilane.

The recyclability of the process was faced next. The reaction between reagents 10a and 11 was carried out under optimized conditions using ChCl:glycerol (1:2) as solvent. Once the reaction was finished, the organics were extracted with 2-MeTHF, a VOC solvent considered to be a sustainable. The catalyst remained in the DES phase, while unreacted starting materials and products were extracted. Adding a fresh batch of reagents, allowed to run the reaction again without using more solvent or catalyst. The reaction gave the same range of yields for three cycles, starting to decrease gradually after that. The recyclability was also tested using neat glycerol as solvent, obtaining a gradual decrease in the yield after each cycle (Figure 13). The 2-MeTHF phase was analysed by ICP-MS, finding that 7.9% of the initial Pd loading was extracted alongside with the product when glycerol was used as solvent, while 16.5% leaching was observed in the case of using DES as medium. This leaching process is probably the main reason for the decreased yield observed during recyclability experiments.

**Figure 13.** Recyclability study.
To prove the applicability of the process, the model reaction between 4'-bromoacetophenone and PhSi(OMe)$_3$ was performed on a gram scale (Scheme 22).

![Scheme 22. Gram-scale Hiyama reaction.](image)

This reaction, was carried out with 12 mL of glycerol as solvent, stirred at 100 °C for 24 h, cooled to room temperature and extracted with 2-MeTHF (Figure 14).

![Figure 14. Images of the reaction media (lower phase) after adding 2-MeTHF (upper phase) a) 1 mmol scale, 4th run, b) gram-scale.](image)

The upper organic phase was evaporated to dryness and analysed by $^1$H NMR to afford 1.13 g of product 12a (96% yield, 97% purity) without the need of aqueous work-up or chromatography purification (Figure 15).

The E-factor of this process was calculated, obtaining a value of 25.6, being a reasonable value for fine-chemical and pharmaceutical products industries.\(^{203}\) This gram-scale reaction was also conducted in DES, obtaining only

Chapter II. Palladium-catalysed C-C Cross-Coupling Reactions

a 73% conversion to the desired product. However, a purification step was required to obtain the pure product, in contrast to the result obtained in glycerol as solvent.

E-Factor calculation:

- Initial reaction mass: 30.055g
- Product mass: 1.13 g
- Waste mass: 19.755g - 1.13g = 28.925g

\[
\text{E-Factor} = \frac{g(\text{waste})}{g(\text{product})} = \frac{28.925g}{1.13g} = 25.6
\]

Equation 1. E-factor determination.

**Figure 15.** $^1$H NMR of crude product 12a obtained in a gram-scale without purification steps.

Regarding the mechanism of the reaction, it was believed to proceed via Pd(0)/Pd(II) cycle according to literature precedents. Therefore, we analysed the crude material by HRTEM trying to find Pd NPs. Nevertheless, no nanoparticles were found (neither in DES nor in glycerol as reaction media, Figure 16).
Chapter II. Palladium-catalysed C-C Cross-Coupling Reactions

Figure 16. a, b) TEM after model reaction in DES and glycerol, respectively. No Pd NPs found. c) TEM of preformed Pd NPs.

The model reaction was also carried out using preformed Pd NPs (1 mol%) and no conversion at all was observed, recovering the unreacted starting material. To confirm that the reaction was not being catalysed by nanoparticles, a mercury test was performed, in such a way that in the presence of Pd NPs, an amalgam with Hg would be formed, inhibiting its catalytic activity. The reaction was set up under standard conditions and a sample was analysed by GC after 30 min of reaction time, observing a 11% conversion to desired product. Then, 250 mol% of Hg was added to the reaction mixture. After 24 h, the reaction was worked-up and analysed again, showing 77% yield.

The obtained yield was slightly lower than the corresponding yield under optimized reaction conditions (89%), which may indicate that some Pd NPs are present in the reaction mixture, but they are not the main active catalytic species (Scheme 23). Furthermore, the pincer complex could be isolated unchanged by column chromatography after reaction completion (in a 66% yield).

An XPS analysis of the crude material was also conducted. Despite the low catalyst loading, the binding energy of Pd(II) species could be distinguished, but no Pd(0) was observed (Figure 18). These facts might suggest that the reaction performed in these kind of neoteric medium is probably occurring through the Pd(II)/Pd(IV) catalytic system, which have been reported for a similar pincer-type catalyst.

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Since, in general, better results were obtained in neat glycerol than in the corresponding eutectic mixture with CHCl, two control experiments were performed trying to decide if Cl⁻ anions could be occupying a vacant in the coordination sphere of the complex and thus, limiting its catalytic activity. The model reaction was carried out employing catalyst 9b, bearing an Cl⁻ anion instead of an I⁻. The model reaction was also tested under standard conditions in glycerol but adding 5 equivalents of NaCl (Scheme 23). The yields for these two tests were of 87% and 83%, respectively, quite similar to the standard result, being an indirect proof that Cl⁻ anions are not affecting the outcome of the reaction.

![Figure 17. ¹H NMR of catalyst 9a recovered after reaction.](image)

![Figure 18. XPS of crude material after reaction under standard conditions.](image)
Other cross coupling reactions were also tested employing catalyst 9a in ChCl:glycerol as solvent. In general, poor results were obtained. The Suzuki reaction between 4'-bromoacetophenone and phenylboronic acid using K$_2$CO$_3$ as base, afforded the corresponding biaryl in a modest 35% yield after 24h reaction time. Slightly better results were obtained with the Sonogashira coupling, although, again long reaction times were needed to afford moderate yields. Regarding the Heck coupling, no product was observed at all using activated substrates (Scheme 24).

These preliminary results suggested that the pincer complex was not an especially active catalyst in DES medium. Although the pincer is robust enough to remain unchanged from the unusual properties of these solvents, its catalytic activity seemed not to be very high for most cross-coupling reactions. For this reason, we decided to develop a new catalytic system focusing on the compatibility of ligand with the ionic nature of DES media.
Scheme 24. Other C-C cross-coupling reaction in DES.
3. PYRIDINIOPHOSPHINE LIGANDS IN Pd CATALYSED CROSS COUPLING REACTIONS

3.1. INTRODUCTION

With the aim to perform a rational design of new ligands compatible with palladium chemistry in DES, we started by checking the literature. When this project started, the number of reports about cross-coupling reactions in DESs was scarce. However, an inspiring work regarding the Stille reaction was found. In that case, the ternary mixture of lactose:DMU:NH$_4$Cl was employed as eutectic mixture. This reaction was especially interesting, because it was one of the few examples in which a ligand was added to the DES media. Triphenylarsine was employed as palladium ligand, achieving the coupling of 4-bromoanisole and tetraphenylstannane in 87% yield. However, when the reaction was carried out using CyJohnPhos (a Hartwig-Buchwald-type ligand), only a modest 61% yield was obtained. These facts clearly demonstrate the importance of appropriate design of the ligand in order to get good results in this new type of reaction media.

Since the pincer complex was not especially active, we aimed to develop DESs compatible phosphine ligands. Phosphines are typically the best palladium ligands for cross-coupling reactions, although, according to the literature, it seemed that traditional ligands are not so effective in this kind of solvents. We thought in cationic pyridiniophosphine structures as ligands in the palladium-catalysed cross-coupling reactions in unconventional media. Due to the ionic nature of some of the DES components, like choline chloride, we expected that an ionic ligand would increase the compatibility of the corresponding metal complex with the medium.

3.2. RESULTS

We started by the synthesis of a cationic pyridiniophosphine ligand with a chloride as counter ion (Scheme 25). In order to do this, we started by the N-alkylation of 2-hydroxypyridine, followed by chlorination which afford salts 19.

---

Then, the dicyclohexylphosphine was inserted in order to obtain the final ligands (20a-20c).

Scheme 25. Synthesis of pyridiniophosphine ligands. a) CuI (10 mol%), K$_2$CO$_3$ (2.1 eq.), DMSO (1 M), 24 h; b) oxalyl chloride (2 eq.), 1,2-dichloroethane (0.5 M), 60 °C, 4 h; c) HPCy$_2$ (2 eq.), MeCN (0.5 M), reflux, 18 h.

Once we prepared these ligands we started to test them in different C-C cross-coupling reactions, starting by the Suzuki-Miyaura reaction (Figure 19, Table 9). Optimization studies were performed in order to determine the best catalyst. The reaction worked poorly with only 0.1 mol% of an uncomplexed palladium(II) salt (Table 9, entries 1-2), but when a pyridiniophosphine ligand was added, the yield raised up to 49% after 2 h (entry 3). The fine tuning of electronic properties of N-substitution showed that neutral phenyl substituent gave a better result than electron-poor 2-pyridyl or electron-rich 2-thienyl moieties (entries 3-5).

Figure 19. Effect of ligands in Suzuki coupling in DES.
Other traditional phosphine ligands were also tested, showing only a slight increase in the yield in relation to the uncomplexed palladium salt, or no effect at all (entries 6-8). Surprisingly, CyJohnPhos (20d), which only differs from ligand 20a by the cationic nature, gave the same result as in absence of ligand. Since the best results were obtained with cationic pyridiniophosphines, it has been proven that, in a system as polar as DES, these ligands are more suitable. Finally, the reaction was repeated increasing the catalyst loading, showing a good yield with just 1 mol% of palladium source and 3 mol% of ligand (entry 10), amounts inferiors to those previously reported, evidencing that the adequate design of ligand is mandatory.

Table 9. Optimization of the catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source (mol%)</th>
<th>Ligand (mol%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂ (0.1)</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>PdCl₂ (0.1)</td>
<td>20a (0.3)</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>PdCl₂ (0.1)</td>
<td>20b (0.3)</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂ (0.1)</td>
<td>20c (0.3)</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>PdCl₂ (0.1)</td>
<td>PCy₃ (0.3)</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>PdCl₂ (0.1)</td>
<td>P(Fu)₃ (0.3)</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>PdCl₂ (0.1)</td>
<td>20d (0.3)</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>PdCl₂ (0.5)</td>
<td>20a (1.5)</td>
<td>64</td>
</tr>
<tr>
<td>10</td>
<td>PdCl₂ (1.0)</td>
<td>20a (3.0)</td>
<td>88</td>
</tr>
</tbody>
</table>

*a Yield determined by GC using tridecane as internal standard. b P(Fu)₃ stands for tri(furan-2-yl)phosphine. c 20d stands for [1,1’-biphenyl]-2-ylcyclohexylphosphine.

With the best palladium salt and ligand established, a study to find the best reaction conditions was performed (Table 10). First, different temperatures were tested, obtaining the best results at 100 °C under conventional heating (entries 1-5). Then we tried a sort of bases (entries 7-11), founding out that both, potassium and caesium carbonates provided the best yields. We decided to follow the study with the less expensive K₂CO₃. Finally, different eutectic mixtures were tested as solvent (entries 12-16). Best results were obtained with ChCl:ethylene glycol.
followed closely by ChCl:glycerol. Since the latest is a more environmental-friendly system and the difference in the obtained yield was minimal, it was the chosen solvent for carrying out the study of the scope.

Table 10. Optimization of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>K_2 CO_3</td>
<td>ChCl:urea (1:2)</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>K_2 CO_3</td>
<td>ChCl:urea (1:2)</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>K_2 CO_3</td>
<td>ChCl:urea (1:2)</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>K_2 CO_3</td>
<td>ChCl:urea (1:2)</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>K_2 CO_3</td>
<td>ChCl:urea (1:2)</td>
<td>56</td>
</tr>
<tr>
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<td>100^b</td>
<td>K_2 CO_3</td>
<td>ChCl:urea (1:2)</td>
<td>44</td>
</tr>
<tr>
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<td>100</td>
<td>Cs_2 CO_3</td>
<td>ChCl:urea (1:2)</td>
<td>86</td>
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<tr>
<td>8</td>
<td>100</td>
<td>Et_3 N</td>
<td>ChCl:urea (1:2)</td>
<td>38</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>NaOH</td>
<td>ChCl:urea (1:2)</td>
<td>44</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>tBuOK</td>
<td>ChCl:urea (1:2)</td>
<td>38</td>
</tr>
<tr>
<td>11</td>
<td>100</td>
<td>TABOH^c</td>
<td>ChCl:urea (1:2)</td>
<td>72</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>K_2 CO_3</td>
<td>ChCl:ethylene glycol (1:2)</td>
<td>97</td>
</tr>
<tr>
<td>13</td>
<td>100</td>
<td>K_2 CO_3</td>
<td>ChCl:resorcinol (1:1)</td>
<td>43</td>
</tr>
<tr>
<td>14</td>
<td>100</td>
<td>K_2 CO_3</td>
<td>ChCl:glycerol (1:2)</td>
<td>92</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>K_2 CO_3</td>
<td>ChCl:trifluoroacetamide (1:2)</td>
<td>34</td>
</tr>
<tr>
<td>16</td>
<td>100</td>
<td>K_2 CO_3</td>
<td>Ph_3 PMeBr:glycerol (1:2)</td>
<td>75</td>
</tr>
</tbody>
</table>

^a Yield determined by GC using tridecane as internal standard. ^b Reaction carried out under microwave irradiation. ^c TABOH stands for tetrabutylammonium hydroxide.

With the optimized conditions, the scope of the Suzuki reaction was evaluated. Thus, different activated and deactivated aryl iodides and bromides were cross-coupled with phenylboronic acid (Table 11). In general, very good isolated yields (80–98%) were obtained for biaryls 12 regardless of the electronic nature of the employed aryl iodide or bromide (Table 11, entries 1–4 and 6–13). However, the catalytic system showed only moderate activity when an activated aryl chloride such as 1-chloro-4-nitrobenzene reacted with phenylboronic acid affording 4-nitro-1,1'-biphenyl (12b) in a 46% yield after 10 h (Table 11, entry 5).
Table 11. Scope of the Suzuki-Miyaura reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Hal</th>
<th>x</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCO</td>
<td>I</td>
<td>0.1</td>
<td>12a</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>MeCO</td>
<td>Br</td>
<td>1</td>
<td>12a</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>NO₂</td>
<td>Br</td>
<td>1</td>
<td>12b</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>NO₂</td>
<td>I</td>
<td>0.1</td>
<td>12b</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>NO₂</td>
<td>Cl</td>
<td>1</td>
<td>12b</td>
<td>46&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>I</td>
<td>0.1</td>
<td>12h</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>Br</td>
<td>1</td>
<td>12h</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>t-Bu</td>
<td>I</td>
<td>0.1</td>
<td>12i</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>t-Bu</td>
<td>Br</td>
<td>1</td>
<td>12i</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>OCH₂Ph</td>
<td>I</td>
<td>0.1</td>
<td>12g</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>OCH₂Ph</td>
<td>Br</td>
<td>1</td>
<td>12g</td>
<td>96</td>
</tr>
<tr>
<td>12</td>
<td>MeO</td>
<td>I</td>
<td>0.1</td>
<td>12f</td>
<td>81</td>
</tr>
<tr>
<td>13</td>
<td>MeO</td>
<td>Br</td>
<td>1</td>
<td>12f</td>
<td>80</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield determined by GC using tridecane as internal standard. <sup>b</sup> Reaction time: 10 h.

The Sonogashira reaction was also evaluated. Preliminary attempts to perform this reaction pointed out Ph₃PMeBr-glycerol (1:2) as the optimal DES. Because of that, reaction between 4'-idoacetophenone (10a') and phenylacetylene (2a) was evaluated in the aforementioned DES as reaction medium (Table 12). Despite that the reaction worked well with just one equivalent of 2a (entry 1), using 2 equivalents raised the obtained yield to 95% (entry 3), whereas increasing the amount to 1.2 equivalents did not affect to the reaction yield (entry 2). When the reaction was carried out employing Pd(OAc)₂ instead of PdCl₂ as palladium source, the obtained yield was slightly lower (entry 4).

Different bases were also tested (entries 5-8), obtaining better results with organic bases. Specifically, the best result was obtained with 'Pr₂NH (entry 4). With the best base chosen, its amount was decreased, obtaining similar results with just 2 equivalents (entry 9), but observing a significant drop in the yield when only one equivalent was employed (entry 10). Surprisingly, when the catalyst amount was decreased to 0.1 mol%, the yield was practically kept in the same range (entry 11), avoiding the formation of minor by-products. The optimal temperature was
also determined. Decreasing the reaction temperature to 50 °C produced a drop in the yield to 52% (entry 12) whereas when it was decreased to 80 °C the yield was maintained (entry 13). Finally, other DES were tested with these optimised conditions (entries 15-17), but poorer results were obtained. It should be pointed out that no copper source was needed in any case.

Table 12. Optimization of the Sonogashira reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd] (mol%)</th>
<th>20a (mol%)</th>
<th>T (°C)</th>
<th>2a (eq.)</th>
<th>Base</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>3.0</td>
<td>100</td>
<td>1</td>
<td>Pr₂NH (3)</td>
<td>89</td>
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<tr>
<td>2</td>
<td>1.0</td>
<td>3.0</td>
<td>100</td>
<td>1.2</td>
<td>Pr₂NH (3)</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>3.0</td>
<td>100</td>
<td>2</td>
<td>Pr₂NH (3)</td>
<td>95</td>
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<tr>
<td>4</td>
<td>1.0</td>
<td>3.0</td>
<td>100</td>
<td>2</td>
<td>K₂CO₃ (3)</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>3.0</td>
<td>100</td>
<td>2</td>
<td>NaOAc (3)</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>3.0</td>
<td>100</td>
<td>2</td>
<td>Et₃N (3)</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>3.0</td>
<td>100</td>
<td>2</td>
<td>Pr₂NH (3)</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>1.0</td>
<td>3.0</td>
<td>100</td>
<td>2</td>
<td>Pr₂NH (1)</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>1.0</td>
<td>3.0</td>
<td>100</td>
<td>2</td>
<td>Pr₂NH (3)</td>
<td>&gt;99</td>
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<tr>
<td>10</td>
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<td>3.0</td>
<td>100</td>
<td>2</td>
<td>Pr₂NH (2)</td>
<td>52</td>
</tr>
<tr>
<td>11</td>
<td>0.1</td>
<td>0.3</td>
<td>100</td>
<td>2</td>
<td>Pr₂NH (3)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>12</td>
<td>0.1</td>
<td>0.3</td>
<td>50</td>
<td>2</td>
<td>Pr₂NH (2)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>13</td>
<td>0.1</td>
<td>0.3</td>
<td>80</td>
<td>2</td>
<td>Pr₂NH (2)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>14</td>
<td>0.1</td>
<td>0.3</td>
<td>120</td>
<td>2</td>
<td>Pr₂NH (2)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>15</td>
<td>0.1</td>
<td>0.3</td>
<td>80</td>
<td>2</td>
<td>Pr₂NH (2)</td>
<td>71d</td>
</tr>
<tr>
<td>16</td>
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<td>0.3</td>
<td>80</td>
<td>2</td>
<td>Pr₂NH (2)</td>
<td>62e</td>
</tr>
<tr>
<td>17</td>
<td>0.1</td>
<td>0.3</td>
<td>80</td>
<td>2</td>
<td>Pr₂NH (2)</td>
<td>62</td>
</tr>
</tbody>
</table>

* Yield determined by GC using tridecane as internal standard.  
  b Reaction carried out employing Pd(OAc)$_2$ instead of PdCl$_2$.  
  c Reaction carried out in ChCl:ethylene glycol (1:2).  
  d Reaction carried out in ChCl:urea (1:2).  
  e Reaction carried out in ChCl:glycerol (1:2).

The scope of the Sonogashira coupling employing this methodology was evaluated (Table 13). Good to excellent yields were obtained using aryl iodides bearing electron-withdrawing (entries 1, 4 and 7), and electron-donating groups (entries 5 and 9). Steric hindrance seemed to be an issue for this reaction as it can be seen in entry 9. Heteroaryl iodides were also tested with good results (entries...
Chapter II. Palladium-catalysed C-C Cross-Coupling Reactions

When the reaction was performed with aryl bromides using this approach, only 15% yield was obtained (entry 2) and we decided to increase the catalyst amount to 1 mol%. With this amount, the reaction worked fine only with electron-poor systems (entries 3, 8, 12). 2-chloropyridine was also tested (entry 13), proving that the reaction could take place with electron-poor heteroaryl chlorides.

Table 13. Scope of Sonogashira reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>X</th>
<th>Product</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-COMe</td>
<td>I</td>
<td>22a</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-COMe</td>
<td>Br</td>
<td>22a</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4-COMe</td>
<td>Br</td>
<td>22a</td>
<td>75b</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-CF3</td>
<td>I</td>
<td>22b</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4-Me</td>
<td>I</td>
<td>22c</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4-Me</td>
<td>Br</td>
<td>22c</td>
<td>9b</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4-NO2</td>
<td>I</td>
<td>22d</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4-NO2</td>
<td>Br</td>
<td>22d</td>
<td>89b</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2-Me</td>
<td>I</td>
<td>22e</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2-Me</td>
<td>Br</td>
<td>22e</td>
<td>20b</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1-NO2</td>
<td>I</td>
<td>22f</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2-Me</td>
<td>Br</td>
<td>22f</td>
<td>99b</td>
<td></td>
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<td>13</td>
<td>Cl</td>
<td>Br</td>
<td>22f</td>
<td>36b</td>
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<td>14</td>
<td>I</td>
<td>Br</td>
<td>22g</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Br</td>
<td>Br</td>
<td>22g</td>
<td>67b</td>
<td></td>
</tr>
</tbody>
</table>

*a Isolated yield after flash chromatography. b Reaction carried out with 1.0 mol% of PdCl₂ and 3 mol% of 20a.

The Heck cross-coupling reaction was tested as well. At first, reaction between 1-iodo-4-nitrobenzene and methyl acrylate was evaluated (Table 14). When only 0.1 mol% of PdCl₂ was employed the reaction did not take place (entry 1). Then the catalyst loading was increased until 0.5 mol%, and the reaction yield was still poor (entry 2). Other DESs were tested without increasing the catalyst loading, obtaining good yields with CHCl₂:glycerol (1:2) and Ph₃PMeBr:glycerol (1:2) as solvents (entries 3, 5).
Table 14. Optimization of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂ (0.1) + 20a (0.3)</td>
<td>ChCl:urea (1:2)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂ (0.5) + 20a (1.5)</td>
<td>ChCl:urea (1:2)</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>PdCl₂ (0.5) + 20a (1.5)</td>
<td>ChCl:glycerol (1:2)</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>PdCl₂ (0.5) + 20a (1.5)</td>
<td>ChCl:F₃CCONH₂ (1:2)</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂ (0.5) + 20a (1.5)</td>
<td>Ph₃PMeBr:glycerol (1:2)</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>PdCl₂ (0.5) + 20a (1.5)</td>
<td>Betaine:oxalic acid (1:2)</td>
<td>11</td>
</tr>
</tbody>
</table>

*Yield determined by GC using tridecane as internal standard.

Then, the scope of the reaction was evaluated, using methyl acrylate and different substituted aryl iodides (Chart 1). The reaction took place with moderate to good yields with aryl iodides bearing electron-withdrawing and electron-donating groups. Reaction worked worse with 2-substituted aryl iodides, probably owing to the steric hindrance.

The Hiyama reaction was also tested using the mixture of PdCl₂ and phosphine 20a as catalyst. However, a low yield was observed, while the results obtained with the Pd NCN pincer 9a were much better (Table 7). This fact confirms that 9a was a better catalyst for the Hiyama reaction under otherwise identical reaction conditions (Scheme 26), while the combination of PdCl₂ and phosphine 20a proved to be more active for the Suzuki, Heck and Sonogashira reactions (Scheme 24).

Scheme 26. Hiyama reaction using phosphine ligand.
On the other hand, the recyclability of the DES and catalyst was evaluated. Once the reaction finished, cyclopentyl methyl ether, a potential green alternative solvent,\textsuperscript{159,210} was added to the reaction mixture in order to perform an extraction. All organic compounds were removed and the mixture of DES and catalyst, lower phase in the decantation process, was reused under the same reaction conditions. This study was repeated for the three studied cross-coupling reactions, obtaining excellent yields even after the five cycle for the Suzuki and Sonogashira couplings (Figure 20).

We next turned to DFT studies (M06/6-311G**(SDD)(IEFPCM-CH\textsubscript{3}CN) to shed some light into the structures and energies of the Pd complexes with the different ligands 20a, 20b and 20c (Figure 21).\textsuperscript{211} We were especially interested in the stoichiometry and the coordination modes of the complexes. For comparison purposes, we also included the ligand 20d, a neutral counterpart of ligand 20a, which could provide information about the similarities or differences of our ionic


\textsuperscript{211} DFT calculations were performed by the group of Prof. Dr. Enrique Gómez-Bengoa at the University of Basque Country.
complexes with the well-known PdCl$_2$(PR$_3$)$_2$ type of ligands. For the sake of accuracy, we used the complete ligands, without any structural simplification, at the expense of a significant computation time.

Figure 20. Cross-coupling recyclability experiments.

First, ligand 20a can operate only as a monodentate ligand, and we found computationally that the most stable complex corresponds to the trans dicoordinated square-planar trans-[PdCl$_2$(20a)$_2$] (G = 0.0 kcal/mol, Scheme 27). The Free Gibbs (G) energy of the cis isomer is 18.5 kcal/mol higher than the trans, and the sum of monocoordinated complex PdCl$_2$ (3a) and one more equivalent of the free ligand 20a is even less favourable (+23.7 kcal/mol). This preference is consistently repeated regardless the number of chlorine atoms introduced in the computed structures, as in the forms of PdCl$_2$(20a)$_2$$^+$ 2Cl$, PdCl$_2$(20a)$_2$$^+$, or Pd(20a)$_4$$^+$.

Figure 21. Phosphine ligands 20a-d used in the computational study.
The same trend was observed for the neutral ligand 20d, as the trans-PdCl₂L₂ complex is the most stable one, over the cis (+14.4 kcal/mol) and the monocoordinated species (+37.1 kcal/mol). This finding indicates that the ionic or neutral nature of the ligands (20a vs 20d) is not affecting significantly the structure and coordination mode of the complexes, and that pyridinium chloride-based ligands like 20a can act as ionic surrogates of the well-known triphenyl or tricyclohexyl phosphine substrates.

![Scheme 27. Computed structures and Free Gibbs energies for the complexes of ligands 20a and 20d at M06/6-311G**(iefpcm,solvent=MeCN) level of theory.](image)

On the other hand, the complexes formed by ligands 20b and 20c were computed (Scheme 28). Due to their bidentate nature, we hypothesised that their geometrical requirements could be different to the previous ligand 20a. However, the complexation energies showed that for 20b, the trans di-coordinated complex Pd(20b)₂²⁺ 2Cl⁻ renders again the most stable situation, with a narrower energy gap (5.5 kcal/mol) with its cis-Pd(20b)₂²⁺ 2Cl⁻ counterpart.

The monocoordination as in Pd(20b)²⁺ is again heavily penalized probably due to the poor coordination ability of the pyridine ring in 20b. Remarkably, the thiophene containing ligand 20c shows a divergent behaviour, and the coordination of a single equivalent (like in Pd(20c)²⁺ Cl⁻), is preferred over than any of the
dicoordinated cis or trans isomers of Pd(20c)$_2^{2+}$ 2Cl$^-$ in 10.9 and 19.5 kcal/mol respectively.

![Scheme 28. Computed structures and Free Gibbs energies for the complexes of ligands 20b and 20c at M06/6-311G**(iepcm.solvent=MeCN) level of theory.](image)

Finally, experimental UV-VIS studies were in agreement with the DFT findings for the coordination of ligands 20. Thus, the spectrophotometric titrations of acetonitrile solutions ($5.0 \times 10^{-5}$ M) of ligands 20a ($\lambda = 300$ and 313 nm), 20b ($\lambda = 233$ nm) and 20d ($\lambda = 243$ nm) with increasing amounts of an acetonitrile solution of Pd(OAc)$_2$ ($2.5 \times 10^{-4}$ M) confirmed the formation of a 1:2 metal:ligand complex. A similar study with the thiophene-derived ligand 20c ($\lambda = 273$ nm) also confirmed the formation of a 1:1 metal:ligand complex, as anticipated by the DFT calculations.

![Figure 22. UV–VIS spectra on successive addition of 10 µL Pd(OAc)$_2$ ($2.5 \times 10^{-4}$M) to a 2 mL solution of ligand 20a ($5.0 \times 10^{-5}$M). Found molar ratio = 1:2 (Metal:Ligand).](image)
These experiments were performed with Pd(OAc)$_2$ instead of PdCl$_2$ due to the low solubility of the latter one. Nevertheless, since the catalytic experiments in DESs were performed with PdCl$_2$, another test was performed with PdCl$_2$(MeCN)$_2$, obtaining the same results. For this reason, the counterion of the initial palladium salt did not seem to interfere with the phosphine coordination.

**Figure 23.** UV-VIS spectra on successive addition of 10 µL Pd(MeCN)$_2$Cl$_2$ (2.5 x 10$^{-4}$M) to a 2 mL solution of ligand 20a (5.0 x 10$^{-5}$M). Found molar ratio = 1:2 (Metal:Ligand).

**Figure 24.** UV-VIS spectra on successive addition of 10 µL Pd(OAc)$_2$ (2.5 x 10$^{-4}$M) to a 2 mL solution of ligand 20b (5.0 x 10$^{-5}$M). Found molar ratio = 1:2 (Metal:Ligand).
Figure 25. UV-VIS spectra on successive addition of 10 μL Pd(OAc)$_2$ (2.5 x 10$^{-4}$ M) to a 2 mL solution of ligand 20c (5.0 x 10$^{-5}$ M). Found molar ratio ≈ 1:1 (Metal:Ligand).

Finally, $^{31}$P{¹H} NMR studies were performed in order to confirm the coordination of the phosphine to palladium. Thus, a 2/1 mixture of 20a/PdCl$_2$ was analysed by $^{31}$P{¹H} NMR (DMSO- d$_6$, 121 MHz) and compared with the results obtained for the free ligand 20a (Figure 27).

The $^{31}$P{¹H} NMR spectrum of free ligand 20a showed a broad singlet at -2.25 ppm (while its $^{31}$P NMR spectrum showed a sharp singlet at -2.25 ppm). However, in the in situ prepared palladium complex a small signal corresponding to the free ligand was observed, together with a broad singlet at 43.15 ppm. This latter signal corresponds to the resonance frequency of the phosphine ligand coordinated to the metal.

Figure 26. UV-VIS spectra on successive addition of 10 μL Pd(OAc)$_2$ (2.5 x 10$^{-4}$ M) to a 2 mL solution of ligand 20c (5.0 x 10$^{-5}$ M). Found molar ratio = 1:2 (Metal:Ligand).
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Figure 27. a) $^{31}\text{P}$ (green) and $^{31}\text{P}[^{1}\text{H}]$ (blue) NMR spectra (DMSO-d$_6$, 121 Mz) of ligand 20a. b) $^{31}\text{P}[^{1}\text{H}]$ NMR spectrum (DMSO-d$_6$, 121 Mz) of PdCl$_2$(20a)$_2$. 
CHAPTER III

C-S Cross-coupling reactions
1. GENERAL INTRODUCTION

Organometallic complexes typically undergo elementary reactions, releasing products that usually contain new C-C or C-H bonds. These processes have been extensively studied and applied to the synthesis of bulk and fine chemicals. Although the backbone of these molecules is usually composed by C-C bonds, their function is mainly driven by the presence of heteroatoms. Chapters I and II of this thesis are focused on the study of C-C coupling reactions. However, the carbon-heteroatom coupling reactions are also of capital relevance in Organic Chemistry.

Taking into account that the production of pharmacologically active compounds, that contain generally more than a carbon-heteroatom bond, is considered one of the less environmental-friendly industries, to provide sustainable methods for the synthesis of these relevant high value-added products is an urgent demand. Thus, the study of organometallic-catalysed processed for carbon-heteroatom bond formation under environmentally bening conditions is of great interest.

Among the criteria for reaching sustainability in chemical processes, selectivity, waste production, toxicity, energy or the overall number of synthetic steps are factors to be taken into account to design an efficient transformation. So, new strategies such as multicomponent reactions (MCRs), diversity-oriented synthesis (DOS) or multiple bond-forming transformations (MBFTs) are tools which try to maximize all these aspects. This is achieved by maximising the bonds formed in a single synthetic step, reducing the use of solvents, reagents and purification steps, thus saving time and resources. However, the scope of the transformations based on these approaches is often quite limited, not being extensible for the synthesis of related substructures.

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One of these multicomponent reactions with potentially relevant application in the pharmaceutical industry is the SO$_2$ incorporation into organic motifs. Sulfur dioxide-based reactions can afford sulfones, sulfonamides and related compounds with high added value products. However, the toxic character of SO$_2$ and its gaseous nature are two main drawbacks for its direct use in reactions leading to sulfur derivatives.\(^\text{210}\)

Sulfones are interesting functional groups in drug industry\(^\text{220-221}\) or as intermediates in the total synthesis of complex molecules.\(^\text{222}\) On the other hand, the sulfonamide functional group is one of the most frequently found in pharmacologically active compounds,\(^\text{223}\) including those related to new research\(^\text{224}\) on anticancer active molecules.\(^\text{225}\) Despite the undeniable interest of sulfones and sulfonamides, the synthetic methods for their synthesis has not been so broadly exploited.

Regarding sulfones, their syntheses is usually based on strategies such as sulfide oxidation\(^\text{226}\) or alkylation of sulfinate salts.\(^\text{227-229}\) Those methods provide the desired products usually in good yields, but they need starting materials with pre-formed C-S bonds, relying entirely on the commercial availability of those compounds. More interesting is the palladium-catalysed insertion of SO$_2$ into organic motifs,\(^\text{230}\) although the need of using high pressures of a toxic gas have limited the extent of these studies.

Concerning sulfonamides, traditional methods for their syntheses are still prevailing.\(^\text{231}\) For more than a century, sulfonamides have been mostly prepared


from amines and activated sulfonyl derivatives, usually a sulfonyl chloride. This methodology is efficient but relies entirely on the use of stoichiometric sulfonyl chlorides, which are not stable or commercially affordable. For this reason, these reagents are frequently in situ prepared, using harsh reaction conditions, and handled under inert atmosphere, making the use of dry volatile organic solvents mandatory. Therefore, new methodologies which avoid the use of unstable and toxic reagents and reaction mediums are demanded.

In this regard, the search for appropriate SO₂ surrogates has become an important research field during the last years. Employing such compounds, avoids the need of specialised pressure-resistant equipment and deliver safer and more controlled methods.

One of these surrogates, which is attracting great interest, is 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO). This reagent, prepared from 1,4-Diazabicyclo[2.2.2]octane (DABC) and SO₂(g) is a bench stable solid which can replace SO₂ in several reactions. The synthesis of sulfoxones employing this reagent has been achieved by different means. For instance, the reaction of organomagnesium, organolithium or organozinc compounds with DABSO afford the corresponding sulfinites, which can be subsequently alkylated, or arylated under palladium catalysis, to yield unsymmetrically substituted sulfoxones. The use of organometallic reactants can be avoided by means of using Pd catalysts to generate a sulfinate from aryl halides and DABSO, with a subsequent alkylation step. Arylboronic acids are also possible substrates.

capable to react with DABSO affording arylsulfonates under copper\textsuperscript{243} or palladium\textsuperscript{244} catalysis.

Not only sulfones, but also sulfonamides have also been synthesised using DABSO as SO\textsubscript{2} source. This strategy has been described starting from arylmagnesium reagents,\textsuperscript{245} aryl halides\textsuperscript{246} or aryl boronic acids.\textsuperscript{247} Related palladium\textsuperscript{248-249} and/or gold-catalysed\textsuperscript{250-251} procedures have been found effective for the preparation of N-aminosulfonamides. All these strategies are usually highly efficient and can be performed in one-pot manner, although with multiple steps required and usually with a different volatile organic solvent used for each step.

Alternatively, sodium and potassium metabisulfite have also been proposed as a SO\textsubscript{2} surrogates. These inexpensive inorganic chemicals have been employed as preservative additives in food industry (Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} E-223; K\textsubscript{2}S\textsubscript{2}O\textsubscript{3} E-224). They are known to yield SO\textsubscript{2} under heating or in the presence of water, generating only Na\textsubscript{2}SO\textsubscript{3} as waste, thus avoiding the generation of pollutant organic by-products. Aryl halides have been coupled with SO\textsubscript{2}, generated from K\textsubscript{2}S\textsubscript{2}O\textsubscript{3}, affording sulfonates under Pd catalysis, reacting latter with electrophiles to afford sulfones or with a chlorinating reagent and an amine to yield sulfonamides.\textsuperscript{252} A one-pot, one-step procedure for the synthesis of sulfones was also reported, employing arylboronic acids and activated electrophiles. The reaction was catalysed by 10 mol\% of Pd(MeCN)\textsubscript{2}Cl\textsubscript{2} and 10 mol\% of a phosphine ligand, using DME as solvent and 1.1 equivalents of TBAB as additive.\textsuperscript{253} Moreover, gold-catalysed versions of this reaction have been reported as well.\textsuperscript{254-255} Cyclic sulfonamides and

\textsuperscript{244} V. Vedovato, E. P. A. Talbot, M. C. Willis, Org. Lett. 2018, 20, 5493-5496.
\textsuperscript{246} E. F. Flegeau, J. M. Harrison, M. C. Willis, Synlett 2016, 27, 101-105.
sulfinamides have also been obtained via a Pd-catalysed insertion of SO$_2$ from K$_2$S$_2$O$_5$.  

In view of the literature results, the main drawback of this SO$_2$ surrogate seemed to be its low solubility in typical organic solvents. For this reason, the aforementioned reports needed a mixture of solvents or the use of additives which improved the solubility of this salt. Still, the use of metabisulfite anion possess advantages over the use of other SO$_2$ surrogates, and a proper reaction medium could improve the results obtained so far. Thus, the multicomponent synthesis of sulfones and sulfinamides from M$_2$S$_2$O$_5$ in DES as reaction medium was envisaged. A few precedents of organosulfur compounds being synthesised in DES medium though simple organic transformations were already reported, encouraging us to test the multicomponent SO$_2$ fixation in this type of reaction medium. Due to the nature of eutectic solvents, all the inorganic salts and organic reagents would become soluble, increasing the effectiveness of metabisulfite anion as SO$_2$ source. Furthermore, the enhanced SO$_2$ solubility that this type of medium exhibits was also a potential benefit for carrying out these reactions in DESs.

2. PALLADIUM-CATALYSED SYNTHESIS OF SULFONES AND RELATED DERIVATIVES

With these precedents, the sulfonylation reaction of phenylboronic acid (21a) with sodium metabisulfite (25), as SO$_2$ source, was tested (Table 15). Pentyl bromide was added from the beginning of the reaction, trying to perform the sulfonylation and subsequent alkylation of the corresponding sodium benzenesulfinate (27a) in a multicomponent approach. The reaction was tested employing only 1 mol% of PdCl$_2$. In view of previous literature reports, a phosphine ligand seems to be necessary for the reaction to proceed at good reaction rates. Thus, it was decided to use the DES-compatible phosphine 20a (3 mol%) as ligand. First, different eutectic mixtures were tested as solvents (entries 1-15). The reaction failed in most of the tested DES, being 32% yield one of the highest results obtained (entry 1).

---

Table 15. Solvent and ligand optimization study.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>DES (molar ratio)</th>
<th>Ligand</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ChCl:urea (1:2)</td>
<td>20a</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>ChCl:(HOCH\textsubscript{2})\textsubscript{2} (1:2)</td>
<td>20a</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>ChCl:glycerol (1:2)</td>
<td>20a</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Ph:PMeBr:glycerol (1:2)</td>
<td>20a</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Glucose:malic acid (1:2)</td>
<td>20a</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>AcChCl:urea (1:2)</td>
<td>20a</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>ChCl:resorcinol (1:1)</td>
<td>20a</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>ChCl:tartaric acid (1:1)</td>
<td>20a</td>
<td>Trace</td>
</tr>
<tr>
<td>9</td>
<td>ChCl:malic acid (1:1)</td>
<td>20a</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>ChCl:glucose (2:1)</td>
<td>20a</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>ChCl:glucose.H\textsubscript{2}O (1:1:1)</td>
<td>20a</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>ChCl:CF\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>20a</td>
<td>63</td>
</tr>
<tr>
<td>13</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>20a</td>
<td>99</td>
</tr>
<tr>
<td>14</td>
<td>ChCl:imidazole (3:7)</td>
<td>20a</td>
<td>Trace</td>
</tr>
<tr>
<td>15</td>
<td>ChCl:tiourea (1:2)</td>
<td>20a</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>-</td>
<td>48</td>
</tr>
<tr>
<td>17</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>P(Fu)\textsubscript{3}</td>
<td>34</td>
</tr>
<tr>
<td>18</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>PC\textsubscript{y} \textsubscript{2}</td>
<td>12</td>
</tr>
<tr>
<td>19</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>PPh\textsubscript{3}</td>
<td>55</td>
</tr>
<tr>
<td>20</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>20d</td>
<td>21</td>
</tr>
<tr>
<td>21</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>P(CH\textsubscript{2}OH)\textsubscript{3}</td>
<td>29</td>
</tr>
<tr>
<td>22</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>20b</td>
<td>61</td>
</tr>
<tr>
<td>23</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>20c</td>
<td>70</td>
</tr>
<tr>
<td>24</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>20a</td>
<td>40\textsuperscript{d}</td>
</tr>
<tr>
<td>25</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>20a</td>
<td>44\textsuperscript{e}</td>
</tr>
<tr>
<td>26</td>
<td>ChCl:CH\textsubscript{3}CONH\textsubscript{2} (1:2)</td>
<td>20a</td>
<td>40\textsuperscript{f}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: 21a (1 mmol), 25 (2.2 mmol), 26a (2 mmol), PdCl\textsubscript{2} (0.01 mmol), ligand (0.03 mmol), DES (2 mL), 80 °C, 24 h. \textsuperscript{b} Yield determined by GC using tridecane as internal standard. \textsuperscript{c} P(Fu)\textsubscript{3} stands for tri(furan-2-yl)phosphine. \textsuperscript{d} Reaction performed using only 1.2 eq. of pentyl bromide. \textsuperscript{e} Reaction performed using only 1.2 eq. of Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5}. \textsuperscript{f} Reaction performed using only 0.01 mmol of ligand 20a.

For that reason, HBD similar to urea were tested, obtaining better results with ChCl:CF\textsubscript{3}CONH\textsubscript{2} (1:2, entry 12) and a full conversion to the product with...
ChCl:acetamide (1:2, entry 13). The reaction was tested without ligand, with the yield being halved (entry 16). Other commercially available phosphines (entries 17-21) or other cationic pyridinophosphines (entries 22-23) gave lower yields. Moreover, reducing the excess of the alkylation reagent (entry 24) or the SO₂ surrogate (entry 25) also led to a lower yield. Finally, changing the ligand/metal ratio to 1:1 in order to obtain a more active Pd(I) species did not improve the reaction yield (entry 26).

Other possible safe sources of SO₂ were also tested (Table 16). First, sodium metabisulfite was replaced by K₂S₂O₅, which had already proven its usefulness in similar processes. Nevertheless, a poor yield was observed (entry 2), probably due to the higher solubility in DES of the sodium salt. DABSO was tested as well under the same reaction conditions, obtaining a very low conversion to the desired product. Other reported sulfur sources, which have been reported to undergo insertion into organic molecules were tested, although the reaction did not work with Na₂S₂O₄, S₈ or rongalite (NaO₂SCH₂OH).

Table 16. Study of SO₂ surrogates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[S]</th>
<th>Yield of 28a (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na₂S₂O₅</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>K₂S₂O₅</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>DABSO</td>
<td>13.0</td>
</tr>
<tr>
<td>4</td>
<td>Na₂S₂O₄</td>
<td>5.8</td>
</tr>
<tr>
<td>5</td>
<td>S₈</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>NaO₂SCH₂OH</td>
<td>Trace</td>
</tr>
</tbody>
</table>

*Reaction carried out using compounds 21a (1.0 mmol), sulphur source (2.2 mmol) and 26a (2.0 mmol) in 2 mL of DES. b Yield determined by GC using tridecane as internal standard.

Moreover, alternatives to phenylboronic acid were explored. Unfortunately, the reaction failed with other aryl sources such as trifluoroborates, pinacol boronic esters, triethoxyarylsilanes or silicates (Table 17).

Table 17. Study of aryl sources.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ph-X</th>
<th>Yield of 28a (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhB(OH)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>PhBF&lt;sub&gt;3&lt;/sub&gt;K</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>PhBPin</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>PhSi(OEt)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction carried out using compounds 2 (1.0 mmol), 3 (2.2 mmol), 4 (2.0 mmol) and 1 mol% of metal salt in 2 mL of DES. <sup>b</sup> Yield determined by GC using tridecane as internal standard.

Finally, despite the good results obtained with palladium chloride, other metallic catalysts were tested (Table 18). It should be noticed that the inexpensive FeCl<sub>2</sub> also afforded the desired product 28a in a 90% yield. Nevertheless, this catalyst failed with other substrates (Table 19), while PdCl<sub>2</sub> seemed to be more versatile.

Due to the unique properties of DES, the catalytic system could be recycled using 2-MeTHF as a sustainable VOC solvent for the decantation process, with products being extracted, while the catalyst remained in the DES phase. The reaction was repeated five times by the addition of fresh reagents, without adding more metal, ligand or solvent. The yield of the first three cycles was maintained, although it started to decrease slightly in the fourth cycle and a significant drop in the reaction yield was observed in the fifth cycle. The observed turnover number (TON) after five cycles was 387, much higher than the previous reports using K<sub>2</sub>S<sub>2</sub>O<sub>5</sub> as SO<sub>2</sub> source, ranging from 6.6 to 15.8.<sup>252-255</sup>

Table 18. Study of metal sources as catalyst.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal salt</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>PdCl\textsubscript{2}</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>CrCl\textsubscript{2}</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>FeCl\textsubscript{2}</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>NiCl\textsubscript{2}</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>CuCl\textsubscript{2}</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>RuCl\textsubscript{3}</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>IrCl\textsubscript{4}</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>FeCl\textsubscript{3}</td>
<td>64</td>
</tr>
<tr>
<td>10</td>
<td>FeCl\textsubscript{3}.6H\textsubscript{2}O</td>
<td>44</td>
</tr>
<tr>
<td>11</td>
<td>Fe(NO\textsubscript{3})\textsubscript{3}.9H\textsubscript{2}O</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>FeSO\textsubscript{4}.7H\textsubscript{2}O</td>
<td>45</td>
</tr>
<tr>
<td>13</td>
<td>FeCl\textsubscript{2}.4H\textsubscript{2}O</td>
<td>41</td>
</tr>
<tr>
<td>14</td>
<td>PdO-Fe\textsubscript{3}O\textsubscript{4}</td>
<td>49\textsuperscript{c}</td>
</tr>
<tr>
<td>15</td>
<td>Fe\textsubscript{3}O\textsubscript{4}</td>
<td>15\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction carried out using compounds 2a (1.0 mmol), 3 (2.2 mmol), 4 (2.0 mmol) and 1 mol\% of metal salt in 2 mL of DES. \textsuperscript{b} Yield determined by GC using tridecane as internal standard. \textsuperscript{c} 50 mg of PdO-Fe\textsubscript{3}O\textsubscript{4} and no ligand was used (1.3 mol\% Pd). \textsuperscript{d} 50 mg of Fe\textsubscript{3}O\textsubscript{4} and no ligand was used.

![Graph showing recyclability study](image)

Figure 28. Recyclability study.

Under optimized conditions, the scope of boronic acids was evaluated (Table 19.). The reaction gave moderate to good yields with electron-donating substituents (entries 2-6), while sterically hindered or electron-withdrawing substituents afforded lower yields (entries 7-8). On the other hand, heteroaromatic
boronic acids were tested, obtaining good yields with thienyl moieties (entries 10-11), while using a pyridyl reagent product was not observed (entry 12). In view of the good results obtained with iron chloride during the optimisation, it was tested again with different substrates, but in all cases the obtained yields with FeCl₂ (Table 19, footnote b) were lower than those obtained by the palladium-catalysed process.

Table 19. Scope of boronic acids.α

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield of 28 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>28a</td>
<td>99 (90)</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC₆H₄</td>
<td>28b</td>
<td>51 (72)</td>
</tr>
<tr>
<td>3</td>
<td>3-MeC₆H₄</td>
<td>28c</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>2-MeC₆H₄</td>
<td>28d</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>4-HOC₆H₄</td>
<td>28e</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>4-MeOC₆H₄</td>
<td>28f</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>2,6-(MeO)₂C₆H₄</td>
<td>28g</td>
<td>17 (0)</td>
</tr>
<tr>
<td>8</td>
<td>4-(CF₃)C₆H₄</td>
<td>28h</td>
<td>25 (13)</td>
</tr>
<tr>
<td>9</td>
<td>Z-PhCH=CH</td>
<td>28i</td>
<td>25 (13)</td>
</tr>
<tr>
<td>10</td>
<td>2-thienyl</td>
<td>28j</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>1-thienyl</td>
<td>28k</td>
<td>68 (51)</td>
</tr>
<tr>
<td>12</td>
<td>4-pyridyl</td>
<td>28l</td>
<td>0</td>
</tr>
</tbody>
</table>

α Reaction carried out using compounds 21 (1.0 mmol), 25 (2.2 mmol) and 26a (2.0 mmol) in 2 mL of DES. All yields presented are isolated yields. β Reaction carried out using FeCl₂ (1 mol%) instead of PdCl₂. γ Reaction carried out using 3.0 mmol of ArB(OH)₂, 6.6 mmol 25 and 1.0 mmol of 26a.

In order to prove the versatility of the synthesis, other electrophiles were tested (Table 20). The reaction proceeded with different alkyl halides as electrophiles (entries 1-5). Product 28o (entry 4) was obtained in a moderate yield, but the related acyclic allylic sulfone was not detected in the crude mixture, demonstrating that the mechanism of the latest step of the reaction did not seem to occur via a radical pathway. Less conventional electrophiles such as diaryliodonium salts could be employed (entry 6). A SₛAr reaction also took place between 2-chlorobenzo[d]thiazole and the sulfinate intermediate, affording product 28r with excellent yield (entry 7).α S. Liang, R.-Y. Zhang, L.-Y. Xi, S.-Y. Chen, X.-Q. Yu, J. Org. Chem. 2013, 78, 11874-11880.
10-13) could also be employed as electrophiles. Finally, the use of H$_2$N-OSO$_3$H afforded the corresponding sulfonamide (entry 14).

Table 20. Scope of electrophiles.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>28a</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Ph'Br</td>
<td>28m</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>Br$^2$Br</td>
<td>28n</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>Ph'O</td>
<td>28o</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>PhF</td>
<td>28p</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>PhBF$_4$</td>
<td>28q</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>Cl$^-$Py</td>
<td>28r</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>Br$^-$Py</td>
<td>28s</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>Br$^-$PhSO$_2$H</td>
<td>28t</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>O=</td>
<td>28u</td>
<td>10 (46)$^c$</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: PhB(OH)$_2$ + Na$_2$S$_2$O$_5$ + R-X + PdCl$_2$ (1 mol%) + 20a (3 mol%) + CH$_2$CH$_2$CONH$_2$ (1:2) (0.5 M) at 80 °C, 24 h.

$^b$ Isolated yield.

$^c$ Isolated yield after column chromatography.
Table 20. Scope of electrophiles. a (Cont.)

<table>
<thead>
<tr>
<th></th>
<th>Electrophile</th>
<th>Sulfinate Salt</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>HO</td>
<td>HO-S-Ph</td>
<td>28v</td>
<td>38 (99)c</td>
</tr>
<tr>
<td>12</td>
<td>OMe</td>
<td>MeO-S-Ph</td>
<td>28w</td>
<td>57</td>
</tr>
<tr>
<td>13</td>
<td>CN</td>
<td>NC-O-S-Ph</td>
<td>28x</td>
<td>13 (41)c</td>
</tr>
<tr>
<td>14</td>
<td>H₂N-O-SO₂H</td>
<td>H₂N-S-Ph</td>
<td>28y</td>
<td>98</td>
</tr>
</tbody>
</table>

a Reaction carried out using compounds 21a (1.0 mmol), 25 (2.2 mmol) and 26 (2.0 mmol) in 2 mL of DES. b Isolated yields. c Reaction carried out using 3.0 mmol of ArB(OH)₂, 6.6 mmol Na₂S₂O₅ and 1.0 mmol of electrophile.

Sulfinate salts have been employed as starting materials in the synthesis of different aryl sulfides. In those cases, iodine was added to the sulfinate allowing the synthesis of aryl sulfides via C-H functionalization by a thiolation of phenol or phenylamine derivatives. In view of those precedents, the in situ generation of aryl sulfinites and their corresponding transformations into aryl sulfides in a one-pot manner was proposed. Adding molecular iodine to the aryl sulfinate salt in a protic media, yields the corresponding thiol or disulphide, which could act as an electrophile.

In this way, a three steps process-transformation was performed in one pot (formation of the sulfinate salt, transformation to thiol derivative and reaction with nucleophiles). The obtained results are depicted in Table 21, showing moderate to good yields using phenol derivatives (entries 1-3), N,N-dimethylaniline (entry 4), 1,3,5-trimethoxybenzene (entry 5) or even indole (entry 6).

---

Table 21. Scope of aryl sulfides.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>29a</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>29b</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>29c</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>29d</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>29e</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>29f</td>
<td>63</td>
</tr>
</tbody>
</table>

a Reaction carried out using compounds 21a (1.0 mmol), 25 (2.2 mmol) in 2 mL of DES during 12 h, then I₂ (2 mmol) was added and stirred for 20 min and finally phenol/aniline derivative (2 mmol) was added and stirred for 12 h at 80 °C. b All examples are shown with yields of isolated product.

A radical process could also take place in this new reaction media (Table 22), affording the corresponding disulfide in the absence of any other reagent (entries 1-2). If a hydroxy-functionalized alkene is added, the double bond reacts with the radical thiol with a subsequent cyclization to afford products 30c-30e (entries 3-
Another radical-mediated reaction is the synthesis of 28z from phenylpropiolic acid catalysed by phosphoric acid.\textsuperscript{270-271}

\begin{table}[h]
\centering
\caption{Scope using radical scavengers.\textsuperscript{a}}
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Radical Scavenger & Product & Yield (%)\textsuperscript{b} \\
\hline
1 & - & \includegraphics[width=1cm]{product1} & 95 \\
2 & - & \includegraphics[width=1cm]{product2} & 66 \\
3 & HO & \includegraphics[width=1cm]{product3} & 62 \\
4 & HO & \includegraphics[width=1cm]{product4} & 42 \\
5 & HO & \includegraphics[width=1cm]{product5} & 98 \\
6 & Ph=\text{COH} & \includegraphics[width=1cm]{product6} & 32\textsuperscript{c} \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} Reaction carried out using compounds 21a (1.0 mmol), 25 (2.2 mmol) in 2 mL of DES during 12 h, then I\textsubscript{2} (2 mmol) was added and stirred for 20 min and finally enol (2 mmol) was added and stirred for 12 h at 80 °C. \textsuperscript{b} All examples are shown with yields of isolated product. \textsuperscript{c} Instead of I\textsubscript{2}, phenylpropiolic acid (2 mmol) and H\textsubscript{3}PO\textsubscript{4} (4 mmol) were added to the reaction media after 8 h and the reaction proceeded for 16 h.

Intrigued by the unique properties of this catalytic system, the evolution of the reaction between phenylboronic acid (21a) and sodium metabisulfite (25) to form

sodium benzenesulfinate was monitored by HPLC (Figure 29). Assuming a simple equation rate and that the reaction conditions allow a pseudo-first order approximation for all reagents, the equation rate can be expressed as:

$$\ln r_0 = a \ln [A]_0 + k$$

**Equation 2.** Pseudo-first order equation rate.

Where $[A]$ is the initial concentration of reagent. Therefore, we could estimate the reaction order for both reagents by the estimation of the reaction rate for each trial and their representation. For both reagents, PhB(OH)$_2$ and Na$_2$S$_2$O$_5$, we obtained a value very close to 1.

![Figure 29. Plot time-yield, and correlation between initial rates and the corresponding reagent concentration.](image-url)
On the other hand, a graphical method was employed for the determination of the reaction order of the ligand and catalyst founding a zero-order dependence for the ligand, meanwhile for PdCl₂ the order was 0.25 (Figure 30). This fact suggested that the ligand plays a key role in the formation of the Pd(0) nano-catalyst, but not in the rate-determining step of the reaction, with the mechanism seeming not to be a single step mechanism.

Furthermore, since Pd NPs are formed during the reaction, we prepared different shaped palladium nanocrystals (Pd NCs) in order to evaluate their activity and compare it with our catalytic system (Figure 31).

---

Chapter III. C-S Cross-coupling reactions

The highest activity was achieved with the nanoparticles obtained from PdCl₂ and cationic phosphine ligand 20a, followed by the octahedral, cubic and finally decahedral ones. Decahedral particles are reported to be very stable, with almost a spherical structure, which may explain its lower activity. On the other hand, the activity of the cubic and octahedral particles was very similar, being the octahedral slightly more active, probably due to the exposed surface facets {111} in front of the ones on the cubic nanoparticles {100}.

After the reaction, NCs were recovered and analysed, with average sizes kept in the same range (Table 23).

Table 23. Pd NCs size distribution.

<table>
<thead>
<tr>
<th>Shape</th>
<th>Size before reaction (nm)</th>
<th>Size after reaction (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cubic</td>
<td>24.2 ± 3.7</td>
<td>30.8 ± 7.9</td>
</tr>
<tr>
<td>Octahedral</td>
<td>27.8 ± 8.6</td>
<td>26.8 ± 7.8</td>
</tr>
<tr>
<td>Decahedral</td>
<td>13.3 ± 4.2</td>
<td>12.5 ± 2.9</td>
</tr>
<tr>
<td>PdCl₂ + 20a</td>
<td>-</td>
<td>0.8 ± 0.3</td>
</tr>
</tbody>
</table>

Regarding the shape, the well-defined facets were slightly lost, due to leaching processes (Figure 32). The crude TEM of our standard catalytic system (PdCl₂ and ligand 20a), showed Pd clusters of 0.8 nm of average size. Since the radius of Palladium is $R_{\text{atom}} = 0.169$ nm, the number of Pd atoms per cluster (N)
C-S Cross-coupling reactions

can be estimated using the following equation:\textsuperscript{275}

\[
N = \left( \frac{R_{\text{cluster}}}{R_{\text{atom}}} \right)^3 = \left[ \frac{(0.408 \times 10^{-9})}{0.169 \times 10^{-9}} \right]^3 \approx 14
\]

Equation 3. Atom per cluster calculation.

Figure 32. TEM images corresponding to palladium nanoparticles a) cubes b) cubes after reaction c) octahedron d) octahedron after reaction e) decahedron f) decahedron after reaction g) PdCl\textsubscript{2} + 20a after reaction.

In such small particles, the electronic structure seems to play a key role, with high surface area/volume ratio explaining its higher activity. This can be correlated with the reaction order obtained for PdCl₂, which was found to be 0.25, suggesting maybe that only ¼ of the Pd atoms are catalytically active, which means that in a 14-atom palladium cluster, only around 3 atoms have catalytic activity.²⁷²

3. COPPER-CATALYSED SYNTHESIS OF SULFONAMIDES AND RELATED DERIVATIVES

The above described synthesis of sulfones proved its versatility, but only one sulfonamide was synthesised (28y). Reactions of aryl sulfinates with different nitrogen-containing compounds to afford sulfonamides have been widely described in literature, but most of the rely on the use of stoichiometric chlorinating reagents to form sulfonyl chlorides and its subsequent reaction with nucleophilic anilines.

Nevertheless, since a green approach to the sulfonamide synthesis, was being pursued, it was planned to avoid the sulfinate functionalisation. Thus, an electrophilic nitrogen source was needed to react with sulfinates. Nitrocompounds were reported to react with sulfinates, affording the corresponding sulfonamides after reduction.²⁷⁶

On the other hand, and trying to increase the sustainability of the process, aryloboronic acids were planned to be replaced by greener aryl sources. It was decided to use triarylboron compounds as starting materials, as these reagents are non-toxic,²⁷⁷ and unlike other organometallic molecules (such as boron or tin derivatives) they can react with 3 equivalents of an electrophile (in this case SO₂), increasing the atom economy of the process. As the Bi-C bond energy is quite low, the reactivity displayed by these reagents could offer very interesting possibilities; although it has not been fully exploited.²⁷⁸ The reaction of triarylboron compounds with Na₂S₂O₅ as SO₂ source would provide aryl sulfinates that could react in situ with nitrocompounds, affording sulfonamides after reduction. It is worth to mention that a palladium-catalysed sulfone synthesis was reported by a

denitrating coupling of aryl sulfonates and nitrocompounds,279 although in this case the expected product was the corresponding sulfonamide.

During the sulfinate synthesis, Na$_2$SO$_3$ is generated as by-product, which is able to react with water generating NaHSO$_3$. This latter compound is considered a potential reductant, as it has been broadly established in organic synthesis.280,282 Therefore, the Na$_2$SO$_3$ released during the reaction course, can be further used, reducing the by-product formation, which is one of the criteria of the Green Chemistry principles.5

The study started with a survey to find the best reaction conditions, employing triphenylbismuthane (31a), Na$_2$S$_2$O$_3$ (25), and nitrobenzene (32a) as model reaction to yield N-phenylbenzenesulfonamide (33a) under copper catalysis (Table 24). Starting with ChCl:acetamide (1:2) as solvent, different copper sources and ligands were analysed (entries 2, 4-13), finding that just 1 mol% of CuCl yielded the desired product in 43% yield at 80 °C without the need of using any external ligand or base in the reaction. Different DESs were tested next, but none of them could increase the reaction yield (entries 14-25).

Despite the fact that the reaction did not proceed in ChCl:urea (1:2, entry 21), yields around 50% were obtained both, in ChCl:acetamide (1:2, entry 7) and AcChCl:urea (1:2, entry 23). Consequently, it was decided to introduce a new mixture, AcChCl:acetamide (1:2), which, to the best of our knowledge, has been not described previously in the literature. The reaction yield was increased to 66% (entry 26). Increasing the amount of nitrobenzene to 1.5 equivalents afforded a better yield (entry 27), while when using 2 equivalents 99% yield of product 33a was obtained (entry 28). Lower yields were obtained with other metal catalysts (entries 29-30). Decreasing the excess of sodium metabisulfite decreased the yield likewise (entries 31-32). Finally, lowering the reaction temperature to 60 °C had a detrimental impact in the reaction outcome (entry 33), while the yield was maintained at higher temperatures (entry 34).

Table 24. Optimisation of reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>DES (molar ratio)</th>
<th>[M] (1 mol%)</th>
<th>Ligand (mol%)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield of 33a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuCl₂</td>
<td>-</td>
<td>50</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>32a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuCl₂</td>
<td>-</td>
<td>80</td>
<td>1</td>
<td>35⁶</td>
</tr>
<tr>
<td>33a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuCl₂</td>
<td>L1 (1)</td>
<td>80</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>34a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuCl₂</td>
<td>L2 (2)</td>
<td>80</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>35a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuCl₂</td>
<td>20a (2)</td>
<td>80</td>
<td>24</td>
<td>61</td>
</tr>
<tr>
<td>36a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuCl₂</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>37a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuCl₂</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>38a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuO</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>39a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuO</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>40a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuBr</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>41a</td>
<td>ChCl:acetamide (1:2)</td>
<td>Cu</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>42a</td>
<td>ChCl:acetamide (1:2)</td>
<td>CuCl</td>
<td>20a (2)</td>
<td>80</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>43a</td>
<td>ChCl:glycerol (1.2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>44a</td>
<td>Ph₃PMeBr:glycerol (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>45a</td>
<td>ChCl:HOCH₂ (1.2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>46a</td>
<td>ChCl:glucose (2:1)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>47a</td>
<td>ChCl:formic Ac (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>48a</td>
<td>ChCl:sorbitol (1:1)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>49a</td>
<td>DecA:menthol (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>50a</td>
<td>ChCl:urea (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>51a</td>
<td>Urea:acetamide (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>52a</td>
<td>AcChCl:urea (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>52</td>
</tr>
<tr>
<td>53a</td>
<td>Betaine:PhCO₂H (2.3)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>54a</td>
<td>Betaine:acetamide (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>55a</td>
<td>AcChCl:urea (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>66</td>
</tr>
<tr>
<td>56a</td>
<td>AcChCl:acetamide (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>72³⁴</td>
</tr>
<tr>
<td>57a</td>
<td>AcChCl:acetamide (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>99⁶</td>
</tr>
<tr>
<td>58a</td>
<td>AcChCl:acetamide (1:2)</td>
<td>FeCl₃</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>43⁶</td>
</tr>
<tr>
<td>59a</td>
<td>AcChCl:acetamide (1:2)</td>
<td>NiCl₂</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>6⁶</td>
</tr>
<tr>
<td>60a</td>
<td>AcChCl:acetamide (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>22²⁺</td>
</tr>
<tr>
<td>61a</td>
<td>AcChCl:acetamide (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>80</td>
<td>24</td>
<td>40²⁺</td>
</tr>
<tr>
<td>62a</td>
<td>AcChCl:acetamide (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>60</td>
<td>24</td>
<td>49⁹</td>
</tr>
<tr>
<td>63a</td>
<td>AcChCl:acetamide (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>100</td>
<td>24</td>
<td>99⁹</td>
</tr>
<tr>
<td>64a</td>
<td>AcChCl:acetamide (1:2)</td>
<td>CuCl</td>
<td>-</td>
<td>100</td>
<td>24</td>
<td>99⁹</td>
</tr>
</tbody>
</table>

*Conditions: Ph₃Bi (0.2 mmol), Na₂S₂O₅ (1.32 mmol), PhNO₂ (0.6 mmol) in 1.5 mL of DES. *Yields determined by GC using tridecane as standard. *Reaction carried out under MW irradiation. *Reaction carried out using 1.5 eq. of PhNO₂. *Reaction carried out using 2.0 eq. of PhNO₂. *Reaction carried out using 1.0 eq. of Na₂S₂O₅. *Reaction carried out using 1.6 eq. of Na₂S₂O₅.
The possibility of designing the solvent by using DESs was proven by the introduction of the eutectic mixture AcChCl:acetamide (1:2). In view of results, both components of the DES mixture have an important effect in the reaction course (Figure 34). Additionally, it is worth to mention that the reaction failed when VOC solvents or water were employed. Thus, the choice of an appropriate DES was proven to be crucial for the reaction to proceed with good yields.

As for the previous synthesis of sulfones, other SO₂ surrogates were tested (Table 25). In this case, both, sodium and potassium metabisulfites offered excellent yields (entries 1-2). It was decided to continue the studies with the cheaper Na₂S₂O₅, which gave a slightly higher yield. DABSO also afforded the desired product in a moderate yield (entry 3), while the reaction did not proceed with other sulfur sources (entries 4-6).
Table 25. Study of SO$_2$ surrogates.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>SO$_2$ source</th>
<th>Yield of 33a (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na$_2$S$_2$O$_5$</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$S$_2$O$_5$</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>DABSO</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>Na$_2$S$_2$O$_4$</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>S$_8$</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>NaO$_2$SCH$_2$OH</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Reaction carried out using compounds 31a (0.2 mmol), sulphur source (1.32 mmol) and 32a (1.2 mmol) in 1.5 mL of DES. $^b$ Yield determined by GC using tridecane as internal standard.

Other aryl sources were also tested as possible replacements for triaryl bismuthines (Table 26). Despite the good results obtained in the sulfone synthesis with phenylboronic acid (under Pd catalysis), this multicomponent reaction proceeds with a very low yield when Ph$_3$Bi was replaced by PhB(OH)$_2$ (entry 2). Due to the excellent results presented recently regarding the use of organometallic reagents in DESs, different organometallic reagents were also tested, but none of them could afford the expected sulfonamide (entries 3-5).

Table 26. Study of aryl sources.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl source</th>
<th>Yield of 33a (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph$_3$Bi</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>PhB(OH)$_2$</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>PhMgBr</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ph$_3$Al</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>PhZnBr</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Reaction carried out using compounds aryl sources (1 eq.), Na$_2$S$_2$O$_5$ (2.2 eq.) and 32a (2 eq.) in DES (0.4 M). $^b$ Yield determined by GC using tridecane as internal standard.
With these optimised conditions in hand, the scope of nitrocompounds was evaluated (Chart 2). No effect on the electronic properties of the substituents of the nitroarene was observed. Therefore, good to excellent yields were obtained for all kinds of nitroarenes bearing neutral, electron-donating or electron-withdrawing groups. Although triaryltribiumines have been described to undergo cross-coupling reactions with aryl halides, the multicomponent reaction proven to be chemoselective to the sulfonamide product, as no Suzuki-type by-product were observed. The reaction was also compatible with nitroalkanes, although the product was obtained in lower yield (33m). When 1,3-dinitrobenzene was employed as starting material, two reactions took place in the same substrate affording product (33i).

Then, the scope of Ar3Bi was evaluated (Table 27). Reaction worked with good to excellent yields for triaryltribium reagents bearing neutral or electron donating groups (entries 1-6), although lower yields were obtained with electron-withdrawing groups (entries 7-10). Besides, steric hindrance seemed to have an important detrimental effect in the reaction outcome (entry 9).

Table 27. Scope of triarylbismuthines.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Product</th>
<th>Yield of 33(%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>33a</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC(_6)H(_4)</td>
<td>33n</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>1-naphtyl</td>
<td>33o</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>4-MeO(_6)H(_4)</td>
<td>33p</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>3,4,5-C(_6)H(_3)</td>
<td>33q</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>4-Me(_6)N(_6)H(_4)</td>
<td>33r</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>4-F(_6)H(_4)</td>
<td>33s</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>4-Br(_6)H(_4)</td>
<td>33t</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td>2-CF(_3)C(_6)H(_4)</td>
<td>33u</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>3-CF(_3)C(_6)H(_4)</td>
<td>33w</td>
<td>48</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: Ar\(_3\)Bi (0.2 mmol), NaN\(_2\)S\(_2\)O\(_5\) (1.32 mmol), PhNO\(_2\) (0.6 mmol), CuCl (1 mol%) in 1.5 mL of DES. \(^b\) Isolated yields.

More complex structures and functional groups were also tolerated. In fact, the synthesis of a biologically active anti-leprosy compound in a just one step was accomplished with good yield (33x, Figure 35).\(^{285}\)

![Figure 35. Multicomponent synthesis of biologically active compound.](image)

The synthesis of different sulfur derivatives were also found to be compatible with this process. The reaction between triarylbismuthines, NaN\(_2\)S\(_2\)O\(_5\) and electrophiles to yield the corresponding sulfones was also evaluated (Table 28).

Surprisingly, the reaction proceeded smoothly without the need of copper salt, suggesting that the role of copper is probably related to the reduction step.

Table 28. Scope of sulfones.<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>Ph</td>
<td>28m 90</td>
</tr>
<tr>
<td>2</td>
<td>Cl-O</td>
<td>Ph</td>
<td>28p 75</td>
</tr>
<tr>
<td>3</td>
<td>S-N-Cl</td>
<td>N-S-P</td>
<td>28r 85</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>S-N</td>
<td>28a' 83</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: Ph₃Bi (0.2 mmol), Na₂S₂O₅ (1.32 mmol), electrophile (1.2 mmol) in 1.5 mL of DES. <sup>b</sup> Isolated yield.

As before, adding molecular iodine to the protic medium containing aryl sulfinites yielded the corresponding thiol or disulfide.<sup>269</sup> Those molecules could react with different nucleophiles (Table 29, entries 1-2) or radical scavengers (entries 3-4) affording the corresponding sulfides in a one-pot manner.

One of the advantages of using DESs as reaction media is the possibility to recover and recycle the solvent. Nevertheless, this usually involves the use of volatile organic compounds (VOC) as extraction solvents.<sup>91</sup> As a result of this, the issues regarding the use of harmful and toxic solvents cannot be avoided. In this case, a gram-scale reaction was performed. Once it was completed, a solution of NaHCO₃ (sat. aqueous) was added, instead of an extraction being performed. In this way, product 33a was obtained as a precipitate, which was filtered and rinsed...
with water. Thus, the use of VOC solvents was completely avoided during the whole process, obtaining 1.19 g of compound 33a (85% yield). (Scheme 29, Figure 36).

Table 29. Scope of aryl sulfides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nu-H</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>29c</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>29f</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>30c</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>30e</td>
<td>73</td>
</tr>
</tbody>
</table>

Table 29. Scope of aryl sulfides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nu-H</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>29c</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>29f</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>30c</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>30e</td>
<td>73</td>
</tr>
</tbody>
</table>

*a Reaction conditions: Ph$_3$Bi (0.2 mmol), Na$_2$S$_2$O$_5$ (1.32 mmol) in 1.5 mL of DES were stirred at 80 °C for 5 h, then I$_2$ (1.2 mmol) was added and the mixture was stirred for 20 min. Finally, Nu-H was added (1.2 mmol) and the mixture was stirred for another 8 h at 80 °C. b Isolated yield.

Scheme 29. Gram-scale sulfonamide synthesis.
To obtain some insights about the possible reaction mechanism, a series of control experiments were carried out. Scheme 30-a shows the optimised reaction conditions. The reaction is not catalysed by copper nanoparticles, since adding in 2.5 eq. of Hg did not affect the reaction outcome (Scheme 30-b). Running the reaction under argon atmosphere slightly decreased the product yield, due to the possible role of moisture interacting with the DES (very hygroscopic) and acting as a source of protons in the reduction step and NaHSO₃ formation from Na₂S₂O₅ (Scheme 30-c). Moreover, oxygen can be involved in the copper oxidation cycle or in the possible final oxidation of bismuth by-product to form Bi₂O₃.

Since Ar₃Bi and SO₂ produce sodium phenylsulfinate, several reactions were tested with this reagent. Running the reaction with sodium bencesulfinate without sodium metabisulfite did not yield any product, confirming the dual role of sodium metabisulfite as SO₂ source and reductant (Scheme 31-a). Surprisingly, reaction works without adding the copper catalyst, although a very low yield was obtained (Scheme 31-b).
Chapter III. C-S Cross-coupling reactions

Scheme 30. Mechanistic tests.

The reaction is inhibited by the use of a radical scavenger (TEMPO), involving a possible radical mechanism (Scheme 32-a). As depicted in Table 28, synthesis of sulfones took place smoothly without the need of a copper catalyst. This result suggested that CuCl is only involved in the reduction step. Nevertheless, an attempt to carry out the sulfone synthesis in the presence of TEMPO also inhibited the product formation (Scheme 32-b). On the contrary, the coupling of phenylsulfinate and nitrobenzene using sodium bisulfite as reductant and copper chloride took place both, in the presence and absence of TEMPO (2,2,6,6-
tetramethylpiperidine 1-oxyl), although with lower yield in the latter case (Scheme 32-c). This fact confirmed that radical species were mainly present in the sulfinate formation from Na$_2$S$_2$O$_5$ and Ph$_3$Bi (first reaction step), but not in the reduction step.

$$\text{PhSO}_2\text{Na} + \text{PhNO}_2 + \text{Na}_2\text{S}_2\text{O}_5 \rightarrow \text{AcChCl:acetamide} \rightarrow \text{PhNH}_2\text{SO}_2\text{Ph}$$

a) Ph$_3$Bi + Na$_2$S$_2$O$_5$ + Cl$^-$ + S

b) Ph$_3$Bi + Na$_2$S$_2$O$_5$ + Cl$^-$ + S

c) Ph$_3$Bi + Na$_2$S$_2$O$_5$ + Cl$^-$ + S

Scheme 32. Radical trapping experiments.

In view of this results, a possible mechanism was proposed (Scheme 33). A first step may involve the disaggregation of Na$_2$S$_2$O$_5$ through an homolytic cleavage of the S-S bond. This step includes the formation of radical intermediates, which is in accordance with the radical-trapping experiments. These radical intermediates suffer a disproportionation to afford electrophilic SO$_2$ and the by-product Na$_2$SO$_3$. Next, SO$_2$ undergoes insertion between C-Bi bond.

Given that a large excess of chloride anions is present in the medium, BiCl$_3$ may be released, alongside the corresponding sulfinate. Finally, the sulfinate reacts with the nitroarene, being reduced by NaHSO$_2$ (generated from Na$_2$SO$_3$ and moisture) to yield the final sulfonamide in a process catalysed by copper.

Since the DESs employed in this reaction, AcChCl:acetamide (1:2), had not been previously described, a complete physicochemical characterisation was performed. Firstly, a number of samples with different proportion of AcChCl and acetamide were prepared by mixing the two components and grinding them together until an intimate mixture was obtained. Those samples were subjected to DSC (Differential Scanning Calorimetry) to confirm that a eutectic phase was being formed. With the melting point of each of those samples, a phase diagram could be plotted, showing a eutectic point for a molar ratio 1:2 (AcChCl:acetamide, Figure 37).

Despite of having a melting point around 60 °C, the mixture did not immediately return to solid state when cooled to room temperature.\(^{288}\) This eutectic mixture is very viscous at room temperature, making the nucleation and crystal growth process more difficult to happen.\(^{289}\) For this reason, the mixture was subjected to a cyclic DSC. In the first cycle, (Figure 38-blue), the melting point of the DES could be observed. Then, the sample was cooled to -90 °C and heated up again to 160 °C (Figure 38-red). In this second cycle, no melting point was observed. Instead, a glass transition temperature \(T_g\) could be determined, confirming the glass nature of the mixture (Figure 38).

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Figure 37. Phase diagram of the eutectic mixture AcChCl:acetamide.

Figure 38. DSC of the mixture AcChCl:acetamide (1:2) with 2 consecutive cycles of heating/cooling.

The DES density was also measured at 28 °C by means of a 50 mL pycnometer (Equation 4).

\[
\rho_{\text{DES}} = \frac{m_{\text{DES}}}{m_{\text{water}}} \rho_{\text{water}} = 1.09 \text{ g/mL (28 °C)}
\]

Equation 4. DES density calculation.
Then, the pH value was measured. It was a very important parameter to be measured for a new solvent, since it can be crucial for its corrosion, catalytic or dissolution properties. The pH can therefore limit its industrial applicability. In non-aqueous solutions, pH depends on temperature and on the chemical potential of hydrogen. This chemical potential depends on the presence of ions and hydrogen-bonding with other species.\textsuperscript{290} It was observed that the pH value decreased linearly with acetamide molar fraction (Figure 39); meaning that the more hydrogen bonds are available, the lower is the chemical potential of hydrogen and so a lower pH value is obtained.

\[ \text{pH} = -2.5371\chi_{\text{acetamide}} + 7.4643 \]
\[ R^2 = 0.99877 \]

\textbf{Figure 39.} pH values depending on the acetamide molar fraction.

Once the physicochemical properties were evaluated, an assessment of this new DES toxicity and biodegradability was performed in order to determine if it could be considered a sustainable solvent.\textsuperscript{291} As it was mentioned in the Thesis Introduction, DESs were proposed as a green alternative to ILs in 2001. Since then, a large number of new mixtures have been introduced, but in most cases, the low toxicity of the mixture has just been assumed without proper toxicity evaluations. In order to consider DESs as green solvents, their real toxicity and the potential biodegradability of DESs must be established.\textsuperscript{292}


\textsuperscript{291} Microbiological experiments were kindly performed by Javier Torregrosa-Crespo and Prof. Dr. Rosa M. Martínez-Espinosa at the Departamento de Agroquímica y Bioquímica. División de Bioquímica y Biología Molecular at the University of Alicante.

Only a few studies regarding this matter have been performed; mainly using prokaryotic microbes and in some cases eukaryotic organisms. However, there is still controversy about their potential toxicity; several reports support the theory that DESs are non-toxic, eco-friendly, biodegradable and benign solvents, whilst other similar studies demonstrated exactly the opposite.

In most of the reported literature, toxicity is checked by using traditional standard protocols, such as solid culture media in plates with disks in which the DES is embedded. This approach has an important limitation, the high density and viscosity of DESs. These two properties restrict the DESs diffusion from the disk to their surroundings, thus giving results that may not reflect real interaction between the DESs and cells. Analysis of toxicity in liquid media minimize this negative impact, especially in those cases in which the DESs are particularly dense or show high viscosity.

A few studies about the toxicity of the DES using bacteria as model organisms suggest that pH decreases significantly in culture media supplemented with DES; however, pH has not been continuously monitored in this kind of studies. For this reason, pH was monitored in buffered and unbuffered culture media supplemented with DES and its separated components (AcChCl or acetamide). It was found that traditional sterilisation protocols (autoclaving) caused the AcChCl hydrolysis, releasing acetic acid to the culture medium. DES hydrolysis and the consequent pH depletion also take place during the incubation just due to the incubation of culture media. However, E. coli growth and its metabolic activity is also involved in pH depletion. Thus, samples were sterilised by UV or filtration, and then added to the sterilised media.

To analyse E. coli tolerance and potential DES toxicity, cells were grown in buffered Luria Bertani broth (LB) media supplemented with 600 mM DES and

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inoculated with *E. coli* cells grown in standard media (non-preadapted cells). This DES concentration was chosen based on the concentrations previously reported in the literature. Cells were not able to grow under these conditions and the preliminary conclusion pointed was that 600 mM DES is toxic for this bacterium. It is important to highlight that microorganisms can induce specific reactions or pathways when they are exposed to compounds that are unusual in their natural environments or microcosmos at the laboratory.

**Figure 40.** *E. coli* growth curves. Cells were grown in LB media supplemented with different concentrations of DES. Legend of colours: Orange = control (LB media without DES); Yellow = LB + 150 mM DES inoculated with pre-adapted cells; Grey = LB + 150 mM DES inoculated with non-pre-adapted cells; light blue = LB + 300 mM DES and preadapted cells; green = LB + 450 mM DES and preadapted cells; dark blue = LB + 600 mM DES and preadapted cells; dark red = LB + 750 mM DES and preadapted cells. In each curve, dots correspond to the average of three values obtained from three biological replicates and standard deviation of these values was between ± 0.01 and ± 0.16.

Considering this, several physiological studies were done to analyse the growth of pre-adapted *E. coli* cells. Thus, cells growth in the presence of 150 mM DES were used as inoculum for cultures containing 300 mM, etc. Figure 40 displays the growth curves of *E. coli* pre-adapted cells in LB containing different concentrations of DES.

---

In order to identify the maximum concentration of DES tolerated/assimilated by *E. coli*, the rest of the cultures with higher DES concentrations were always inoculated with cells pre-adapted to the concentration of DES immediately prior to the exposure. When the limit of 300 mM was exceeded, cellular adaptation started. At concentrations of 450 and 600 mM, the growth curves showed diauxic form and higher Lag phase. Diauxic curves have been previously reported from *E. coli* and many other bacteria (diphasic growth represented by two growth curves intervened by a short lag phase). These curves could be the result of: i) cellular growth usually using two different substrates at different time (one of the substrates could be used preferentially and when it is exhausted, the second substrate is metabolised) or ii) cellular growth affected by physico-chemical parameters that can be changing during the incubation period. The maximum OD shown by the cultures with 450 mM DES was slightly higher (up to 4.5) than those reported from cultures with lower DES concentration. This profile could suggest that pre-adapted *E. coli* cells were able to grow nicely in the presence of 450 mM DES and may metabolise it or their derivatives when DES is hydrolysed.

In the case of 600 mM, the percentage of cellular inhibition exceeded 30%, the Lag phase of growth increased significantly, and the final OD is half of the OD density reached by the other cultures. These results suggested that concentrations around 600 mM are somehow tolerated but affect negatively, not only cellular growth, but also metabolic activities.

The highest concentration tested in our experiments was 750 mM and at this concentration cell growth was no detected. Consequently, DES concentrations above this value are toxic for *E. coli*. Regarding to the potential toxicity of the individual components of the DES here described (AcChCl and acetamide), *E. coli* cells were grown in the presence of 600 mM DES (higher DES concentration allowing cellular growth) and in the presence of the two individual components at the final concentrations (600 mM AcChCl and 1.2 M acetamide, Figure 41).
Figure 41. *E. coli* growth curves. Cells were grown in buffered LB media supplemented with 600 mM DES, 600 mM AcChCl or 1.2 M MeCONH$_2$. DES was sterilised by UV and then added to sterilised media. AcChCl and MeCONH$_2$: were sterilised by filtration and then added to sterilised media. Legend of colours: Blue = control (LB media without DES); Purple = LB + 1.2M MeCONH$_2$; Green = LB + 600 mM AcChCl; Red = LB + 600 mM DES. In all cases, cultures were inoculated with pre-adapted cells. In each curve, dots correspond to the average of three values obtained from three biological replicates and standard deviation of these values was between ± 0.01 and ± 0.2.

The value of the Lag phase is closed in the three cultures (DES, AcChCl and MeCONH$_2$; between 25 and 28 hours) but it is higher than the Lag phase observed in control cultures. Final maximum OD in Acetamide-culture is higher than in control cultures. However, final OD in DES and AcChCl cultures (around 2.5) is lower than in control cultures. DES is more toxic than its constituent elements separately, based on the higher inhibition percentage and the lower duplication rate. pH depletion was observed in both AcChCl-cultures and acetamide-cultures: 6.5 vs 7.4 at the end of the stationary phase of growth, respectively. This depletion was higher in the presence of AcChCl, which correlates to the lower cellular growth detected in these cultures compared to MeCONH$_2$-cultures. Comparing cellular rates from DES, AcChCl and MeCONH$_2$ cultures, it can be concluded that the individual components are less toxic than DES as it has been previously reported for most of the DES described up to now.

In view of these results and an analysis of the studies reported up to now, it can be concluded that a large proportion of DESs are considered as “biodegradable” because most the components forming DESs are natural products. However, in
most of the works reported, accurate experiments to test biodegradability have not been conducted. In addition, crossed reactions between the DESs and the salts/nutrients of the culture media could often take place, but they have not been considered so far in the toxicity studies. For instance, hydrolysisation of the DES could occur in liquid culture media, as it is the case of the here described DES, thus promoting crossing reactions between the products of the DES hydrolysisation by-products and the salts, amino acids, carbohydrates, etc; within the culture media.

None of the studies reported up to now have considered cellular preadaptation to the DESs to be tested. As a consequence of this, there is a loss of information in terms of real capability of the cells to tolerate or even assimilate DESs. This study has demonstrated that single assays in the presence of 600 mM of the here described DES is toxic for the cells. However, when the cells were pre-adapted to this concentration growth could be monitored.

AcChCl:acetamide (1:2) here described is not toxic for E. coli, and maybe for other similar species, at concentrations between 0 and 300 mM. The DES used in this range of concentrations could be labelled as “environmentally friendly”. At concentrations between 300 mM and 450 mM, cells can tolerate the DES, even though cellular growth and metabolic activities are slightly affected by it. Above 600 mM, the DES is toxic causing complete inhibition of growth. This toxicity is not only due to the chemical composition of DES, but also due to the high acidification of the media caused by the DES hydrolysis. Thus, concentrations above 600 mM could allow its use as bactericide or even to explore potential inhibitory effect on tumoral cells.
EXPERIMENTAL PART
1. GENERAL

1.1. SOLVENTS AND SUBSTRATES

All reagents listed in the present research work, whose preparation has not been described, were purchased with the best commercial grade and were used without purification (Acros, Aldrich, Alfa Aesar, Fluka, Fluorochem, Merck, etc). The solvents used in the reactions that required anhydrous conditions were dried under standard conditions before their use. Other solvents employed (hexane, ethyl acetate, diethyl ether, methanol, ethanol, etc.) were the best grade commercially available.

1.2. INSTRUMENTATION

The X-ray fluorescence analyses (XRF) were carried out on the units of Technical Services Research at the University of Alicante on a PHILIPS MAGIX PRO (PW2400) X-ray spectrometer equipped with a rhodium X-ray tube and a beryllium window.

The gas adsorption analysis was performed on the units of Technical Services Research at the University of Alicante with an automatic volumetric equipment of physical adsorption gas and degassing AUTOSORB-6 and AUTOSORB DEGASSER, both from Quantachrome. N₂ was used as gas.

The X-ray photoelectron spectroscopy (XPS) analyses were executed on the units of the Technical Services of Investigation at the University of Alicante in a VG-Micotech Multilab 3000 equipped with a hemispheric electron analyser with 9 channeltrons (pass energy between 2 and 200 eV) and an X-ray tube with Mg and Al anodes.

The transmission electron microscopy (TEM) analyses were carried out on the units of the Technical Services of Investigation at the University of Alicante on a JEOL JEM-2010 microscope, equipped with a X-ray detector OXFORD INCA Energy TEM 100 or on a JEOL JEM-1400 Plus equipped with an ORIUS camera model GATAN.
DSC analyses were performed on a METTLER TOLEDO equipment, model TGA/SDTA851e/LF/1600, and EM analysis on a PFEIFFER VACUUM, model THERMOSTAR GSD301T.

Melting points were obtained with a Reichert Thermovar apparatus. Crystals were obtained from mixtures of ethyl acetate/hexane, unless otherwise specified.

The purity of volatile compounds and the chromatographic analysis (GC) was performed with a Younglin 6100GC equipped with a flame ionization detector (FID) and a capillary column HP-5 (5% crosslinking PH ME siloxane) 30 m length, 0.25 mm internal diameter and 0.25 μm thick sheet, using nitrogen (2 mL/min) as carrier gas, 10 psi pressure in the injector block temperature 270 °C injection volume 0.75 μL sample injected and 5 mm/min speed recording. The selected program was 60 °C initial temperature for 3 minutes 15 °C/min heating rate to 270 °C, where the temperature is held for ten minutes. The retention times (t_r) are given in minutes under these conditions.

Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV light.

FT-IR spectra were obtained on a JASCO 4100LE (Pike Miracle ATR) spectrophotometer. The samples were analyzed directly. UV-Vis spectra were recorded in a SHIMADZU UV-1603 apparatus.

Proton nuclear magnetic resonance spectra (1H NMR), carbon (13C NMR) and phosphorus (31P NMR) were performed in the unit of Nuclear Magnetic Resonance of the Technical Services Research at the University of Alicante with a Bruker AC-300 or Bruker Avance-400 (300/400 MHz for 1H, 100/75 MHz for 13C, and 162/121 MHz for 31P). CDCl3, MeOD-d4 and DMSO-d6 were used as solvents (unless otherwise is indicated) and tetramethylsilane (TMS) or phosphoric acid (H3PO4) as an internal standard for 1H NMR and 31P NMR, respectively. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in Hz.

pH measurements were performed using a Mettler Toledo SevenEasy S20 pH-meter.
Reactions carried out under microwave irradiation were performed on a MW CEM Discovery 908010 apparatus.

The mass spectrometric analysis was performed using a spectrometer Agilent GC/MS-5973N, performing studies in the form of electron impact (EI) at 70 eV ionization source and helium as the mobile phase. Samples were introduced by injection through a gas chromatograph Hewlett-Packard HP-6890, equipped with a HP-5MS column 30 m length, 0.25 mm internal diameter and 0.25 µm film thickness (crosslinking 5% PH ME siloxane). Ions derived from the breaks are given as m/z with brackets relative percent intensities.

The analysis of mass spectrometry with inductively coupled plasma (ICP-MS) were performed in the units of Technical Services Research at the University of Alicante with a mass spectrometer with inductively coupled plasma THERMO ELEMENTAL, model VG PQ ExCell. The high resolution mass spectrometry analyses (HRMS) were performed in units Mass Spectrometry of the Technical Services Research at the University of Alicante with a spectrometer Finnigan MAT95-S. DIP analyses were performed using an Agilent mass spectrometer, model Network 5973 Mass Selective with direct sample introduction to the ion source through the SIS (Scientific Instrument Services) probe Direct Insertion Probe (73DIP-1)

Column chromatography was performed on glass columns, using as stationary phase silica gel Merck 60, with a particle size of 0.040 to 0.063 mm (flash silica), or 0.063 to 0.2 mm. Samples were introduced into the column prior preparation of slurry with the initial eluent, eluting with mixtures of hexane and ethyl acetate of increasing polarity, unless otherwise specified.

Samples purified by distillation were processed at a Büchi Glass Oven B-585 Kugelrohr attached to an Edwards T-Station 75 turbomolecular pump.

Centrifuge separations were performed in a Hettich Zentrifugen Universal 300 at 5500 rpm.

HPLC analysis were carried out using an Agilent 1100 Series with a Kinetex 5u C18 100A column.
2. CROSS DEHYDROGENATIVE COUPLING
2.1. SYNTHESIS OF CuO-Fe₃O₄

To a stirred solution of the metal salt CuCl₂ (0.13 g, 1 mmol) in deionized water (120 mL) was added commercially available Fe₂O₃ (17 mmol, 4 g, powder <5μm, BET area: 9.86 m²/g). After 10 min at room temperature, the mixture was slowly basified with NaOH (1M) until pH around 13. The mixture was stirred during one day at room temperature in air. After that, the catalyst was filtered and washed several times with deionized water (3 x 10 mL). The solid was dried at 100 °C during 24 h in a standard glassware oven, obtaining the expected catalyst.

2.2. SYNTHESIS OF N-ARYLATED 1,2,3,4-TETRAHYDROISOQUINOLINES

General procedure: CuI (200 mg, 1.0 mmol) and potassium phosphate (4.25 g, 20.0 mmol) were placed into a 50 mL two-neck flask. The flask was evacuated and back-filled with argon. 2-Propanol (10 mL), ethylene glycol (1.11 mL), 1,2,3,4-tetrahydroisoquinoline (2 mL, 15 mmol) and the corresponding iodoaryl (10 mmol) were added successively by using a syringe at room temperature. The reaction mixture was heated at 90 °C for 24 h and then allowed to cool to room temperature. Diethyl ether (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted with diethyl ether (2 x 20 mL). The combined organic phases were washed with brine and dried over sodium sulphate. The solvent was removed and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) as an eluent to yield products 1:

2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (1a).³⁰¹ White solid; m.p. = 69-71 °C; t₉ = 15.3; Rᵣ = 0.6 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃): δ = 7.20-7.10 (m, 4H, ArH), 7.00-6.90 (m, 4H, ArH), 4.33 (s, 2H, ArCH₂N), 3.48 (t, J = 5.9 Hz, 2H, CH₂CH₂N), 2.98 (t, J = 5.9 Hz, 2H, CH₂CH₂N); ¹³C NMR (75 MHz, CDCl₃): δ = 156.7 (d, J = 238.0 Hz), 147.4 (d, J = 1.5 Hz), 134.5, 134.3, 128.6, 126.5, 126.4, 126.0, 117.1 (d, J = 7.5 Hz, 2C), 115.5 (d, J = 22.0 Hz, 2C), 51.9, 47.8, 29.0; IR (ATR): ν = 1505,

Experimental Part

1205 cm⁻¹; MS (EI) m/z (%): 228 (M⁺+1, 14), 227 (M⁺, 95), 226 (100), 104 (72), 103 (15), 95 (12), 78 (12).

2-phenyl-1,2,3,4-tetrahydroisoquinoline (1b).³⁰⁶ Pale yellow solid; m.p. = 45-47 °C; t₁ = 15.4; Rf = 0.8 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃): δ = 7.30-7.25 (m, 2H, ArH), 7.2-7.1 (m, 4H, ArH), 6.96 (d, J = 8.0 Hz, 2H, ArH), 6.82 (t, J = 7.3 Hz, 1H, ArH), 4.39 (s, 2H, ArCH₂N), 3.53 (t, J = 5.8 Hz, 2H, CH₂CH₂N), 2.96 (t, J = 5.8 Hz, 2H, CH₂CH₂N); ¹³C NMR (75 MHz, CDCl₃): δ = 150.5, 134.8, 134.4, 130.2 (2C), 129.2, 126.5, 126.3, 126.0, 118.6, 115.1 (2C), 50.7, 46.5, 29.1; IR (ATR): ν = 3058, 3023, 1598, 1500, 1386 cm⁻¹; MS (EI) m/z (%): 210 (M⁺+1, 10), 209 (M⁺, 82), 208 (M⁺-1, 100), 104 (56), 78 (10), 77 (17).

2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1c).³⁰² Pale orange solid; m.p. 92-94 °C; t₁ = 18.6; Rf = 0.5 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃): δ = 7.20-7.10 (m, 4H, ArH), 7.00-6.95 (m, 2H, ArH), 6.90-6.80 (m, 2H, ArH), 4.29 (s, 2H, ArCH₂N), 3.77 (s, 3H, OCH₃), 3.44 (t, J = 5.8 Hz, 2H, CH₂CH₂N), 2.98 (t, J = 5.8 Hz, 2H, CH₂CH₂N); ¹³C NMR (75 MHz, CDCl₃): δ = 153.6, 145.5, 134.7 (2C), 128.8, 126.6, 126.4, 126.0, 118.1 (2C), 114.7 (2C), 55.8, 52.8, 48.6, 29.2; IR (ATR): ν = 2808, 1509, 1239, 1036 cm⁻¹; MS (EI) m/z (%): 240 (M⁺+1, 16), 239 (M⁺, 100), 238 (M⁺-1, 93), 224 (22), 135 (27), 120 (20), 104 (24).

Procedure for the preparation of 2-tosyl-1,2,3,4-tetrahydroisoquinoline (1d).³⁰³ To a mixture of 1,2,3,4-tetrahydroisoquinoline (0.27 g, 2 mmol) and pyridine (0.5 mL), p-toluenesulfonyl chloride (0.46 g, 2.4 mmol) in dry dichloromethane (5 mL) was added slowly and stirred at room temperature for 1 h. The reaction mixture was then washed with aqueous 1 N HCl (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic phases were washed with water (10 mL), brine solution (10 mL) and dried over anhydrous sodium sulphate. The filtered solution was concentrated and purified by column chromatography to yield desired product. 2-tosyl-1,2,3,4-tetrahydroisoquinoline (1d): Pale yellow solid; m.p. 132-134 °C (ethanol); t₁ = 15.6; Rf = 0.4 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃): δ = 7.35-7.30 (m, 2H, ArH), 7.40-7.30 (m, 2H,

Experimental Part

ArH), 7.14 (dd, J = 5.6, 3.5 Hz, 2H, ArH), 7.10-7.00 (m, 2H, ArH), 4.24 (s, 2H, ArCH$_2$N), 3.35 (t, J = 5.9 Hz, 2H, CH$_2$CH$_2$N), 2.93 (t, J = 5.9 Hz, 2H, CH$_2$CH$_2$N), 2.42 (s, 3H, Ar-CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 143.8, 133.3, 133.1, 131.7, 129.8 (2C), 129.0, 128.9, 127.8 (2C), 126.8, 126.4, 47.6, 43.8, 28.9, 21.6; IR (ATR): $\nu$ = 3064, 1489, 1338, 1163 cm$^{-1}$; MS (EI) $m/z$ (%): 287 (M$^+$, 5), 286 (M$^+$-1, 14), 132 (100), 131 (29), 130 (32), 105 (26), 104 (53), 103 (15), 91 (29), 77 (16).

2.3. SYNTHESIS OF 1-SUBSTITUTED-N-ARYLATED 1,2,3,4-
TETRAHYDROISOQUINOLINES

To a stirred solution of the corresponding tetrahydroisoquinoline 1 (0.5 mmol) and a catalyst (100 mg) in 1 mL of DES were added the corresponding nucleophiles 2 (1 mmol). The resulting mixture was stirred at 50 °C for 3 days until the end of the reaction. The mixture was quenched with water and extracted with EtOAc (3 $\times$ 5 mL). The organic phases were dried over MgSO$_4$, followed by evaporation under reduced pressure to remove the solvent. The product was usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding product 3:

2-(4-fluorophenyl)-1-(phenylethynyl)-1,2,3,4-
tetrahydroisoquinoline (3a): Brown oil; t = 21.0; $R_t$ = 0.6
(hexane/ethyl acetate: 4/1); $^{1}$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.40-7.35 (m, 1H, ArH), 7.30-7.20 (m, 8H, ArH), 7.10-7.05 (m, 2H, ArH), 7.05-7.00 (m, 2H, ArH), 5.54 (s, 1H, ArCHN), 3.65-3.60 (m, 2H, CH$_2$CH$_2$N), 3.20-3.10 (m, 1H, CH$/\text{CH}_2$N), 2.96 (dt, J = 16.3, 3.6 Hz, 1H, CH$_2$/CH$_2$N); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 157.4 (d, $J = 239.3$ Hz), 146.4, 135.1, 134.0, 131.7 (2C), 129.0, 128.1 (3C), 127.4, 127.2, 126.2, 122.8, 119.4 (d, $J = 7.7$ Hz, 2C), 115.5 (d, $J = 22.2$ Hz, 2C), 88.1, 85.3, 53.7, 44.0, 29.0; IR (ATR): $\nu$ = 3056, 3026, 1506, 1489 cm$^{-1}$; MS (EI) $m/z$ (%): 328 (M$^+$+1, 9), 327 (M$^+$, 50), 326 (M$^+$-1, 100), 222 (10), 207 (14), 204 (27), 203 (33), 202 (36), 102 (22); HRMS calcd. (%) for C$_{23}$H$_{18}$FN: 327.1423; found: 327.1412.
2-phenyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3b): Yellow oil; \( t_f = 21.3 \); \( R_f = 0.6 \) (hexane/ethyl acetate: 4/1); \( ^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.40-7.35 \) (m, 1H, ArH), 7.35-7.25 (m, 4H, ArH), 7.25-7.20 (m, 6H, ArH), 7.12 (dd, \( J = 8.7, 0.9 \) Hz, 2H, ArH), 6.88 (dd, \( J = 7.7, 6.8 \) Hz, 1H, ArH), 5.64 (s, 1H, ArCHN), 3.80-3.90 (m, 1H, CH\(_2\)CH\(_2\)N), 3.67 (ddd, \( J = 12.4, 10.2, 4.0 \) Hz, 1H, CH\(_2\)CH\(_2\)N), 3.14 (ddd, \( J = 16.1, 10.2, 6.1 \) Hz, 1H, CHHCH\(_2\)N), 2.97 (dt, \( J = 16.1, 4.0 \) Hz, 1H, CHHCH\(_2\)N); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 149.5, 135.4, 134.4, 131.7 \) (2C), 129.1 (2C), 128.9, 128.0 (2C), 128.0, 127.4, 127.2, 126.2, 123.0, 119.6, 116.7 (2C), 88.6, 84.7, 52.3, 43.4, 28.9; IR (ATR): \( v = 3059, 3024, 3096, 1501, 1490 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 310 (M\(^+\) + 1, 13), 309 (M\(^+\), 63), 308 (100), 204 (27), 203 (21), 202 (27), 77 (8).

2-(4-methoxyphenyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3c): Brown oil; \( t_f = 25.1 \); \( R_f = 0.5 \) (hexane/ethyl acetate: 4/1); \( ^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.35 \) (dd, \( J = 5.0, 3.9 \) Hz, 1H, ArH), 7.15-7.35 (m, 8H, ArH), 7.05-7.15 (m, 2H, ArH), 6.95-6.85 (m, 2H, ArH), 5.51 (s, 1H, ArCHN), 3.78 (s, 3H, OCH\(_3\)), 3.45-3.70 (m, 2H, CH\(_2\)CH\(_2\)N), 3.15 (ddd, \( J = 16.4, 6.2, 4.3 \) Hz, 1H, CHHCH\(_2\)N), 2.93 (dt, \( J = 16.4, 3.4 \) Hz, 1H, CHHCH\(_2\)N); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 154.3, 144.1, 135.4, 134.0, 131.7 \) (2C), 129.0, 128.0 (2C), 127.9, 127.5, 127.1, 126.1, 123.1, 120.2 (2C), 114.4 (2C), 88.4, 85.5, 54.6, 54.4, 44.2, 29.0; IR (ATR): \( v = 1509, 1242, 1055 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 339 (M\(^+\), 82), 338 (M\(^+\)-1, 100), 291 (29), 283 (35), 281 (51), 218 (28), 208 (47), 207 (95), 204 (31), 203 (33), 202 (31), 133 (28), 115 (28), 102 (40), 92 (31), 78 (33), 61 (36).

2-(4-fluorophenyl)-1-((4-methoxyphenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (3f): Pale yellow oil; \( t_f = 26.4 \); \( R_f = 0.4 \) (hexane/ethyl acetate: 4/1); \( ^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.35-7.30 \) (m, 1H, ArH), 7.25-7.20 (m, 3H, ArH), 7.15-7.20 (m, 2H, ArH), 7.10-7.05 (m, 2H, ArH), 7.05-7.0 (m, 2H, ArH), 6.75-6.70 (m, 2H, ArH), 5.52 (s, 1H, ArCHN), 3.75 (s, 3H, OCH\(_3\)), 3.65-3.55 (m, 2H, CH\(_2\)CH\(_2\)N), 3.20-3.10 (m, 1H, CHHCH\(_2\)N), 2.94 (dt, \( J = 16.2, 3.6 \) Hz, CHHCH\(_2\)N); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 159.4, 157.4 \) (d, \( J = 238.8 \) Hz),

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146.4, 135.4, 133.9, 133.1 (2C), 128.9, 127.4, 127.2, 126.2, 115.4 (d, J = 22.1 Hz, 2C), 114.9, 113.7 (2C), 86.6, 85.2, 55.2, 53.7, 44.0, 28.9; IR (ATR): ν = 3050, 1604, 1506 cm⁻¹; MS (EI) m/z (%): 357 (M⁺, 82), 356 (M⁺-1, 100), 283 (10), 208 (11), 207 (54), 191 (19), 190 (10), 189 (29), 133 (15), 73 (12), 65 (10); HRMS calcd. (%) for C₂₄H₂₆BrFN: 357.1529; found: 357.1517.

1-((4-bromophenyl)ethyl)-2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (3g): Brown oil; tᵣ = 26.5; Rᵣ = 0.6 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃): δ = 7.40-7.30 (m, 3H, ArH), 7.25-7.15 (m, 3H, ArH), 7.15-6.95 (m, 6H, ArH), 5.52 (s, 1H, ArCHN), 3.60 (dd, J = 8.6, 3.7 Hz, 2H, CH₂CH₂N), 3.13 (dt, J = 16.3, 8.6 Hz, 1H, CH/HCH₃N), 2.95 (dt, J = 16.3, 3.7 Hz, 1H, CH/HCH₃N); ¹³C NMR (75 MHz, CDCl₃): δ = 157.6 (d, J = 239.3 Hz), 146.6, 135.0, 134.1, 133.2, 131.5, 129.2, 127.5 (2C), 126.4, 122.4, 121.9, 119.5 (d, J = 7.7 Hz, 2C), 115.7 (d, J = 22.2 Hz, 2C), 49.5, 84.4, 53.9, 44.2, 29.1; IR (ATR): ν = 3058, 3025, 1657, 1507 cm⁻¹; MS (EI) m/z (%): 408 (M⁺+2, 11), 407 (M⁺+1, 54), 406 (M⁺, 100), 404 (M⁺-2, 94), 284 (26), 282 (27), 350 (15), 226 (10), 224 (25), 207 (10), 203 (23), 202 (83), 201 (16), 200 (12), 122 (15), 95 (17); HRMS calcd. (%) for (C₂₃H₁⁷BrFN - H): 404.0450; found: 404.0437.

2-(4-fluorophenyl)-1-((4-(trifluoromethyl)phenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (3h): Orange oil; tᵣ = 20.2; Rᵣ = 0.5 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃): δ = 7.50-7.45 (m, 2H, ArH), 7.40-7.30 (m, 3H, ArH), 7.25-7.20 (m, 3H, ArH), 7.15-6.95 (m, 4H, ArH), 5.56 (s, 1H, ArCHN), 3.61 (dd, J = 8.5, 3.6 Hz, 2H, CH₂CH₂N), 3.20-3.10 (m, 1H, CH/HCH₃N), 2.96 (dt, J = 16.2, 3.6 Hz, 1H, CH/HCH₂N); ¹³C NMR (75 MHz, CDCl₃): δ = 157.5 (d, J = 239.5), 146.2, 134.6, 134.0, 131.9 (2C), 129.8 (q, J = 32.6 Hz), 129.0, 127.4 (2C), 126.6, 126.3, 125.0 (q, J = 3.6 Hz, 2C), 123.8 (q, J = 271.1 Hz), 119.4 (d, J = 7.7 Hz, 2C), 115.6 (d, J = 22.1 Hz, 2C), 90.8, 84.0, 53.8, 44.0, 28.9; IR (ATR): ν = 3065, 1614, 1507 cm⁻¹; MS (EI) m/z (%): 396 (M⁺+1, 12), 395 (M⁺, 64), 394 (M⁺-1, 100), 272 (46), 203 (10), 202 (31), 95 (12); HRMS calcd. (%) for C₂₃H₁⁷F₃N: 395.1297; found: 395.1287.
**Experimental Part**

1-((3-chlorophenyl)ethynyl)-2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (3i): Yellow oil; t<sub>r</sub> = 23.6; R<sub>f</sub> = 0.7 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃): δ = 7.35-7.30 (m, 1H, ArH), 7.30-7.20 (m, 5H, ArH), 7.15-7.10 (m, 2H, ArH), 7.10-6.95 (m, 4H, ArH), 5.52 (s, 1H, ArCHN), 3.60 (dd, J = 8.3, 3.6 Hz, 2H, CH₂CH₂N), 3.20-3.05 (m, 1H, CH₂=CH-C), 1.55-1.50 (m, 4H, ArCH₂), 1.30-1.15 (m, 2H, CH₂), 0.90-0.85 (m, 3H, CH₃). IR (ATR): ν = 3061, 2924, 1591, 1507 cm⁻¹; MS (EI) m/z (%): 362 (M⁺+1, 42), 361 (M⁺, 67), 360 (M⁺-1, 100), 238 (35), 208 (13), 207 (56), 203 (21), 202 (52), 136 (13); HRMS calcd. (%) for (C₂₃H₁₇ClF₃N): 360.0955; found: 360.0966.

1-((2-bromophenyl)ethynyl)-2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (3j): Brown oil; t<sub>r</sub> = 25.4; R<sub>f</sub> = 0.4 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃): δ = 7.48 (dd, J = 7.9, 1.3 Hz, 1H, ArH), 7.40-7.35 (m, 1H, ArH), 7.29 (dd, J = 7.6, 1.8 Hz, 1H, ArH), 7.25-7.15 (m, 3H, ArH), 7.15-6.95 (m, 6H, ArH), 5.59 (s, 1H, ArCHN), 3.75-3.55 (m, 3H, CH₂CH₂N), 3.15 (m, 1H, CH₂CH₂N), 2.97 (dt, J = 16.3, 3.7 Hz, 1H, CH₂CH₂N); ¹³C NMR (75 MHz, CDCl₃): δ = 157.6 (d, J = 239.1 Hz), 146.4, 143.9, 134.2, 133.5, 132.4, 129.4, 129.1, 127.7, 127.5, 126.9, 126.4, 125.7, 125.1, 119.6 (d, J = 7.6 Hz, 2C), 115.7 (d, J = 22.1 Hz, 2C), 93.1, 84.1, 53.9, 44.3, 29.2; IR (ATR): ν = 3063, 2920, 1507, 1468 cm⁻¹; MS (EI) m/z (%): 407 (M⁺+1, 5), 406 (M⁺, 12), 405 (M⁺-1, 5), 404 (M⁺-2, 12), 281 (20), 209 (36), 207 (100), 202 (11); HRMS calcd. (%) for (C₂₃H₁₇BrF₃N): 404.0450; found: 404.0451.

1-(cyclohex-1-yl-1-yethyl)-2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (3k): Brown oil; t<sub>r</sub> = 21.0; R<sub>f</sub> = 0.6 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃): δ = 7.30-7.25 (m, 1H, ArH), 7.20-7.15 (m, 4H, ArH), 7.05-6.95 (m, 3H, ArH), 5.95-5.90 (m, 1H, C=CH), 5.42 (s, 1H, ArCHN), 3.60-3.50 (m, 2H, CH₂CH₂N), 3.15-3.05 (m, 1H, CH₂CH₂N), 2.91 (dt, J = 16.2, 3.6 Hz, 1H, CH₂CH₂N), 2.00-1.95 (m, 4H, CH₂-C₆H₃H₂-C=), 1.55-1.50 (m, 4H, CH₂-C₆H₃H₂-C=); ¹³C NMR (75 MHz, CDCl₃): δ = 157.3 (d, J = 238.7 Hz), 146.4, 135.6, 134.6, 133.8, 128.9, 127.4, 127.0, 126.1, 120.2, 119.2 (d, J = 7.6 Hz, 2C), 115.4 (d, J = 22.1 Hz, 2C),...
1-(cyclohexylethylnyl)-2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (3I): Yellow oil; \( t = 19.9 \), \( R_t = 0.3 \) (hexane/ethyl acetate: 9/1); \(^1\)H NMR (300 MHz, CDCl\(_3\)); \( \delta = 7.30-7.25 \) (m, 1H, ArH), 7.20-7.10 (m, 3H, ArH), 7.05-6.95 (m, 4H, ArH), 5.32 (s, 1H, ArCHN), 3.52 (dd, \( J = 8.5, 3.6 \) Hz, 2H, CH\(_2\)CH\(_2\)N), 3.10-3.05 (m, 1H, CH/NCH\(_2\)N), 2.89 (dt, \( J = 16.2, 3.6 \) Hz, 1H, CH/CH\(_2\)N), 2.30-2.25 (m, 1H, C\(_6\)H\(_{11}\)), 1.65-1.50 (m, 4H, C\(_6\)H\(_{11}\)), 1.45-1.40 (m, 1H, C\(_6\)H\(_{11}\)), 1.30-1.15 (m, 5H, C\(_6\)H\(_{11}\())); \(^13\)C NMR (75 MHz, CDCl\(_3\)); \( \delta = 157.3 \) (d, \( J = 238.6 \) Hz), 146.6, 136.0, 133.7, 128.8, 127.3, 126.9, 126.0, 119.3 (d, \( J = 7.6 \) Hz, 2C), 115.3 (d, \( J = 22.1 \) Hz, 2C), 89.9, 78.6, 53.2, 43.8, 32.5 (2C), 29.0, 28.8 (2C), 25.8, 24.4; IR (ATR); \( \nu = 3061, 3024, 2927, 2852, 1507 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 334 (M\(^+\) + 1, 11), 333 (M\(^+\), 74), 332 (M\(^+\) - 1, 100), 250 (30), 224 (12), 167 (16), 165 (13), 153 (11), 141 (13), 128 (17), 115 (12), 95 (13); HRMS calcd. (%) for C\(_{23}\)H\(_{24}\)FN: 331.1736; found: 331.1719.

2-(4-fluorophenyl)-1-(nona-1,8-diyn-1-yl)-1,2,3,4-tetrahydroisoquinoline (3m): Pale yellow oil; \( t = 20.5 \), \( R_t = 0.5 \) (hexane/ethyl acetate: 4/1); \(^1\)H NMR (300 MHz, CDCl\(_3\)); \( \delta = 7.30-7.25 \) (m, 1H, ArH), 7.20-7.10 (m, 3H, ArH), 7.05-6.95 (m, 4H, ArH), 5.31 (s, 1H, ArCHN), 3.60-3.50 (m, 2H, CH\(_2\)CH\(_2\)N), 3.09 (dt, \( J = 16.4, 8.3 \) Hz, 1H, CH/NCH\(_2\)N), 2.90 (dt, \( J = 16.4, 3.6 \) Hz, 1H, CH/NCH\(_2\)N), 2.15-2.00 (m, 4H, 2x C=C-C=CH\(_2\)), 1.92 (t, \( J = 2.6 \) Hz, 1H, C=C-H), 1.50-1.15 (m, 6H, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)C=C=C); \(^13\)C NMR (75 MHz, CDCl\(_3\)); \( \delta = 157.4 \) (d, \( J = 238.8 \) Hz), 146.6, 136.1, 133.9, 129.0, 127.5, 127.2, 126.3, 119.2 (d, \( J = 7.6 \) Hz, 2C), 115.5 (d, \( J = 22.1 \) Hz, 2C), 85.7, 84.6, 79.1, 68.4, 53.8, 43.9, 29.1, 28.3, 28.1, 27.9, 18.7, 18.4; IR (ATR); \( \nu = 3303, 2937, 2859, 1508 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 345 (M\(^+\), 38), 344 (M\(^+\) - 1, 100), 302 (12), 276 (27), 264 (13), 262 (31), 250 (27), 226 (12), 224 (19), 207 (18), 155 (13), 153 (13), 142 (11), 141 (23), 95 (13); HRMS calcd. (%) for C\(_{23}\)H\(_{34}\)FN: 345.1893; found: 345.1877.
2-(4-fluorophenyl)-1-(3-((tetrahydro-2H-pyran-2-yl)oxy)-prop-1-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (3n): Colourless oil; \( t_f = 22.3; R_f = 0.4 \) (hexane/ethyl acetate: 4:1); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.30-7.15 \) (m, 4H, ArH), 7.05-6.95 (m, 4H, ArH), 5.39 (s, 1H, ArCHN), 4.56 (t, \( J = 3.2 \) Hz, 1H, O-CH-O), 4.18 (d, \( J = 1.9 \) Hz, 2H, C==C-CH\(_2\)O), 3.80-3.65 (m, 1H, CH\(_2\)CH\(_2\)O), 3.60-3.50 (m, 2H, CH\(_2\)CH\(_2\)N), 3.45-3.35 (m, 1H, CH\(_2\)CH\(_2\)O), 3.10 (ddd, \( J = 16.3, 9.7, 7.0 \) Hz, 1H, CHHCH\(_3\)N), 2.90 (dt, \( J = 16.3, 3.5 \) Hz, 1H, CHHCH\(_3\)N), 1.80-1.40 (m, 6H, CHCH\(_2\)CH\(_2\)CH\(_2\)O); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 157.5 \) (d, \( J = 239.2 \) Hz), 146.5, 135.0, 134.0, 129.1, 127.5, 127.4, 126.3, 119.3 (d, \( J = 7.7 \) Hz, 2C), 115.6 (d, \( J = 22.1 \) Hz, 2C), 96.4, 84.8, 81.2, 62.1, 54.3, 53.3, 43.9, 30.3, 29.0, 25.5, 19.2; IR (ATR): \( \nu = 2923, 2849, 1320, 1021 \text{ cm}^{-1}; \) MS (EI) \( m/z \): 365 (M\(^+\) 16), 364 (M\(^+\) - 1), 281 (16), 280 (16), 264 (56), 263 (37), 262 (100), 250 (19), 248 (29), 235 (12), 226 (22), 224 (21), 207 (27), 141 (21), 140 (12), 139 (13), 129 (14), 128 (14), 122 (15), 115 (26), 95 (18), 85 (17), 84 (46), 83 (24), 57 (12), 56 (25), 55 (60), 54 (12); HRMS calcd. (%) for C\(_{21}\)H\(_{24}\)FNO\(_2\): 365.1791; found: 365.1781.

2-(4-fluorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (3o): Yellow oil; \( t_f = 17.5; R_f = 0.3 \) (hexane/ethyl acetate: 4:1); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.30-7.05 \) (m, 4H, ArH), 6.95-6.85 (m, 4H, ArH), 5.42 (dd, \( J = 8.6, 5.9 \) Hz, 1H, ArCHN), 4.82 (dd, \( J = 12.0, 8.6 \) Hz, 1H, CHHNO\(_2\)), 4.55 (dd, \( J = 12.0, 5.9 \) Hz, 1H, CHHNO\(_2\)), 3.60-3.55 (m, 2H, CH\(_2\)CH\(_2\)N), 3.05-2.95 (m, 1H, CH/CH\(_2\)N), 2.70 (dt, \( J = 16.5, 4.2 \) Hz, 1H, CHHCH\(_3\)N); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 157.1 \) (d, \( J = 239.1 \) Hz), 145.3, 135.2, 132.5, 129.4, 128.0, 126.9, 126.7, 117.8 (d, \( J = 7.6 \) Hz, 2C), (d, \( J = 22.2 \) Hz, 2C), 115.8, 78.7, 58.6, 42.7, 25.7; IR (ATR): \( \nu = 2913, 2843, 1547, 1506 \text{ cm}^{-1}; \) MS (EI) \( m/z \): 286 (M\(^+\) 5), 227 (M\(^+\) - 59), 226 (100), 225 (29), 224 (68), 128 (10), 104 (13), 95 (12).

2-(4-fluorophenyl)-1-(1-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (3p): White solid; m.p. 137-139 °C (ethanol); \( t_f = 24.6; R_f = 0.5 \) (hexane/ethyl acetate: 4:1); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.42 \) (dt, \( J = 8.0, 0.9 \) Hz, 1H, ArH), 7.25-7.1 (m, 6H, ArH), 7.0 (ddd, \( J = 8.0, 6.8, 1.3 \) Hz, 1H, ArH), 6.95-6.85 (m, 4H, ArH), 6.43 (s, 1H, C==CHN), 6.00 (s, 1H, ArCHN), 3.61 (s, 3H, N-CH\(_3\)), 3.60-3.40 (m, 2H, CH\(_2\)CH\(_2\)N), 3.02 (ddd, \( J = 16.1, 9.8, 5.8 \) Hz, 1H, CHHCH\(_3\)N), 2.79 (d, \( J = 16.1, 4.3 \) Hz, CHHCH\(_3\)N); \(^{13}\)C NMR (75 MHz,
CDCl₃); δ = 156.7 (d, J = 237.7 Hz), 146.9, 137.6, 137.4, 135.4, 129.0 (2C), 128.3, 127.2, 126.7, 125.9, 121.8, 120.2, 119.3, 118.6 (d, J = 7.5 Hz, 2C), 117.5, 115.6 (d, J = 22.0 Hz, 2C), 109.3, 57.7, 43.4, 32.8, 26.9; IR (ATR): ν = 3047, 2957, 1505 cm⁻¹; MS (EI) m/z (%): 355 (M⁺ - 1, 1), 262 (20), 186 (13), 170 (37), 169 (14), 168 (23), 142 (10), 141 (26), 115 (12), 104 (12), 94 (66), 78 (100), 77 (43), 76 (16), 66 (16), 65 (16), 52 (13), 51 (22), 50 (17); HRMS calcd. (%) for C₂₆H₂₁FN₂: 356.1689; found: 356.1692.

**Diethyl (2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (3q)³⁰⁵**

Pale pink oil; tₙ = 17.5, R₁ = 0.3 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃); δ = 7.40-7.30 (m, 1H, ArH), 7.25-7.10 (m, 3H, ArH), 7.00-6.85 (m, 4H, ArH), 5.06 (d, J = 20.2 Hz, 1H NCHP), 4.30-3.80, 3.60-3.45 (2m, 1 and 5H, respectively, CH₂CH₂N + 2OCH₂CH₃), 3.10-2.85 (m, 2H, CH₂CH₂N), 1.24 (t, J = 7.07, 3H, OCH₂CH₃), 1.14 (td, J = 7.07, 0.28, 3H, OCH₂CH₃); ¹³C NMR (75 MHz, CDCl₃): δ = 156.5 (d, J = 237.7 Hz), 146.3 (dd, J = 6.4, 1.9 Hz), 136.4 (d, J = 5.5 Hz), 130.5, 128.9 (2C), 127.6, 126.0, 116.7 (d, J = 7.4 Hz, 2C), 115.6 (d, J = 22.1 Hz, 2C), 63.4 (d, J = 7.3 Hz), 62.4 (d, J = 7.7 Hz), 59.4 (d, J = 158.4 Hz), 44.38, 16.5 (d, J = 5.9 Hz), 26.64, 16.4 (d, J = 5.9 Hz); IR (ATR): ν = 1508, 1234, 1018 cm⁻¹; MS (EI) m/z (%): 363 (M⁺, 1), 227 (21), 226 (100), 224 (13).

**2-(2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexanone (3r)³¹⁰** Diastereomeric mixture. Yellow oil; tₙ = 19.7; R₁ = 0.4 (hexane/ethyl acetate: 4/1); ¹H NMR (300 MHz, CDCl₃); δ = 7.25-6.75 (4m, 1, 7, 7 and 1H, respectively, ArH), 5.56 (d, J = 8.5 Hz, 1H, ArCHN), 5.47 (d, J = 5.2 Hz, 1H, ArCHN syn), 3.5-3.7 (2m, 2 and 2H, respectively, CH₂CH₂N), 2.80-2.90 (m, 6H, CH₂CH₂N + CH=C=O), 2.15-2.45 (2m, 2 and 2H, respectively, CH₂-C=O), 1.25-1.9 (m, 12H, 6xCH₃); ¹³C NMR (75 MHz, CDCl₃); δ = 212.1 (anti), 211.9 (syn), 156.3 (d, J = 237.5 Hz, syn), 155.2 (d, J = 235.3 Hz, anti), 146.2 (2C, anti, syn), 140.1 (anti), 135.8 (syn), 135.0 (syn), 134.5 (anti), 128.9 (syn), 128.1 (anti), 128.0 (syn), 127.3 (anti), 126.8 (2C, anti, syn), 126.4 (anti), 125.8 (syn), 117.1 (d, J = 7.3 Hz, syn), 115.5 (d, J = 22.0 Hz, syn), 115.4 (d, J = 22.0 Hz, anti), 113.6 (d, J = 7.3 Hz, anti), 59.4 (anti), 56.5 (syn), 55.8 (syn), 54.7 (anti), 44.1 (anti), 43.5 (syn), 43.2 (anti), 41.4 (syn), 32.8 (anti), 30.5 (syn), 28.8 (anti),

1-(2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)but-3-en-2-one (3s): Yellow oil; t <sub>R</sub> = 17.5; R<sub>f</sub> = 0.4 (hexane/ethyl acetate: 4/1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.20-7.10 (m, 4H, ArH), 7.00-6.80 (m, 4H, ArH), 6.29 (dd, J = 17.6, 10.5 Hz, 1H, C=CH<sub>Ph</sub>), 6.10 (dd, J = 17.6, 1.1 Hz, 1H, C=CH=C), 5.76 (dd, J = 10.5 Hz, 1.1 Hz, 1H, CH=C=CH), 5.37 (t, J = 6.3 Hz, 1H, ArCHN). 3.65-3.45 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>N), 3.19 (dd, J = 16.1, 6.3 Hz, 1H, CHCH=CH=O), 3.04 (m, 1H, CH/CH<sub>2</sub>N), 2.94 (dd, J = 16.1, 6.3 Hz, 1H, CHCH=CH=O), 2.80 (dt, J = 16.2, 4.5 Hz, 1H, CH/CHCH<sub>2</sub>N). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 199.1, 156.5 (d, J = 237.3 Hz), 145.8, 138.2, 136.9, 128.9, 128.7, 127.1, 127.0, 126.4, 116.9 (d, J = 7.4 Hz, 2C), 115.8 (d, J = 22.1 Hz, 2C), 55.9, 46.1, 42.6, 27.1; IR (ATR): ν = 3052, 1676, 987, 956 cm<sup>-1</sup>; MS (EI) m/z (%): 295 (M<sup>+</sup>, 6), 227 (19), 226 (100), 225 (11), 207 (17), 55 (11); HRMS calcd. (%) for C<sub>25</sub>H<sub>23</sub>FNO: 295.1862; found: 295.1845.

(E)-2-(4-fluorophenyl)-1-styryl-1,2,3,4-tetrahydroisoquinoline (3t): Orange oil; t <sub>R</sub> = 21.48; R<sub>f</sub> = 0.6 (hexane/ethyl acetate: 4/1); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.45-7.10 (m, 9H, ArH), 7.05-6.75 (m, 4H, ArH), 6.40 (d, J = 15.9 Hz, 1H, CH=CH-Ph), 6.3 (dd, J = 15.9, 4.7 Hz, 1H, CHCH=CH-Ph), 5.25 (d, J = 4.7 Hz 1H, ArCHN). 3.63 (ddd, J = 12.2, 7.3, 5.1 Hz, 1H, CH<sub>2</sub>CH=CH<sub>2</sub>N), 3.55-3.45 (m, 1H, CH<sub>2</sub>CH<sub>2</sub>NH), 3.10-2.85 (m, 2H, CH<sub>2</sub>CH=CH<sub>2</sub>N). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 156.4 (d, J = 237.0 Hz), 146.5 (2C), 136.9, 136.5, 135.4, 131.0, 130.4, 128.6 (2C), 127.8, 127.6, 127.0, 126.6 (2C), 126.4, 116.6 (d, J = 7.4 Hz, 2C), 115.7 (d, J = 22.1 Hz, 2C), 62.4, 43.9, 28.4; IR (ATR): ν = 3025, 2904, 2834, 1735, 1507 cm<sup>-1</sup>; MS (EI) m/z (%): 329 (M<sup>+</sup>, 52), 328 (M<sup>+</sup>-1, 38), 252 (10), 238 (30), 237 (20), 226 (100), 224 (17), 128 (12), 115 (14), 95 (11), 91 (24); HRMS calcd. (%) for C<sub>24</sub>H<sub>23</sub>FNO: 329.1580; found: 329.1577.

2-(4-fluorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (4a): Yellow solid; m.p. 112-114 °C; t <sub>R</sub> = 16.6; R<sub>f</sub> = 0.5 (hexane/ethyl acetate: 3/2); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.14 (dd, J = 7.7, 1.2 Hz, 1H, ArH), 7.47 (td, J = 7.4, 1.5 Hz, 1H, ArH), 7.40-7.30 (m, 3H, ArH), 7.30-7.20 (m, 1H, ArH), 7.15-7.00 (m, 2H,
ArH), 3.95 (t, J = 6.5 Hz, 2H, CH₂CH₂N), 3.14 (m, J = 6.5 Hz, 2H, CH₂CH₂N), 13C NMR (75 MHz, CDCl₃): δ = 164.5, 160.8 (d, J = 245.6 Hz), 139.2, 138.3, 132.3, 130.1, 129.6, 128.8, 127.3 (d, J = 6.7 Hz, 2C), 127.1, 115.8 (d, J = 22.6 Hz, 2C), 49.7, 28.7. IR (ATR): ν = 1650, 1500 cm⁻¹. MS (EI) m/z (%): 242 (M+1, 16), 241 (M⁺, 91), 240 (M⁻-1, 25), 122 (20), 119 (13), 118 (100), 95 (18), 90 (46), 89 (24); HRMS calcd. (%) for C₁₅H₂₁FNO: 241.0903; found: 241.0907.

3. C-C CROSS COUPLING REACTIONS
3.1. SYNTHESIS OF NCN-PINCER

1,1’-(1,3-phenylene)bis(N,N-dimethylmethanimine) (7).³⁰⁶ To a solution of 1,3-bis(chloromethyl)benzene (1.75 g, 10 mmol) in 14 mL of DCM, HNMe₂ (2.68 mL, 40 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature for 24 h. Once the reaction was completed, the volatiles were removed under reduced pressure. The residue was dissolved in NaHCO₃ (sat., aq.) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were combined, dried over MgSO₄ and evaporated to yield product 7. Colourless liquid; Rf = 0.23 (methanol/ethyl acetate: 1/3); tᵣ =10.2; ¹H NMR (300 MHz, CDCl₃): δ = 7.30-7.20 (m, 4H, ArH), 3.44 (s, 4H, (CH₂)₂NMe₂), 2.25 (s, 12H, N(CH₃)), ¹³C NMR (75 MHz, CDCl₃): δ = 138.8 (2C), 129.8, 128.0, 127.8 (2C), 64.3 (2C), 45.4 (4C); IR (ATR): ν = 2972, 2940, 2813, 2765, 2722, 2704, 1455, 1358, 1146, 1031, 899, 845, 781, 700 cm⁻¹; MS (EI) m/z (%): 192 (M⁺, 15), 150 (12), 149 (100), 148 (25), 147 (37), 105 (57), 104 (73), 103 (12), 58 (76).

1,1’-(2-iodo-1,3-phenylene)bis(N,N-dimethylmethanimine) (8).³⁰⁷ To a solution of compound 7 (760 mg, 4 mmol) in 15 mL of dry benzene, a 2.5 M solution of n-BuLi in hexane (2.4 mL, 6 mmol) was added dropwise at 0 °C under argon atmosphere. The reaction mixture was stirred at rt for 24 h. Then, a solution of I₂ (1.42 g, 5.6 mmol) in 20 mL of dry THF was added and stirred for 1 additional hour. Once the reaction was completed, the solvent was removed under vacuum, and the residue was dissolved in EtOAc and washed with a saturated solution of Na₂S₂O₅. The organic phase was dried under MgSO₄. Product 8 was purified by

column chromatography using hexane/ethyl acetate as eluent. Brown oil; \( R_f = 0.17 \) (hexane/ethyl acetate: 1/4); \( t_f = 13.1 \); ¹H NMR (300 MHz, CDCl₃): \( \delta = 7.30-7.25 \) (m, 3H, ArH), 3.53 (s, 4H, (CH₂)₂NMe₂), 2.32 (s, 12H, N(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃): \( \delta = 141.9 \) (2C), 129.2 (2C), 127.6, 107.6, 69.2 (2C), 45.6 (4C); IR (ATR): \( \nu = 1677, 1592, 1176, 833 \) cm⁻¹; MS (EI) m/z ( %): 317 (M⁺, 9), 275 (18), 231 (13), 207 (14), 192 (10), 191 (67), 149 (12), 148 (15), 147 (16), 146 (13), 105 (41), 104 (22), 103 (13), 58 (100).

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\text{(NCN)Pd(I) (9a)}^{308}
\]
To a solution of 8 (0.638 g, 2 mmol) in dry toluene (13 mL), Pd(dba)₂ (1.15 g, 2 mmol) was added. The mixture was heated to reflux for 2 h. Once the reaction was completed, the solvent was removed under reduced pressure. Product was purified by column chromatography using hexane/ethyl acetate (9/1) for removing the by product and ethyl acetate:MeOH (1:1) for obtaining the product. Yellow solid; \( R_f = 0.50 \) (hexane/ethyl acetate: 1/1); m.p. 201-211 °C; ¹H NMR (300 MHz, CDCl₃): \( \delta = 7.02 \) (t, \( J = 7.5 \) Hz, 1H, ArH), 6.80 (d, \( J = 7.5 \) Hz, 2H, ArH); 4.01 (s, 4H, (CH₂)₂NMe₂); 2.97 (s, 12H, N(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃): \( \delta = 159.4, 145.3 \) (2C), 124.8, 119.9 (2C), 74.1 (2C), 55.0 (4C); IR (ATR): \( \nu = 2998, 2881, 2850, 1460, 1449, 1431, 1092, 958, 843, 803, 759, 701 \) cm⁻¹.

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\text{(NCN)Pd(Cl) (9a')}{309}
\]
To a solution of compound 7 (192 mg, 1 mmol) in 7 mL of dry benzene, a 2.5 M solution of n-BuLi in hexane (0.52 mL, 1.3 mmol) was added dropwise at 0 °C under Ar atmosphere. The reaction mixture was stirred at room temperature for 24 h. Then, a solution of PdCl₂(SMe₂)₂ (301 mg, 1 mmol) in 16 mL of dry THF was added and stirred for 1 additional day. Once the reaction was completed, the solvent was removed under vacuum, and the residue was dissolved in EtOAc and washed with a saturated solution of NaCl. The organic phase was dried under MgSO₄ and filtrated over celite. The solvent was removed under vacuum to afford complex 9a'. Brown solid; \( R_f = 0.33 \) (hexane/ethyl acetate: 1/1); m.p. 191-195 °C; ¹H NMR (300 MHz, CDCl₃): \( \delta = 6.97 \) (t, \( J = 7.5 \) Hz, 1H, ArH), 6.80 (d, \( J = 7.5 \) Hz, 2H, ArH); 4.00 (s, 4H, (CH₂)₂NMe₂); 2.94 (s, 12H, N(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃): \( \delta = 159.4, 145.3 \) (2C), 124.8, 119.9 (2C), 74.1 (2C), 55.0 (4C); IR (ATR): \( \nu = 2998, 2881, 2850, 1460, 1449, 1431, 1092, 958, 843, 803, 759, 701 \) cm⁻¹.

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MHz, CDCl$_3$): $\delta$ = 156.6, 145.1 (2C), 124.5, 119.8 (2C), 74.8 (2C), 53.1 (4C); IR (ATR): $\nu$ = 2979, 2904, 2848, 1450, 1020, 956, 842, 763, 707, 678 cm$^{-1}$.

### 3.2. GENERAL PROCEDURE FOR THE HIYAMA-TYPE REACTION

To a solution of aryl halide (1 mmol), potassium carbonate (2 mmol), catalyst 9a (0.01 mmol) in 2 mL of DES or glycerol, 1.5 mmol of organosilane was added and the resulting mixture was stirred for 24 h at 100 $^\circ$C. The mixture was quenched with water and extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over MgSO$_4$, followed by evaporation under reduced pressure to remove the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products.

**1-[[1,1'-biphenyl]-4-yl]ethanone (12a):** Orange solid; $R_f$ = 0.50 (hexane/ethyl acetate: 4/1); m.p. 109-113 $^\circ$C; $t_c$ = 13.7; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.40 (dt, $J$ = 8.5, 1.9 Hz, 2H, ArH), 7.70-7.60 (dt, $J$ = 8.5, 1.9 Hz, 4H, ArH), 7.50-7.40 (m, 3H, ArH), 2.63 (s, 3H, COCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 197.9, 145.9, 140.0, 135.9, 129.1 (2C), 129.0 (2C), 128.3 (2C), 127.4 (2C), 127.3, 26.8; IR (ATR): $\nu$ = 3082, 1676, 1599, 721 cm$^{-1}$; MS (EI) $m/z$ (%): 196 (M$^+$, 53), 182 (14), 181 (100), 153 (34), 152 (49), 151 (14), 76 (10).

**4-nitro-1,1'-biphenyl (12b):** Yellow solid; $R_f$ = 0.67 (hexane/ethyl acetate: 4/1); m.p. 98-100 $^\circ$C; $t_c$ = 13.8; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.30 (d, $J$ = 9.0 Hz, 2H, ArH), 7.74 (d, $J$ = 9.0 Hz, 2H, ArH), 7.65-7.60 (m, 2H, ArH), 7.55-7.40 (m, 3H, ArH); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 147.8, 147.2, 138.9, 129.3 (2C), 129.1, 127.9 (2C), 127.5 (2C), 124.3 (2C); IR (ATR): $\nu$ = 2921, 1595, 1512, 1340, 773 cm$^{-1}$; MS (EI) $m/z$ (%): 200 (M$^+$+1, 14), 199 (M$^+$, 100), 169 (31), 153 (24), 152 (79), 151 (24), 141 (21).

**3-phenylpyridine (12c):** Yellow oil; $R_f$ = 0.47 (hexane/ethyl acetate: 1/1); $t_c$ = 11.1; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.85 (d, $J$ = 1.7 Hz, 1H), 8.59 (dd, $J$ = 4.9, 1.7 Hz, 1H), 7.91 (dd, $J$ = 7.9, 2.3, 1.7 Hz), 7.67-7.55 (m, 2H), 7.50-7.35 (m, 4H); $^{13}$C NMR (75 MHz,

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Experimental Part

4-fluoro-1,1'-biphenyl (12d).<sup>312</sup> White solid; <br>\( R_f = 0.53 \) (hexane); <br>m.p. 71-73 °C; \( t = 10.0; \) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.60-7.55 \) (m, 4H), 7.50-7.45 (m, 2H), 7.40-7.35 (m, 1H), 7.20-7.10 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 162.6 \) (d, \( J = 246.3 \) Hz), 140.4, 137.5 (d, \( J = 3.2 \) Hz), 128.9 (2C), 128.8 (d, \( J = 8.0 \) Hz, 2C), 127.4, 127.2 (2C), 115.7 (d, \( J = 21.4 \) Hz, 2C); IR (ATR): \( v = 3062, 1231, 756 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 172 (M\(^+\), 100), 171 (M\(^+\)-1, 35), 170 (25).

4-methyl-1,1'-biphenyl (12e).<sup>313</sup> White solid; \( R_f = 0.73 \) (hexane); <br>m.p. 43-45 °C; \( t = 10.9; \) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.57 \) (ddd, \( J = 7.0, 4.1, 2.1 \) Hz, 2H, ArH), 7.55-7.45 (m, 2H, ArH), 7.45-7.40 (m, 2H, ArH), 7.35-7.30 (m, 1H, ArH), 7.25-7.20 (m, 2H, ArH), 2.39 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 141.3, 138.5, 137.2, 129.6 \) (2C), 128.9 (2C), 127.1 (5C), 21.2; IR (ATR): \( v = 3059, 1481, 1379, 754 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 169 (M\(^+\)-1, 13), 168 (M\(^+\), 100), 167 (66), 165 (25), 153 (15), 152 (20).

4-methoxy-1,1'-biphenyl (12f).<sup>313</sup> White solid; \( R_f = 0.67 \) (hexane/ethyl acetate: 19/1); m.p. 76-78 °C; \( t = 12.3; \) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.60-7.50 \) (m, 4H, ArH), 7.41 (t, \( J = 7.5 \) Hz, 2H, ArH), 7.30 (ddd, \( J = 7.3, 3.9, 1.3 \) Hz, 1H, ArH), 6.98 (d, \( J = 8.9 \) Hz, 2H, ArH), 3.85 (s, 3H, OCH\(_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 159.3, 141.0, 133.9, 128.9 \) (2C), 128.3 (2C), 126.8, 114.3 (2C), 55.5; IR (ATR): \( v = 3070, 1604, 1623, 1271, 756 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 185 (M\(^+\)-1, 14), 184 (M\(^+\), 100), 169 (44), 141 (39), 115 (25).

4-(benzyloxy)-1,1'-biphenyl (12g).<sup>312</sup> White solid; \( R_f = 0.20 \) (hexane); m.p. 133-135 °C; \( t = 17.0; \) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.60-7.50 \) (m, 4H, ArH), 7.50-7.25 (m, 8H, ArH), 7.10-7.05 (m, 2H, ArH), 5.11 (s, 2H, CH\(_2\)O);

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<sup>312</sup> N. Iranpoor, S. Rahimi, F. Panahi, RSC Adv. 2016, 6, 3084-3090.

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 158.5, 140.9, 137.1, 134.2, 128.9 (2C), 128.8 (2C), 128.3 (2C), 128.1, 127.6 (2C), 126.9 (2C), 126.8, 115.3 (2C), 70.3; IR (ATR): $v = 2922, 1243, 749$ cm$^{-1}$; MS (EI) $m/z$ (%): 260 (M$^+$, 32), 91 (100).

1,1'-biphenyl (12h).$^{313}$ Yellow solid; $R_f = 0.53$ (hexane), m.p. 68-70°C; $t_c = 10.0$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.70-7.60$ (m, 4H, ArH), 7.55-7.45 (m, 4H, ArH), 7.45-7.35 (m, 2H, ArH); $^1$C NMR (75 MHz, CDCl$_3$): $\delta = 141.4$ (2C), 128.9 (4C), 127.4 (2C), 127.3 (4C); IR (ATR): $v = 3033, 1477, 725$ cm$^{-1}$; MS (EI) $m/z$ (%): 155 (M$^+$ + 1, 14), 154 (M$^+$, 100), 153 (40), 152 (26), 76 (13).

1-(4-vinylphenyl)ethane (14a).$^{196}$ Yellow oil; $R_f = 0.30$ (hexane/ethyl acetate: 9:1); $t_c = 9.5$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.00-7.85$ (m, 2H, ArH), 7.55-7.40 (m, 2H, ArH), 6.76 (dd, $J = 17.6, 10.9$ Hz, 1H, CH$_2$=CH), 5.88 (dd, $J = 17.6, 0.7$ Hz, 1H, HCH=CH), 5.40 (dd, $J = 10.9, 0.7$ Hz, 1H, HCH=CH), 2.60 (s, 3H, CH$_3$); $^1$C NMR (75 MHz, CDCl$_3$): $\delta = 197.7, 142.2, 136.4, 136.0, 128.8$ (2C), 126.4 (2C), 116.9, 26.7; IR (ATR): $v = 3086, 1678, 1604, 1265$ cm$^{-1}$; MS (EI) $m/z$ (%): 146 (M$^+$, 45), 132 (12), 131 (100), 103 (46), 102 (10), 77 (26).

1-nitro-4-vinylbenzene (14b).$^{314}$ Yellow solid; $R_f = 0.53$ (hexane/ethyl acetate: 4:1); m.p. 24-26°C; $t_c = 9.8$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.25-8.10$ (m, 2H, ArH), 7.60-7.45 (m, 2H, ArH), 6.77 (dd, $J = 17.6, 10.9$ Hz, 1H, CH$_2$=CH), 5.93 (dd, $J = 17.6, 0.4$ Hz, 1H, HCH=CH), 5.50 (d, $J = 10.9$ Hz, 1H, HCH=CH); $^1$C NMR (75 MHz, CDCl$_3$): $\delta = 149.9, 138.8, 135.1, 126.9$ (2C), 124.1 (2C), 118.7; IR (ATR): $v = 2927, 1508, 1339$ cm$^{-1}$; MS (EI) $m/z$ (%): 149 (M$^+$, 67), 119 (58), 103 (23), 102 (29), 91 (53), 77 (100), 76 (15), 75 (11), 74 (12), 65 (17), 63 (15), 51 (45), 50 (17).

3-Vinylpyridine (14c).$^{315}$ Yellow oil; $R_f = 0.23$ (hexane/ethyl acetate: 4:1); $t_c = 6.0$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.62$ (d, $J = 2.1$ Hz, 1H, ArH), 8.49 (dd, $J = 5.0, 1.6$ Hz, 1H, ArH), 7.73 (dt, $J = 7.9, 1.8$ Hz, 1H, ArH), 7.30-7.20 (m, 1H, ArH), 6.71 (dd, $J = 17.7, 11.0$ Hz, 1H, CH=CH$_2$), 5.83 (dd, $J = 17.7, 0.5$ Hz, 1H, HCH=CH), 5.39 (dd, $J = 11.0, 0.5$ Hz, 1H, 


HCH=CH); $^1$C NMR (75 MHz, CDCl$_3$): $\delta$ = 148.9, 148.3, 133.5, 133.1, 132.7, 123.5, 116.3; IR (ATR): $\nu$ = 1632, 916, 711 cm$^{-1}$; MS (EI): $m/z$ (%): 105 (M$^+$, 100), 104 (62), 79 (11), 78 (21), 77 (13), 52 (14), 51 (15).

(1H)-1,2-bis(4-fluorophenyl)ethene (15d).$^{316}$ White solid; $R_f$ = 0.57 (hexane); m.p. 124-126 °C (hexane); $t_r$ = 12.7; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.55-7.45 (m, 4H, ArH), 7.20-7.05 (m, 4H, ArH), 6.97 (s, 2H, CH=CH); $^1$C NMR (101 MHz, CDCl$_3$): $\delta$ = 162.5 (d, $J$ = 247.1 Hz, 2C), 133.5 (d, $J$ = 3.0 Hz, 2C), 128.1 (d, $J$ = 8.1 Hz, 4C), 127.4 (2C), 115.8 (d, $J$ = 21.7 Hz, 4C); IR (ATR): $\nu$ = 2920, 1599, 1230, 834 cm$^{-1}$; MS (EI) $m/z$ (%): 216 (M$^+$, 100), 215 (47), 214 (35), 201 (27), 196 (17), 195 (23), 194 (11), 183 (10), 120 (11).

1-methoxy-4-vinylbenzene (14e).$^{314}$ Yellow oil; $R_f$ = 0.37 (hexane/ethyl acetate: 9/1); $t_r$ = 7.7; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.40-7.30 (m, 2H, ArH), 6.90-6.80 (m, 2H, ArH), 6.66 (dd, $J$ = 17.6, 10.9 Hz, 1H, CH=CH$_2$), 5.61 (dd, $J$ = 17.6, 1.0 Hz, 1H, HCH=CH), 5.12 (dd, $J$ = 10.9, 1.0 Hz, 1H, HCH=CH), 3.81 (s, 3H, CH$_3$); $^1$C NMR (75 MHz, CDCl$_3$): $\delta$ = 136.3, 132.4, 127.5 (2C), 115.9, 114.0 (2C), 111.7, 55.4; IR (ATR): $\nu$ = 2937, 1108, 993 cm$^{-1}$; MS (EI) $m/z$ (%): 134 (M$^+$, 100), 119 (46), 91 (41), 65 (16).

Styrene (14f).$^{315}$ Colourless oil; $R_f$ = 0.63 (hexane); $t_r$ = 6.5; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.45-7.35 (m, 2H, ArH), 7.35-7.20 (m, 3H, ArH), 6.70 (dd, $J$ = 17.6, 10.9 Hz, 1H, CH=CH$_2$), 5.73 (dd, $J$ = 17.6, 1.0 Hz, 1H, HCH=CH), 5.23 (dd, $J$ = 10.9, 1.0 Hz, 1H, HCH=CH); $^1$C NMR (75 MHz, CDCl$_3$): $\delta$ = 137.7, 137.0, 128.6 (2C), 127.9, 126.3 (2C), 113.9; IR (ATR): $\nu$ = 3084, 1494, 774 cm$^{-1}$; MS (EI) $m/z$ (%): 104 (M$^+$, 100), 103 (46), 78 (36), 77 (16), 51 (12).

(1H)-1,2-diphenylethene (15f).$^{316}$ White solid; $R_f$ = 0.43 (hexane); m.p. 114-116 °C (hexane); $t_r$ = 12.7; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.56 (dt, $J$ = 3.1, 1.3 Hz, 4H, ArH), 7.45-7.35 (m, 4H, ArH), 7.35-7.25 (m, 2H, ArH), 7.16 (s, 2H, CH=CH); $^1$C NMR (101 MHz, CDCl$_3$): $\delta$ = 137.4 (2C), 128.8 (8C), 127.7 (2C), 126.6 (4C); IR (ATR): $\nu$ =

3020, 1495, 962 cm\(^{-1}\); MS (EI) \textit{m/z} (%): 180 (M\(^+\), 100), 179 (99), 178 (64), 165 (42), 152 (11), 88 (15).

\textbf{(E)-1,2-di(2-thienyl)ethene (15g).}\(^{317}\) Pale yellow solid; \(R_t = 0.43\) (hexane); m.p. 116-118 °C; \(t_r = 13.1; \) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.20-7.15\) (m, 2H, ArH), 7.05 (s, 2H, CH=CH), 7.03 (dd, \(J = 3.6, 1.2\) Hz, 2H, ArH), 6.99 (dd, \(J = 5.0, 3.6\) Hz, 2H, ArH); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 142.5\) (2C), 127.8 (2C), 126.2 (2C), 124.4 (2C), 121.6 (2C); IR (ATR): \(\nu = 2923, 1720, 1018\) cm\(^{-1}\); MS (EI) \textit{m/z} (%): 192 (M\(^+\), 100), 191 (62), 190 (16), 147 (42), 115 (10).

\textbf{(E)-1-(4-(prop-1-en-1-yl)phenyl)ethanone (17c).}\(^{318}\) Colourless oil; \(R_t = 0.53\) (hexane/ethyl acetate: 9/1); \(t_r = 10.6; \) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.90-7.85\) (m, 2H, ArH), 7.40-7.35 (m, 2H, ArH), 6.45-6.35 (m, 2H, CH=CH), 2.54 (s, 3H, CH\(_3\)CO), 1.91 (d, \(J = 5.1\) Hz, 3H, CH\(_3\)CH=); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 197.6, 142.7, 135.4, 130.3, 129.1, 128.8, 125.8, 26.6, 18.8; \) IR (ATR): \(\nu = 3028, 1677, 1601, 1357\) cm\(^{-1}\); MS (EI) \textit{m/z} (%): 160 (M\(^+\), 40), 146 (11), 145 (100), 116 (11), 115 (54), 91 (20).

3.3. SYNTHESIS OF PYRIDINIOPHOSPHINE LIGANDS

3.3.1. General procedure for the preparation of 1-substituted pyridine-2(1H)-ones

To a flame dried 10 mL round bottom flask equipped with a magnetic stir bar were added, Cs\(_2\)CO\(_3\) (682 mg, 2.1 mmol), CuI (19 mg, 0.1 mmol), and ethyl 2-oxocyclohexanecarboxylate (34 mg, 0.2 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, DMSO (1 mL) was added by syringe and pre-stirred for 0.5 h at room temperature. Then a solution of aryl iodide (1 mmol) and 2-hydroxypyridine (114 mg, 1.2 mmol, 1.2 eq.) in DMSO (1 mL) was added via syringe under a counterflow of Ar. The tube was sealed, and the mixture was allowed to stir at the 80 °C. The reaction was monitored by TLC. After the starting material was completely consumed, the reaction was stopped and the mixture was cooled to room temperature. After being rinsed with (5 \(\times\) 10 mL) of ethyl acetate, the


combined filtrate was washed with saturated brine (2 x 10 mL). After the organic layer was dried by Na₂SO₄, it was concentrated by rotary evaporation. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent to give pure products 18.

**1-phenylpyridin-2(1H)-one (18a):** White solid; Rᵣ = 0.5 (ethyl acetate); m.p. 125-126 °C; tᵣ = 13.3; ¹H NMR (300 MHz, CDCl₃): δ = 7.50-7.33 (m, 6H, ArH), 7.30 (ddd, J = 6.8, 2.1, 0.7 Hz, 1H, ArH), 6.61 (ddd, J = 9.2, 0.7, 0.4 Hz, 1H, ArH), 6.21 (td, J = 6.8, 1.3 Hz, 1H, ArH), 13C NMR (75 MHz, CDCl₃): δ = 162.1, 140.7, 139.8, 137.9, 129.1 (2C), 128.2, 126.3 (2C), 121.5, 105.8; IR (ATR): ν = 3040, 1655, 1601, 1526, 1489 cm⁻¹; MS (EI) m/z (%): 171 (M⁺, 98), 170 (M⁺ - 1, 100), 143 (52), 117 (10), 116 (15), 115 (35), 77 (27), 51 (15).

**2H-[1,2'-bipyridin]-2-one (18b):** Grey solid; Rᵣ = 0.43 (ethyl acetate); m.p. 49-51 °C; tᵣ = 13.1; ¹H NMR (300 MHz, CDCl₃): δ = 8.58 (ddd, J = 4.9, 1.0, 0.9 Hz, 1H, ArH), 7.95 (dt, J = 8.2, 1.0 Hz, 1H, ArH), 7.90-7.80 (m, 2H, ArH), 7.40 (ddd, J = 9.2, 6.6, 2.1 Hz, 1H, ArH), 7.33 (ddd, J = 7.2, 4.9, 1.0 Hz, 1H, ArH), 6.65 (ddd, J = 9.2, 1.3, 0.7, 1H, ArH), 6.31 (ddd, J = 7.2, 6.6, 1.3 Hz, 1H, ArH); 13C NMR (75 MHz, CDCl₃): δ = 162.2, 151.9, 148.9, 140.3, 137.8, 136.1, 123.3, 122.0, 121.5, 106.4; IR (ATR): ν = 3059, 1665, 1599, 1536, 1432 cm⁻¹; MS (EI) m/z (%): 173 (M⁺+1, 12), 172 (M⁺, 100), 171 (M⁺ - 1, 28), 144 (21), 143 (12), 118 (64), 117 (16), 79 (21), 78 (29), 51 (15).

**1-(thiophen-2-yl)pyridin-2(1H)-one (18c):** White solid; Rᵣ = 0.36 (hexane/ethyl acetate: 1:1); m.p. 81-83 °C; tᵣ = 13.4; ¹H NMR (300 MHz, CDCl₃): δ = 7.60 (dd, J = 7.0, 1.5 Hz, 1H, ArH), 7.37 (ddd, J = 8.8, 6.6, 2.0 Hz, 1H, ArH), 7.27 (dd, J = 5.5, 1.4 Hz, 1H, ArH), 7.10 (dd, J = 3.8, 1.4 Hz, 1H, ArH), 7.01 (dd, J = 5.5, 3.9 Hz, 1H, ArH), 6.68 (d, J = 9.3 Hz, 1H, ArH), 6.28 (td, J = 7.0, 1.3 Hz, 1H, ArH); 13C NMR (75 MHz, CDCl₃): δ = 161.4, 140.9, 139.4, 136.7, 124.8, 124.3, 121.8, 120.4, 106.8; IR

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Experimental Part

v = 3100, 3080, 1578, 1538, 1294 cm⁻¹; MS (EI) m/z (%): 178 (M⁺ + 1, 11), 177 (M⁺, 100), 149 (33), 148 (40), 78 (15).

3.3.2. General procedure for the preparation of 1-substituted-2-(dicyclohexylphosphino)-pyridin-1-ium chlorides

To a solution of 1-substituted pyridine-2(1H)-one 18 (1 mmol) in 1,2-dichloroethane (5 mL), oxalyl chloride was added (3 mmol, 254 μL). The resulting mixture was heated to 60 °C under magnetic stirring until the reaction was completed (monitored by TLC). Once the starting material was consumed, the volatiles were removed under vacuum. The resulting solid was put in a round-bottom flask and it was evacuated and backfilled with argon (this process was repeated three times). Dry acetonitrile was added (5 mL) and the resulting mixture was heated to 55 °C. Then dicyclohexylphosphine (2 mmol, 261 μL) was added via syringe under a counter flow of argon. The flask was sealed, and the mixture was allowed to stir at reflux. Once the reaction was completed (monitored by TLC analysis) the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using methanol/ethyl acetate as eluent to give pure products 20.

2-(dicyclohexylphosphino)-1-phenylpyridin-1-ium chloride (20a): yellow solid; Rₛ = 0.53 (ethyl acetate/methanol: 2/1); ¹H NMR (300 MHz, CDCl₃): δ = 9.60-9.50 (m, 1H, ArH), 9.00-8.80 (m, 2H, ArH), 8.29 (d, J = 6.9 Hz, 1H, ArH), 7.70-7.60 (m, 3H, ArH), 7.45-7.35 (m, 2H, ArH), 2.05-1.60 (m, 11H, Cy), 1.50-1.00 (m, 11H, Cy); ¹³C NMR (75 MHz, CDCl₃): δ = 161.5 (d, J = 43.2Hz) 149.4, 145.6, 142.3 (d, J = 4.1 Hz), 133.4 (d, J = 3.4 Hz), 131.1 (2C), 129.6 (2C), 129.1, 126.6 (d, J = 4.6 Hz), 35.2 (d, J = 16.9 Hz, 2C), 29.7 (d, J = 15.6 Hz, 2C), 29.6 (d, J = 11.1 Hz, 2C), 26.4 (d, J = 9.0 Hz, 2C), 26.3 (d, J = 11.9 Hz, 2C), 25.5 (2C); ³¹P NMR (CDCl₃, 162 MHz): δ = -2.80; IR (ATR): ν = 2917, 1846, 2360, 1475, 1449 cm⁻¹; MS (DIP) m/z (%): 352 (M⁺-Cl, 18), 341 (87), 339 (22), 263 (18), 262 (14), 186 (13), 170 (11), 156 (16), 153 (17), 152 (10), 151 (49), 150 (19), 83 (100), 81 (11), 55 (49).
2-(dicyclohexylphosphino)-[1,2'-bipyridin]-1-ium chloride (20b): yellow solid; Rf = 0.3 (ethyl acetate/methanol: 2/1); ^1H NMR (300 MHz, CDCl3): δ = 9.84 (d, J = 5.9 Hz, 1H, ArH), 8.84 (t, J = 7.4 Hz, 1H, ArH), 8.65-8.60 (m, 2H, ArH), 8.23 (d, J = 7.9 Hz, 1H, ArH), 8.13 (td, J = 7.8, 1.8 Hz, 1H, ArH), 8.02 (d, J = 8.0 Hz, 1H, ArH), 7.64 (ddd, J = 7.5, 4.8, 0.8 Hz, 1H, ArH), 2.15-1.95 (m, 2H, CHPh), 1.80-1.65 (m, 8H, CH2Cy), 1.55-1.40 (m, 2H, CH2Cy), 1.30-1.15 (m, 10H, CH2Cy); ^13C NMR (75 MHz, CDCl3): δ = 161.1 (d, J = 44.4 Hz), 153.7, 148.7, 148.4, 145.8, 140.1, 133.1, 128.5, 126.6, 122.0 (d, J = 4.7 Hz), 35.0 (d, J = 15.9 Hz, 2C), 30.0 (d, J = 10.9 Hz, 2C), 29.5 (d, J = 16.5 Hz, 2C), 26.5 (d, J = 9.4 Hz, 2C), 26.4 (d, J = 11.7 Hz, 2C), 26.0 (2C); ^31P NMR (CDCl3, 162 MHz): δ = -0.65; IR (ATR): ν = 2928, 2853, 1625, 1444, 1422, 1169 cm⁻¹; MS (DIP) m/z (%): 353 (M⁺-Cl⁻, 15), 272 (18), 271 (100), 264 (28), 232 (17), 189 (34), 188 (19), 187 (62), 186 (18), 171 (11), 157 (23), 153 (11), 151 (32), 150 (13), 83 (73), 81 (12), 79 (13), 78 (15), 67 (10), 55 (43), 44 (29), 41 (20).

2-(dicyclohexylphosphino)-1-(thiophen-2-yl)pyridin-1-ium chloride (20c): yellow solid; Rf = 0.35 (ethyl acetate/methanol: 2/1); ^1H NMR (300 MHz, CDCl3): δ = 9.65 (m, 1H, ArH), 9.07 (m, 1H, ArH), 8.80 (m, 1H, ArH), 8.30 (d, J = 7.1 Hz, 1H, ArH), 7.56 (d, J = 5.4 Hz, 1H, ArH), 7.43 (d, J = 2.6 Hz, 1H, ArH), 7.15 (dd, J = 5.4, 3.6 Hz, 1H, ArH), 2.30-2.00 (m, 2H, CHPh), 1.90-1.60 (m, 8H, CH2Cy), 1.50-1.40 (m, 2H, CH2Cy), 1.30-1.10 (m, 10H, CH2Cy); ^13C NMR (75 MHz, CDCl3): δ = 164.5 (d, J = 42.4 Hz), 151.8, 146.9, 141.7 (d, J = 3.9 Hz), 133.3 (d, J = 3.4 Hz), 129.6, 128.9 (d, J = 3.6 Hz), 127.8, 126.5, 35.8 (d, J = 17.0 Hz, 2C), 30.1 (d, J = 10.6 Hz, 2C), 29.9 (d, J = 16.5 Hz, 2C), 26.8 (d, J = 9.2 Hz, 2C), 26.6 (d, J = 11.6 Hz, 2C), 25.8 (2C); ^31P NMR (CDCl3, 162 MHz): δ = -1.67; IR (ATR): ν = 2923, 2848, 1474, 720, 634 cm⁻¹; MS (DIP) m/z (%): 358 (M⁺-Cl⁻, 100), 151 (32), 83 (74), 55 (51).

3.4. GENERAL PROCEDURE FOR THE SUZUKI-MIYaura REACTION

To a 2 mL of DES solution of the corresponding aryl iodide 10 (1 mmol), PdCl2 (0.001 mmol), ligand 20a (0.003 mmol), and K2CO3 (3 mmol) phenylboronic acid 21a (1.5 mmol) were added. The tube was heated to 100 °C during 2 h under magnetic stirring. Once the reaction was completed, the mixture was quenched with water and extracted with EtOAc (3 x 5 mL). The organic phases were dried over MgSO4, followed by evaporation under reduced pressure to
remove the solvent. The product was purified by chromatography on silica gel (hexane/ethyl acetate) to give the corresponding products 12:

4-(tert-butyl)-1,1′-biphenyl (12i): White solid; \( R_f = 0.5 \) (Hexane); m.p. 50-51 °C; \( t_r = 14.3 \). \(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \( \delta = 7.63-7.53 \) (m, 3H, ArH), 7.54-7.47 (m, 3H, ArH), 7.46-7.39 (m, 2H, ArH), 7.38-7.28 (m, 1H, ArH), 1.37 (s, 9H, 3CIH); \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \( \delta = 150.4, 141.4, 141.2, 138.5, 128.9, 128.8, 127.4, 127.3, 127.2, 127.1, 126.9, 125.8, 34.7, 31.5 \) (3C); IR (ATR) \( \nu = 3035, 2958, 2905, 2866, 1598, 1482, 1391, 1270, 1003, 837, 761 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 210 (M\(^{+}\), 100), 191 (18), 152 (12), 115 (23), 109 (15), 104 (16), 91 (24).

3.5. GENERAL PROCEDURE FOR THE SONOGASHIRA REACTION

To a solution of the corresponding aryl iodide 10 (1 mmol), PdCl\(_2\) (0.001 mmol), ligand 20a (0.003 mmol) and \( \text{Pr}_2\text{NH} \) (2 mmol, 280 \( \mu \)L) in 2 mL of DES, phenylacetylene 2a was added (2 mmol, 220 \( \mu \)L). The tube was heated to 80 °C during 5 h under magnetic stirring. Once the reaction was completed, the mixture was quenched with water and extracted with ethyl acetate (3 x 5 mL). The organic phases were dried over MgSO\(_4\), followed by evaporation under reduced pressure to remove the solvent. The product was purified by chromatography on silica gel (hexane/ethyl acetate) to give the corresponding products 22:

1-(4-(phenylethynyl)phenyl)ethanone (22a): White solid; \( R_f = 0.27 \) (hexane/ethyl acetate: 19/1); m.p. 95-97 °C; \( t_r = 15.7 \). \(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \( \delta = 8.00-7.90 \) (m, 2H, ArH), 7.65-7.60 (m, 2H, ArH), 7.60-7.50 (m, 2H, ArH), 7.40-7.35 (m, 3H, ArH), 2.62 (s, 3H, COCH\(_3\)); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \( \delta = 197.4, 136.3, 131.8 \) (4C), 128.9, 128.6 (2C), 128.4 (2C), 128.3, 122.8, 92.8, 88.7, 26.8; IR (ATR): \( \nu = 1677, 1592, 1176, 833 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 220 (M\(^{+}\), 70), 207 (15), 206 (16), 205 (100), 177 (19), 176 (43), 151 (11).

Experimental Part

1-(phenylethynyl)-4-(trifluoromethyl)benzene (22b).324 White solid; Rf = 0.5 (hexane); m.p. 106-107 °C; t, = 12.4; 1H NMR (300 MHz, CDCl3): δ = 7.65-7.55 (m, 4H, ArH), 7.55-7.50 (m, 2H, ArH), 7.40-7.30 (m, 3H, ArH); 13C NMR (75 MHz, CDCl3): δ = 122.0 (2C), 131.9 (2C), 130.0 (d, J = 32.7 Hz), 129.0, 128.6 (2C), 127.3, 125.4 (dd, J = 7.4, 3.7 Hz, 2C), 124.1 (d, J = 272.2 Hz), 122.7, 91.9, 88.1; IR (ATR): ν = 1608, 1321, 1104, 756 cm⁻¹; MS (EI) m/z (%): 247 (M⁺ + 1, 15), 246 (M⁺, 100), 227 (9), 176 (7).

1-methyl-4-(phenylethynyl)benzene (22c).323 White solid; Rf = 0.4 (hexane); m.p. 73-75 °C; t, = 13.6; 1H NMR (300 MHz, CDCl3): δ = 7.55-7.50 (m, 2H, ArH), 7.43 (dt, J = 7.9, 1.7 Hz, 2H, ArH), 7.35-7.30 (m, 3H, ArH), 7.15 (d, J = 7.9 Hz), 2.36 (s, 3H, CH3); 13C NMR (75 MHz, CDCl3): δ = 138.5, 131.7, 131.6, 129.3, 128.5, 128.2, 123.6, 120.3, 89.7, 88.9; IR (ATR): ν = 3029, 2918, 1508, 1440, 753 cm⁻¹; MS (EI) m/z (%): 193 (M⁺+1, 16), 192 (M⁺, 100), 191 (M⁺-1, 48), 190 (12), 189 (23), 165 (12).

1-nitro-4-(phenylethynyl)benzene (22d).325 Yellow solid; Rf = 0.3 (hexane/ethyl acetate: 19/1); m.p. 111-112 °C; t, = 15.8; 1H NMR (300 MHz, CDCl3): δ = 8.21 (d, J = 8.8 Hz, 2H, ArH), 7.66 (d, J = 8.8 Hz, 2H, ArH), 7.56 (dd, J = 6.6, 3.0 Hz, 2H, ArH), 7.45-7.30 (m, 3H, ArH); 13C NMR (75 MHz, CDCl3): δ = 147.1, 132.4 (2C), 132.0 (2C), 130.4, 129.4, 128.7 (2C), 123.7 (2C), 122.2, 94.8, 87.7; IR (ATR); ν = 1509, 1345, 676, 615 cm⁻¹; MS (EI) m/z (%): 224 (M⁺+1, 16), 223 (M⁺, 100), 193 (26), 177 (11), 176 (46), 165 (16), 151 (17).

1-methyl-2-(phenylethynyl)benzene (22e).326 Colourless oil; Rf = 0.4 (hexane); t, = 13.3; 1H NMR (300 MHz, CDCl3): δ = 7.55-7.45 (m, 3H, ArH), 7.40-7.30 (m, 3H, ArH), 7.25-7.20 (m, 2H, ArH), 7.20-7.10 (m, 1H, ArH), 2.52 (s, 3H, CH3); 13C NMR (75 MHz, CDCl3): δ = 140.3, 131.9, 131.6 (2C), 129.6, 128.5 (2C), 128.4, 128.3, 125.7, 123.7, 123.1, 93.5, 88.5, 20.9; IR (ATR): ν = 3059, 1492, 751, 687 cm⁻¹; MS (EI)

**Experimental Part**

\[ m/z \text{ (%): } 193 (M^+ + 1, 14), 192 (M^+), 191 (M^+ - 1, 94), 190 (12), 189 (31), 165 (19). \]

2-(phenylethynyl)pyridine (22f): \(^{326}\) Brown oil; \( R_f = 0.37 \) (hexane/ethyl acetate: 4/1); \( t_r = 13.5; \) \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \( \delta = 8.62 \) (ddd, \( J = 7.9, 1.8, 1.0 \) Hz, 1H, ArH), 7.67 (td, \( J = 7.7, 1.8 \) Hz, 1H, ArH), 7.60 (ddd, \( J = 4.8, 2.4, 1.5 \) Hz, 2H, ArH), 7.23 (ddd, \( J = 7.6, 4.9, 1.2 \) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 150.1, 143.5, 136.3, 132.1 \) (2C), 129.1, 128.5 (2C), 127.4, 122.8, 122.3, 89.3, 88.7; IR (ATR): \( v = 3049, 2222, 1489, 776 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 180 (M\(^+ + 1\), 16), 179 (M\(^+\), 100), 178 (M\(^+\) - 1, 37), 151 (10).

2-(phenylethynyl)thiophene (22g): \(^{326}\) White solid; \( R_f = 0.6 \) (hexane/ethyl acetate: 19/1); m.p. 50-51 °C; \( t_r = 12.9; \) \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.55-7.45 \) (m, 2H, ArH), 7.40-7.30 (m, 3H, ArH), 7.30-7.25 (m, 2H, ArH), 7.05-6.95 (m, 1H, ArH); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 132.0, 131.5 \) (2C), 128.6, 128.5 (2C), 127.4, 127.2, 123.4, 123.0, 93.2, 82.7; IR (ATR): \( v = 1485, 851, 753, 687 \) cm\(^{-1}\); MS (EI): \( m/z \) (%): 185 (M\(^+ + 1\), 15), 184 (M\(^+\), 100), 152 (12), 139 (14).

3.6. GENERAL PROCEDURE FOR THE HECK REACTION

To a solution of the corresponding aryl iodide 10 (1 mmol), PdCl\(_2\) (0.005 mmol), ligand 20a (0.015 mmol) and NaOAc (1.5 mmol, 123 mg) in 2 mL of DES in a screw- capped tube, methacrylate 23 was added (1.2 mmol, 98 \( \mu \)L). The tube was sealed and heated to 100 °C during 3 h. Once the reaction was completed, the mixture was quenched with water and extracted with ethyl acetate (3 x 5 mL). The organic phases were dried over MgSO\(_4\), followed by evaporation under reduced pressure to remove the solvent. The product was usually purified by chromatography on silica gel (hexane/ethyl acetate) to give the corresponding products 24.

(E)-methyl 3-(4-nitrophenyl)acrylate (24a).\textsuperscript{327} Off-white solid; \( R_t = 0.33 \) (hexane/ethyl acetate: 4/1); m.p. 131-133 °C; \( \tau \text{r} = 13.9; \) \( ^1\text{H} \text{NMR (300 MHz, CDCl}_3): \delta = 8.30-8.15 \) (m, 2H, ArH), 7.73 (d, \( J = 16.1 \) Hz, 1H, \( HC=CH \)), 7.70-7.65 (m, 2H, ArH), 6.57 (d, \( J = 16.1 \) Hz, 1H, \( HC=CH \)), 3.84 (s, 3H, CO\( _2 \text{CH}_3 \)); \( ^{13}\text{C} \text{NMR (75 MHz, CDCl}_3): \delta = 166.5, 148.6, 142.0, 140.6, 128.7 \) (2C), 124.3 (2C), 122.2, 52.2; IR (ATR): \( \nu = 1718, 1509, 1333, 846 \) cm\(^{-1}\); MS (El) \text{m/z} (%)\textsuperscript{328}: 207 (M\(^{+}\), 51), 176 (100), 146 (17), 130 (14), 129 (14), 118 (13), 102 (29), 90 (14), 51 (11).

Methyl cinnamate (24b).\textsuperscript{328} Light yellow solid; \( R_t = 0.53 \) (hexane/ethyl acetate: 4/1); m.p. 33-35 °C; \( \tau \text{r} = 10.40 \) min; \( ^1\text{H} \text{NMR (300 MHz, CDCl}_3): \delta = 7.70 \) (d, \( J = 16.0 \) Hz, 1H, \( HC=CH \)), 7.60-7.50 (m, 2H, ArH), 7.45-7.30 (m, 3H, ArH), 6.44 (d, \( J = 16.0 \) Hz, 1H, \( HC=CH \)), 3.81 (s, 3H, CO\( _2 \text{CH}_3 \)); \( ^{13}\text{C} \text{NMR (75 MHz, CDCl}_3): \delta = 167.5, 145.0, 134.5, 130.4, 129.0 \) (2C), 128.2 (2C), 117.9, 51.8; IR (ATR): \( \nu = 2944, 1711, 1636, 771 \) cm\(^{-1}\); MS (El) \text{m/z} (%)\textsuperscript{328}: 162 (M\(^{+}\), 55), 161 (M\(^{-}\)-1, 29), 131 (100), 103 (57), 102 (15), 77 (30), 51 (15).

(E)-methyl 3-(naphthalen-1-yl)acrylate (24c).\textsuperscript{328} Yellow oil; \( R_t = 0.47 \) (hexane/ethyl acetate: 4/1); \( \tau \text{r} = 14.6; \) \( ^1\text{H} \text{NMR (300 MHz, CDCl}_3): \delta = 8.55 \) (d, \( J = 15.8 \) Hz, 1H, \( HC=CH \)), 8.2 (d, \( J = 8.2 \) Hz, 1H, ArH), 7.95-7.85 (m, 2H, ArH), 7.75 (d, \( J = 7.2 \) Hz, 1H, ArH), 7.65-7.40 (m, 3H, ArH), 6.54 (d, \( J = 15.8 \) Hz, 1H, \( HC=CH \)), 3.87 (s, 3H, CO\( _2 \text{CH}_3 \)); \( ^{13}\text{C} \text{NMR (75 MHz, CDCl}_3): \delta = 167.4, 141.9, 133.7, 131.8, 131.5, 130.6, 128.8, 126.9, 126.3, 125.5, 125.1, 123.4, 120.5, 51.9; IR (ATR): \( \nu = 2947, 1709, 1630, 1165, 799 \) cm\(^{-1}\); MS (El) \text{m/z} (%)\textsuperscript{328}: 212 (M\(^{+}\), 29), 181 (14), 154 (13), 153 (100), 152 (76), 151 (17), 76 (13).

(E)-methyl 3-(o-tolyl)acrylate (24d).\textsuperscript{328} Yellow oil; \( R_t = 0.57 \) (hexane/ethyl acetate: 4/1); \( \tau \text{r} = 11.2; \) \( ^1\text{H} \text{NMR (300 MHz, CDCl}_3): \delta = 7.99 \) (d, \( J = 15.9 \) Hz, 1H, \( HC=CH \)), 7.70-7.45 (m, 1H, ArH), 7.40-7.10 (m, 3H, ArH), 6.36 (d, \( J = 15.9 \) Hz, 1H, \( HC=CH \)), 3.81 (s, 3H, CO\( _2 \text{CH}_3 \)), 2.44 (s, 3H, Ar-CH\(_3\)); \( ^{13}\text{C} \text{NMR (75 MHz, CDCl}_3): \delta = 166.5, 148.6, \)


4. C-S CROSS COUPLING REACTIONS

4.1. SYNTHESIS OF Pd NCS

Synthesis of Decahedral and octahedral NCs. PVP and citric acid were dissolved in 8 mL ultrapure water in a two-necked round bottom flask equipped with a condenser. The mixture was heated to 90 °C under air and magnetically stirred. 3 mL of an aqueous solution of H₂PdCl₄ were quickly added and the mixture was stirred at 90 °C for 26 hours. The product was recovered by centrifugation, washing once with acetone and twice with EtOH in order to remove PVP. The initial concentration of PVP determined the decahedral or octahedral shape of the nanoparticles.
Synthesis of Cubic NCs.\textsuperscript{330} 10 mL of 10 mM H$_2$PdCl$_4$ solution were added to a 200 mL solution of CTAB (12.5 mM) under vigorous stirring and the mixture was heated to 95 °C for 15 min. Then, 1.6 mL of a freshly prepared ascorbic acid solution (100 mM) was added and the resulting mixture was stirred at 95 °C for 30 min. The sample was centrifuged twice and redispersed in water. NaOH was then added (1 pellet per 50 mL solution). Finally, the nanoparticles were washed with ultrapure water. After centrifugation, the samples were redispersed in water and analysed by TEM.

4.2. Pd-CATALYSED SYNTHESIS OF SULFONES

To a stirred solution of aryl boronic acid (1 mmol), sodium metabisulfite (2.2 mmol), PdCl$_2$ (0.01 mmol) and ligand 20a (0.03 mmol) in 2 mL of DES, the corresponding electrophile was added (2 mmol). The solution was stirred at 80 °C for 24 h until the end of the reaction. The mixture was quenched with water and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried over MgSO$_4$, followed by evaporation under reduced pressure to remove the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products 28:

(\textsuperscript{331}Pentylsulfonyl)benzene (28a). Brown oil; $R_f = 0.33$ (hexane/ethyl acetate: 4/1); $t_r = 13.5$. \textsuperscript{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.95-7.85$ (m, 2H, ArH), 7.70-7.60 (m, 1H, ArH), 7.60-7.50 (m, 2H, ArH), 3.15-3.00 (m, 2H, SO$_2$CH$_2$), 1.71 (ddd, $J = 18.9, 9.5, 6.6$ Hz, 2H, SO$_2$CH$_2$CH$_2$), 1.40-1.20 (m, 4H, CH$_2$CH$_2$CH$_3$), 0.85 (t, $J = 7.1$ Hz, 3H, CH$_3$). \textsuperscript{13}C NMR (75 MHz, CDCl$_3$): $\delta = 139.1, 133.6, 129.2$ (2C), 128.0 (2C), 56.2, 30.3, 22.3, 22.0, 13.7. IR (ATR): $v = 2957, 1316, 1142$ cm$^{-1}$. MS (EI) $m/z$ (%): 212 (M$^+$, 0.3), 195 (10), 143 (100), 142 (19), 125 (16), 119 (17), 105 (12), 91 (23), 78 (39), 77 (46), 71 (10), 51 (17).

(Butylsulfonyl)benzene (28a′): Brown oil; \( R_f = 0.63 \) (Hexane/AcOEt 1:1); \( t = 14.2 \); \(^1H\) NMR (300 MHz, CDCl\(_3\)); \( \delta = 8.00-7.85 \) (m, 2H, ArH), 7.70-7.65 (m, 1H, ArH), 6.60-6.50 (m, 2H, ArH), 3.15-3.00 (m, 2H, SO\(_2\)CH\(_2\)CH\(_3\)), 1.75-1.65 (m, 2H, SO\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.50-1.30 (m, 2H, CH\(_2\)CH\(_2\)CH\(_3\)), 0.89 (t, \( J = 7.3 \) Hz, 3H, CH\(_3\)); \(^{13}C\) NMR (101 MHz, CDCl\(_3\)); \( \delta = 139.3, 133.7, 129.4, 128.1, 128.0, 126.2, 124.7, 21.6, 13.6 \); IR (ATR); \( \nu = 2961, 1304, 1142 \) cm\(^{-1}\); MS (El) \( m/z \) (%): 198 (M\(^+\), 0.6), 143 (97), 133 (19), 132 (26), 125 (24), 105 (35), 91 (28), 78 (98), 77 (100), 57 (44), 56 (15), 51 (46).

1-methyl-4-(pentylsulfonyl)benzene (28b): Pale yellow solid; m.p. 44-47°C; \( R_f = 0.37 \) (hexane/ethyl acetate: 4:1); \( t = 14.3 \); \(^1H\) NMR (300 MHz, CDCl\(_3\)); \( \delta = 7.78 \) (d, \( J = 8.3 \) Hz, 2H, ArH), 7.36 (d, \( J = 8.3 \) Hz, 2H, ArH), 3.10-3.00 (m, 2H, SO\(_2\)CH\(_2\)CH\(_3\)), 2.45 (s, 3H, ArCH\(_3\)), 1.75-1.65 (m, 2H, SO\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.35-1.25 (m, 4H, CH\(_2\)CH\(_2\)CH\(_3\)), 0.86 (t, \( J = 7.1 \) Hz, 3H, CH\(_3\)); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)); \( \delta = 144.6, 136.4, 130.0 \) (2C), 128.2 (2C), 56.5, 30.5, 22.5, 22.2, 21.7, 13.8 \); IR (ATR): \( \nu = 2935, 1305, 1141 \) cm\(^{-1}\); MS (El) \( m/z \) (%): 226 (M\(^+\), 1), 183 (12), 170 (11), 162 (12), 161 (20), 158 (10), 157 (100), 156 (31), 155 (12), 139 (31), 133 (22), 119 (12), 107 (13), 105 (41), 93 (16), 92 (99), 91 (77), 89 (12), 65 (31), 55 (11); HRMS calcd. (%) for C\(_{14}H\(_14\)O\(_2\)S (M\(^+\)-C\(_4\)H\(_8\)): 170.0403; found: 170.0399.

1-methyl-2-(pentylsulfonyl)benzene (28c): Colorless oil; \( R_f = 0.3 \), \(^1H\) NMR (300 MHz, CDCl\(_3\)); \( \delta = 7.55-7.65 \) (m, 2H, ArH), 7.50-7.40 (m, 2H, ArH), 3.10-3.05 (m, 2H, SO\(_2\)CH\(_2\)CH\(_3\)), 2.45 (s, 3H, ArCH\(_3\)), 1.75-1.65 (m, 2H, SO\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.40-1.25 (m, 4H, CH\(_2\)CH\(_2\)CH\(_3\)), 0.86 (t, \( J = 7.1 \) Hz, 3H, CH\(_3\)); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)); \( \delta = 139.5, 139.1, 134.4, 129.1, 128.3, 125.1, 30.3, 22.2, 22.1, 21.3, 13.7 \); IR (ATR): \( \nu = 2959, 1295, 1136 \) cm\(^{-1}\); MS (El) \( m/z \) (%): 226 (M\(^+\), 1), 162 (13), 157 (100), 139 (15), 133 (37), 119 (17), 108 (17), 93 (24), 92 (81), 91 (92), 89 (13), 71 (15), 65 (44), 55 (17); HRMS calcd. (%) for C\(_{14}H\(_{14}\)O\(_2\)S (M\(^+\)-C\(_4\)H\(_8\)): 183.0480; found: 183.0477.

1-methyl-2-(pentylsulfonyl)benzene (28d): Colorless oil; \( R_f = 0.43 \), \(^1H\) NMR (300 MHz, CDCl\(_3\)); \( \delta = 8.00 \) (dd, \( J = 7.9, 1.4 \) Hz, 1H, ArH), 7.52

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4-(pentylsulfonyl)phenol (28e). Colorless oil; \( R_f = 0.63 \) (hexane/ethyl acetate 1/1); \( t_c = 16.1 \). \( ^1\text{H} \) NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.93 \) (s, 1H, OH), 7.75-7.70 (m, 2H, ArH), 7.05-6.95 (m, 2H, ArH), 3.10-3.05 (m, 2H, SO\(_2\)CH\(_2\)), 0.85 (t, \( J = 7.1 \) Hz, 3H, CH\(_2\)CH\(_3\)). \( ^1\text{C} \) NMR (75 MHz, CDCl\(_3\)): \( \delta = 161.6, 130.4 \) (2C), 129.4, 116.3 (2C), 56.8, 30.4, 22.5, 22.2, 13.8; IR (ATR): \( \nu = 3368, 2959, 1284, 1126 \) cm\(^{-1}\); MS (7El): \( m/z (%) \) 228 (M\(^{+}\)), 135 (17), 121 (10), 109 (36), 107 (20), 94 (100), 93 (100), 85 (10), 159 (48), 158 (58), 1157 (18), 141 (39), 65 (35), 55 (16); HRMS calcd. (%) for C\(_{12}\)H\(_8\)O\(_2\): 159.0116; found: 159.0115.

1-methoxy-4-(pentylsulfonyl)benzene (28f)\(^{333}\). Colorless oil; \( R_f = 0.30 \) (hexane/ethyl acetate 4/1); \( t_c = 15.6 \). \( ^1\text{H} \) NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.83 \) (d, \( J = 9.0 \) Hz, 2H, ArH), 7.02 (d, \( J = 9.0 \) Hz, 2H, ArH), 3.89 (s, 3H, OCH\(_3\)), 3.10-2.95 (m, 2H, SO\(_2\)CH\(_2\)), 1.80-1.65 (m, 2H, SO\(_2\)CH\(_2\)CH\(_3\)), 1.40-1.20 (m, 4H, CH\(_2\)CH\(_2\)CH\(_3\)). \( ^1\text{C} \) NMR (75 MHz, CDCl\(_3\)): \( \delta = 163.8, 130.9, 130.3 \) (2C), 114.5 (2C), 56.7, 55.8, 30.5, 22.6, 22.2, 13.8; IR (ATR): \( \nu = 2960, 1293, 1236, 1136 \) cm\(^{-1}\); MS (7El): \( m/z (%) \) 242 (M\(^{+}\)), 173 (13), 172 (77), 171 (27), 155 (49), 149 (10), 123 (37), 121 (12), 108 (100), 107 (22), 92 (20), 77 (24), 64 (11).

1,3-dimethoxy-2-(pentylsulfonyl)benzene (28g): Colorless oil; \( R_f = 0.33 \) (hexane/ethyl acetate 1/1); \( t_c = 16.0 \). \( ^1\text{H} \) NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.38 \) (t, \( J = 8.5 \) Hz, 1H, ArH), 6.57 (d, \( J = 8.5 \) Hz, 2H, ArH), 3.84 (s, 6H, 2xOMe), 3.45-3.30 (m, 2H, SO\(_2\)CH\(_2\)), 1.80-1.60 (m, 2H, SO\(_2\)CH\(_2\)CH\(_3\)), 1.40-1.20 (m, 4H, CH\(_2\)CH\(_2\)CH\(_3\)), 0.79 (t, \( J = 7.1 \) Hz, 3H, CH\(_2\)CH\(_3\)). \( ^1\text{C} \) NMR (75 MHz, CDCl\(_3\)): \( \delta = 159.9 \) (2C), 134.9,

1-(pentylsulfonyl)-4-(trifluoromethyl)benzene (28h): Colorless oil; $R_f = 0.47$ (hexane/ethyl acetate: 4/1); $t_r = 12.6$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.07$ (d, $J = 8.1$ Hz, 2H, ArH), 7.86 (d, $J = 8.1$ Hz, 2H, ArH), 3.25-3.05 (m, 2H, SO$_2$CH$_2$CH$_3$), 1.80-1.65 (m, 2H, SO$_2$CH$_2$CH$_3$), 1.45-1.15 (m, 4H, CH$_2$CH$_2$CH$_2$). 0.87 (t, $J = 7.1$ Hz, 3H, CH$_2$CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 142.8$, 135.5 (q, $J = 33.2$ Hz), 128.9 (2C), 126.5 (q, $J = 3.5$ Hz, 2C), 123.2 (q, $J = 273.8$ Hz), 56.3, 30.4, 22.3, 22.2, 13.8; IR (ATR): $\nu = 2362$, 1319, 1132 cm$^{-1}$; MS (EI) $m/z$ (%): 281 (M$^+$+1, 0.2), 263 (21), 261 (14), 211 (100), 210 (11), 193 (14), 187 (26), 173 (72), 159 (24), 146 (33), 145 (74), 143 (15), 125 (13), 95 (16), 71 (45), 70 (37), 55 (23); HRMS calcd. (%) for C$_{12}$H$_7$F$_2$S$_2$: 261.0761; found: 261.0756.

3-(pentylsulfonyl)thiophene (28j): Colorless oil; $R_f = 0.23$ (hexane/ethyl acetate: 4/1); $t_r = 13.5$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.08$ (dd, $J = 3.1$, 1.3 Hz, 1H, ArH), 7.49 (dd, $J = 5.1$, 3.1 Hz, 1H, ArH), 7.39 (dd, $J = 5.1$, 1.3 Hz, 1H, ArH), 3.20-3.05 (m, 2H, SO$_2$CH$_2$). 1.80-1.70 (m, 2H, SO$_2$CH$_2$CH$_3$). 1.45-1.25 (m, 4H, CH$_2$CH$_2$CH$_3$). 0.87 (t, $J = 7.0$ Hz, 3H, CH$_2$CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 139.8$, 132.6, 128.4, 126.0, 56.5, 30.3, 22.4, 22.2, 13.8; IR (ATR): $\nu = 2957$, 1297, 1135 cm$^{-1}$; MS (EI) $m/z$ (%): 218 (M$^+$, 37), 175 (10), 162 (11), 152 (19), 151 (10), 150 (11), 149 (100), 148 (42), 131 (20), 126 (13), 125 (13), 111 (13), 100 (48), 99 (12), 98 (17), 97 (27), 85 (23), 84 (40), 83 (18), 71 (18), 70 (12), 55 (20); HRMS calcd. (%) for C$_{9}$H$_6$O$_2$S$_2$: 218.0435; found: 218.0433.
2-(pentylsulfonyl)thiophene (28k). Colorless oil; $R_f = 0.27$ (hexane/ethyl acetate: 4/1); $t_r = 13.3$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.72$ (dd, $J = 5.0, 13.3$ Hz, 1H, ArH), 7.69 (dd, $J = 3.8, 1.3$ Hz, 1H, ArH), 7.17 (dd, $J = 5.0, 3.8$ Hz, 1H, ArH), 3.30-3.10 (m, 2H, SO$_2$CH$_2$), 1.90-1.70 (m, 2H, SO$_2$CH$_2$CH$_2$), 1.40-1.25 (m, 4H, CH$_2$CH$_2$CH$_2$), 0.88 (t, $J = 7.1$ Hz, 3H, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 140.4, 134.1, 133.9, 128.0, 57.8, 30.3, 22.8, 22.2, 13.8$; IR (ATR): $\nu = 2957, 1314, 1137$ cm$^{-1}$; MS (EI) $m/z$ (%): 218 ($M^+$, 1), 153 (18), 152 (18), 149 (57), 148 (23), 147 (15), 131 (32), 125 (15), 111 (21), 99 (59), 97 (34), 85 (13), 84 (100), 71 (15), 70 (16), 69 (20), 55 (25); HRMS calcd. (%) for C$_8$H$_2$O$_2$S$_2$ (M$^+$-C$_6$H$_4$): 174.9887; found: 174.9885.

(Benzylsulfonyl)benzene (29m).$^{334}$ White solid; m.p. 144-146 °C; $R_f = 0.27$ (hexane/ethyl acetate: 4/1); $t_r = 14.9$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.65-7.55$ (m, 3H, ArH), 7.46 (t, $J = 7.7$ Hz, 2H, ArH), 7.35-7.20 (m, 3H, ArH), 7.08 (d, $J = 7.0$ Hz, 2H, ArH), 4.31 (s, 2H, CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 137.9, 133.8, 130.9$ (2C), 129.0 (2C), 128.8, 128.7 (2C), 128.6 (2C), 128.2, 63.0; IR (ATR): $\nu = 1302, 1125, 755$ cm$^{-1}$; MS (EI) $m/z$ (%): 232 ($M^+$, 3%), 91 (100).

1-bromo-4-((phenylsulfonyl)methyl)benzene (28n).$^{334}$ Off-white solid; m.p. 189-191 °C; $R_f = 0.57$ (hexane/ethyl acetate: 1/1); $t_r = 16.8$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.70-7.60$ (m, 3H, ArH), 7.55-7.45 (m, 2H, ArH), 7.45-7.35 (m, 2H, ArH), 7.00-6.90 (m, 2H, ArH), 4.26 (s, 2H, CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 137.8, 134.1, 132.5$ (2C), 131.9 (2C), 129.2 (2C), 127.3, 123.4, 62.3; IR (ATR): $\nu = 1270, 1114, 729$ cm$^{-1}$; MS (EI) $m/z$ (%): 312 ($M^+$Br$^{+}$, 3), 310 ($M^+$Br$^{+}$, 3), 171 (100), 169 (100), 90 (24), 89 (21).

((Cyclopropylmethyl)sulfonyl)benzene (28o).$^{335}$ Colorless oil; $R_f = 0.2$ (hexane/ethyl acetate: 4/1); $t_r = 12.9$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.00-7.90$ (m, 2H, ArH), 7.70-7.65 (m, 1H, ArH), 7.60-7.50 (m, 2H, ArH), 3.03 (d, $J = 7.2$ Hz, 2H, SO$_2$CH$_2$), 1.05-0.95 (m, 1H, CH$_2$CH$_2$), 0.60-0.50 (m, 2H, CH$_2$CH$_2$), 0.15-0.10 (m, 2H, CH$_2$CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 139.3, 133.7, 129.2$ (2C), 128.5 (2C), 61.4, 4.9, 4.4 (2C); IR

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Experimental Part

1-phenyl-2-(phenylsulfonyl)ethane (28p).\textsuperscript{336} White solid; m.p. 83-85 °C; \( R_t = 0.5 \) (hexane/ethyl acetate: 1/1); \( t_t = 16.5 \); \( ^1\)H NMR (300 MHz, CDCl\(_3\)); \( \delta = 7.95-7.85 \) (m, 4H, ArH), 7.70-7.60 (m, 2H, ArH), 7.54 (t, \( J = 7.7 \) Hz, 2H, ArH), 7.47 (t, \( J = 7.7 \) Hz, 2H, ArH), 4.74 (s, 2H, CH\(_2\)); \( ^{13}\)C NMR (75 MHz, CDCl\(_3\)); \( \delta = 188.1, 138.8, 138.6, 134.5, 129.4 \) (2C), 129.3 (2C), 129.2 (2C), 128.7 (2C), 127.8 (4C). IR (ATR): \( \nu = 1672, 1307, 1153 \) cm\(^{-1}\); MS (EI) m/z (%): 260 (M\(^+\), 0.6), 196 (31), 105 (100), 94 (11), 91 (10), 77 (51), 51 (15).

Sulfonyldibenzene (28q).\textsuperscript{226} White solid; m.p. 117-118 °C; \( R_t = 0.30 \) (hexane/ethyl acetate: 4/1); \( t_t = 14.57 \) min; \( ^1\)H NMR (300 MHz, CDCl\(_3\)); \( \delta = 8.00-7.90 \) (m, 4H, ArH), 7.60-7.55 (m, 6H, ArH); \( ^{13}\)C NMR (75 MHz, CDCl\(_3\)); \( \delta = 141.7 \) (2C), 133.3 (2C), 129.4 (4C), 127.8 (4C). IR (ATR): \( \nu = 3066, 1307, 1152 \) cm\(^{-1}\); MS (EI) m/z (%): 218 (M\(^+\), 34), 125 (100), 97 (14), 77 (32), 51 (17).

2-(phenylsulfonyl)benzo[d]thiazole (28r).\textsuperscript{265} White solid; m.p. 153-156 °C (ethanol); \( R_t = 0.30 \) (hexane/ethyl acetate: 4/1); \( t_t = 17.8 \); \( ^1\)H NMR (300 MHz, CDCl\(_3\)); \( \delta = 8.20-8.10 \) (m, 3H, ArH), 8.00-7.90 (m, 1H, ArH), 7.70-7.60 (m, 1H, ArH), 7.60-7.50 (m, 4H, ArH); \( ^{13}\)C NMR (75 MHz, CDCl\(_3\)); \( \delta = 167.4, 153.0, 138.6, 137.1, 134.7, 129.6 \) (2C), 129.0 (2C), 128.0, 127.6, 125.6, 122.3. IR (ATR): \( \nu = 1367, 1157, 719 \) cm\(^{-1}\); MS (EI) m/z (%): 275 (M\(^+\), 7), 211 (36), 210 (100), 207 (12), 77 (38).

2-(phenylsulfonyl)pyridine (28s).\textsuperscript{337} White solid; m.p. 81-83 °C; \( R_t = 0.53 \) (hexane/ethyl acetate: 1/1); \( t_t = 15.0 \); \( ^1\)H NMR (300 MHz, CDCl\(_3\)); \( \delta = 8.67 \) (ddd, \( J = 4.7, 1.7, 0.9 \) Hz, 1H, ArH), 8.21 (dt, \( J = 7.9, 1.1 \) Hz, 1H, ArH), 8.10-8.00 (m, 2H, ArH), 7.93 (td, \( J = 7.9, 1.7 \) Hz, 1H, ArH), 7.70-7.50 (m, 3H, ArH), 7.47 (ddd, \( J = 7.7, 4.7, 1.1 \) Hz, 1H, ArH); \( ^{13}\)C NMR (75 MHz, CDCl\(_3\)); \( \delta = 158.9, 150.6, 139.0, 138.2, 133.9, 129.2.

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(2C), 129.0 (2C), 127.0, 122.3; IR (ATR): \( \nu = 3085, 1305, 1150 \text{ cm}^{-1} \); MS (EI) \( m/z \) (%): 156 (15%), 155 (100), 154 (67), 78 (20), 77 (12), 51 (16).

**5-(phenylsulfonyl)thiophene-2-carbaldehyde (28i)**

Yellow solid; m.p. 69-71 °C; \( R_f = 0.47 \) (hexane/ethyl acetate: 1/1); \( t_c = 16.1; ^1H \text{ NMR (300 MHz, CDCl}_3): \delta = 9.94 \text{ (s, 1H, ArCHO, 8.05-8.00 (m, 2H, ArH), 7.72 (dd, } J = 11.0, 4.0 \text{ Hz, 2H, ArH), 7.70-7.60 (m, 1H, ArH), 7.60-7.50 (m, 2H, ArH);} ^13C \text{ NMR (75 MHz, CDCl}_3): \delta = 182.9, 151.3, 149.2, 140.8, 134.8, 134.2, 133.0, 129.8 (2C), 127.8 (2C); IR (ATR): \( \nu = 1671, 1323, 1151 \text{ cm}^{-1}; \) MS (EI) \( m/z \) (%): 253 (M^+ + 1, 11), 252 (M^+, 64), 207 (36), 159 (19), 125 (100), 97 (15), 77 (45), 51 (23).

**4-(phenylsulfonyl)butan-2-one (28u)**

Colorless oil; \( R_f = 0.27 \) (hexane/ethyl acetate: 1/1); \( t_c = 13.7; ^1H \text{ NMR (300 MHz, CDCl}_3): \delta = 7.95-7.90 \text{ (m, 2H, ArH), 7.75-7.65 (m, 1H, ArH), 7.65-7.55 (m, 2H, ArH), 3.45-3.35, (m, 2H, SO}_2\text{CH}_3), 3.00-2.90 (m, 2H, CH}_2\text{CO), 2.19 (s, 3H, CH}_3); ^13C \text{ NMR (75 MHz, CDCl}_3): \delta = 203.8, 139.1, 134.1, 129.5 (2C), 128.1 (2C), 50.7, 36.0, 30.0; IR (ATR): \( \nu = 1718, 1305, 1136 \text{ cm}^{-1}; \) MS (EI) \( m/z \) (%): 184 (42), 142 (58), 136 (14), 125 (31), 110 (11), 105 (35), 78 (40), 77 (100), 70 (28), 55 (80).

**3-(phenylsulfonyl)propanoic acid (28v)**

White solid; \( R_f = 0.43 \) (ethyl acetate/methanol: 2/1); m.p. 125-127 °C (ethanol); \( t_c = 13.9; ^1H \text{ NMR (300 MHz, CD}_2\text{OD): \delta = 8.00-7.90 \text{ (m, 2H, ArH), 7.80-7.70 (m, 1H, ArH), 7.65-7.55 (m, 2H, ArH), 3.50-3.40 (m, 2H, SO}_2\text{CH}_3), 2.70-2.60 (m, 2H, CH}_2\text{CO); ^13C \text{ NMR (75 MHz, CD}_2\text{OD): \delta = 172.2, 139.9, 135.3, 130.6, 129.3 (2C), 129.2 (2C), 52.3, 28.5; IR (ATR): \( \nu = 1701, 1320, 1156 \text{ cm}^{-1}; \) MS (EI) \( m/z \) (%): 141 (31), 125 (54), 105 (10), 104 (74), 90 (52), 78 (19), 77 (100), 62 (36), 55 (30), 51 (32).

**Methyl 3-(phenylsulfonyl)propanoate (28w)**

Colorless oil; \( R_f = 0.47 \) (hexane/ethyl acetate: 1/1); \( t_c = 14.0; ^1H \text{ NMR (300 MHz, CDCl}_3): \delta = 7.95-7.85 \text{ (m, 2H, ArH), 7.75-7.65}

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(m, 1H, ArH), 7.65-7.55 (m, 2H, ArH), 3.64 (s, 3H, OCH3), 3.50-3.40 (m, 2H, SO2CH3), 2.80-2.70 (m, 2H, CH2CO); 13C NMR (75 MHz, CDCl3): δ = 170.5, 138.5, 134.1, 129.5 (2C), 128.2 (2C), 52.4, 51.5, 27.7; IR (ATR): ν = 2926, 1735, 1307, 1148 cm⁻¹; MS (EI) m/z (%): 228 (M⁺, 1), 141 (29), 125 (56), 104 (66), 87 (50), 78 (20), 77 (100), 59 (34), 51 (33).

3-(phenylsulfonyl)propanenitrile (28x). White solid; Rf = 0.53 (hexane/ethyl acetate: 1/1); m.p. 91-93 °C; tR = 13.4; 1H NMR (300 MHz, CDCl3): δ = 8.00-7.90 (m, 2H, ArH), 7.60-7.70 (m, 1H, ArH), 7.70-7.60 (m, 2H, ArH), 3.45-3.35 (m, 2H, SO2CH3), 2.90-2.80 (m, 2H, CH2CN); 13C NMR (75 MHz, CDCl3): δ = 137.6, 134.9, 129.9 (2C), 128.4 (2C), 116.1, 51.2, 12.1; IR (ATR): ν = 2237, 1305, 1153 cm⁻¹; MS (EI) m/z (%): 195 (M⁺, 21), 141 (66), 78 (11), 77 (100), 51 (27).

Benzenesulfonamide (28y). White solid; Rf = 0.4 (hexane/ethyl acetate: 1/1); m.p. 149-151 °C (ethanol); tR = 12.3; 1H NMR (300 MHz, DMSO-d6): δ = 7.90-7.80 (m, 2H, ArH), 7.65-7.50 (m, 3H, ArH), 7.37 (br s, 2H, NH2); 13C NMR (75 MHz, DMSO-d6): δ = 144.2, 131.8, 128.9 (2C), 125.6 (2C); IR (ATR): ν = 3354, 1330, 1153, 754 cm⁻¹; MS (EI) m/z (%): 157 (M⁺, 43), 141 (28), 94 (19), 93 (36), 77 (100), 51 (32), 50 (12).

E-(2-(phenylsulfonyl)vinyl)benzene (28z). Yellow oil; Rf = 0.4 (hexane/ethyl acetate: 4/1); tR = 16.7; 1H NMR (300 MHz, CDCl3): δ = 8.00-7.95 (m, 2H, ArH), 7.69 (d, J = 15.4 Hz, 1H, SO2CH=CH), 7.65-7.35 (m, 8H, ArH), 6.86 (d, J = 15.4 Hz, 1H, CH=CHSO2); 13C NMR (75 MHz, CDCl3): δ = 142.7, 140.8, 135.3, 132.5, 131.4, 129.5 (2C), 129.2 (2C), 128.7 (2C), 127.8 (2C), 127.4; IR (ATR): ν = 3060, 1304, 1143, 743 cm⁻¹; MS (EI) m/z (%): 244 (M⁺, 46%), 207 (17), 179 (23), 177 (21), 119 (52), 103 (65), 102 (100), 91 (96), 77 (79), 51 (34).

4.3. Pd-CATALYSED SYNTHESIS OF ARYL SULFIDES

A solution of aryl boronic acid (1 mmol), sodium metabisulfite (2.2 mmol), PdCl2 (0.01 mmol) and ligand 20a (0.03 mmol) in 2 mL of DES was stirred for 12 h at 80 °C. Then, molecular iodine was added (2 mmol) and the mixture was stirred

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for 20 minutes. After that time, the corresponding nucleophile or radical scavenger was added (2 mmol), and the mixture was allowed to stir for 12 additional hours until the end of the reaction. The mixture was quenched with water and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried over MgSO$_4$, followed by evaporation under reduced pressure to remove the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products 29/30.

1-(phenylthio)naphthalen-2-ol (29a). Yellow solid; $R_t = 0.57$ (hexane/ethyl acetate: 4/1); m.p. 82-84 °C; $t_t = 16.4$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.2$ (dd, $J = 8.5, 0.6$ Hz, 1H, ArH), 7.91 (d, $J = 8.9$ Hz, 1H, ArH), 7.81 (d, $J = 8.0$ Hz, 1H, ArH), 7.49 (ddd, $J = 8.5, 6.9, 1.4$ Hz, 1H, ArH), 7.40-7.30 (m, 2H, ArH + OH), 7.20-7.05 (m, 4H, ArH), 7.05-7.00 (m, 2H, ArH); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 157.0, 135.4, 135.3, 129.5, 128.6, 128.0, 126.4 (2C), 125.9, 124.7, 123.8, 116.9, 108.0; IR (ATR): $\nu = 3398, 3056, 1195$ cm$^{-1}$; MS (EI) $m/z$ (%): 253 (M$^+$1, 22), 252 (M$^+$, 100), 219 (12), 191 (21), 147 (19), 146 (37).

1-((4-hydroxyphenyl)thio)naphthalene-2-ol (29b): White solid, $R_t = 0.2$ (hexane/ethyl acetate: 4/1); m.p. 146-148 °C; $t_t = 18.9$; $^1$H NMR (300 MHz, CD$_2$OD): $\delta = 8.33$ (d, $J = 8.5$ Hz, 1H, ArH), 7.83 (d, $J = 8.9$ Hz, 1H, ArH), 7.76 (d, $J = 8.0$ Hz, 1H, ArH), 7.44 (ddd, $J = 8.3, 7.0, 1.2$ Hz, 1H, ArH), 7.29 (ddd, $J =$ 8.0, 7.0, 1.2 Hz, 1H, ArH), 7.25 (d, $J = 8.9$ Hz, 1H, ArH), 7.05-6.95 (m, 2H, ArH), 6.70-6.60 (m, 2H, ArH); $^{13}$C NMR (75 MHz, CD$_2$OD): $\delta =$ 158.6, 157.1, 137.1, 133.0, 130.8, 130.3 (2C), 129.4, 128.4, 127.1, 125.8, 124.4, 118.6, 117.0 (2C), 111.6; IR (ATR): $\nu = 3357, 3296, 1169, 748$ cm$^{-1}$; MS (EI) $m/z$ (%): 268 (M$^+$, 100), 175 (34), 146 (57), 144 (12), 115 (12), 94 (17); HRMS calcd. (%) for C$_{10}$H$_{12}$O$_2$S: 268.0558; found: 268.0542.

3,5-dimethyl-4-(phenylthio)phenol (29c). White solid; $R_t = 0.33$ (hexane/ethyl acetate: 4/1); m.p. 98-101 °C; $t_t = 15.4$; $^1$H NMR (300 MHz, CD$_2$OD): $\delta =$ 7.25-7.15 (m, 2H, ArH), 7.10-7.00 (m, 1H, ArH); 6.95-6.90 (m, 2H, ArH), 6.70 (s, 2H, ArH), 5.19 (s, 1H, OH), 2.39 (s, 6H, 2xCH$_3$); $^{13}$C NMR (75 MHz, CD$_2$OD): $\delta =$ 156.2, 146.1 (2C), 138.7, 129.0 (2C), 125.3 (2C), 124.6, 121.7, 115.5 (2C), 22.0 (2C); IR (ATR): $\nu =$ 3280, 2919, 690 cm$^{-1}$; MS (EI) $m/z$ (%): 231 (M$^+$+1, 17), 230 (M$^+$, 100), 152 (23), 151 (10), 91 (15).
N,N-dimethyl-4-(phenylthio)aniline (29d). White solid; \( R_f = 0.53 \) (hexane/ethyl acetate: 4/1); m.p. 63-65 °C; \( t_r = 15.54 \) min; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.40-7.35 \) (m, 2H, ArH), 7.20-7.15 (m, 2H, ArH), 7.10-7.00 (m, 3H, ArH), 6.70-6.65 (m, 2H, ArH), 2.95 (s, 6H, 2\( \times \)CH\(_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 150.7, 140.4, 136.2 \) (2C), 128.2 (2C), 126.9 (2C), 125.0, 117.5, 113.1 (2C), 40.4 (2C); IR (ATR): \( v = 2898, 1509, 1368, 739 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 229 (M\(^+\), 100), 228 (18), 197 (23), 196 (24), 184 (14), 152 (21).

Phenyl(2,4,6-trimethoxyphenyl)sulfane (29e). White solid; \( R_f = 0.30 \) (hexane/ethyl acetate: 4/1); m.p. 119-121 °C; \( t_t = 16.5; \) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.20-7.10 \) (m, 2H, ArH), 7.05-7.00 (m, 3H, ArH), 6.21 (s, 2H, ArH), 3.86 (s, 3H, OCH\(_3\)), 3.79 (s, 6H, 2\( \times \)OCH\(_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 163.0, 162.6 \) (2C), 138.8, 128.6 (2C), 125.7 (2C), 124.4, 98.8, 91.3 (2C), 56.4, 55.5; IR (ATR): \( v = 3010, 1576, 1122 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 276 (M\(^+\), 100), 228 (12).

3-(Phenylthio)-1H-indole (29f). White solid; \( R_f = 0.20 \) (hexane/ethyl acetate: 4/1); m.p. 147-149 °C (ethanol); \( t_t = 16.9; \) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 8.34 \) (br s, 1H, NH), 7.61 (d, \( J = 7.49 \) Hz, 1H, ArH), 7.44 (d, \( J = 2.6 \) Hz, 1H, ArH), 7.41 (d, \( J = 8.2 \) Hz, 1H, ArH), 7.30-7.20 (m, 1H, ArH), 7.20-7.00 (m, 6H, ArH); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 139.3, 136.6, 130.8, 129.2, 128.8 \) (2C), 126.0 (2C), 124.9, 123.2, 121.0, 119.8, 111.7, 102.9; IR (ATR): \( v = 3406, 1338, 737 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 225 (M\(^+\), 100), 224 (40), 223 (18), 193 (20), 148 (13), 77 (12).

1,2-diphenylsulfane (30a). White solid; \( R_f = 0.7 \) (hexane/ethyl acetate: 4/1); m.p. 57-59 °C; \( t_t = 13.9; \) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 7.55-7.45 \) (m, 4H, ArH), 7.35-7.15 (m, 6H, ArH); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 137.2 \) (2C), 129.2 (4C), 127.7 (4C), 127.3 (2C); IR (ATR): \( v = 3028, 2922, 686 \) cm\(^{-1}\); MS (EI) \( m/z \) (%): 219 (M\(^+\)+1, 15), 218 (100), 185 (16), 154 (17), 109 (66), 65 (18).

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1,2-bis(4-methoxyphenyl)disulfane (30b). Yellow oil; $R_f = 0.43$ (hexane/ethyl acetate: 4:1); $t_r = 17.2$; $^1H$ NMR (300 MHz, CDCl$_3$): $\delta = 7.45-7.35$ (m, 4H, ArH), 6.85-6.80 (m, 4H, ArH), 3.79 (s, 6H, 2xOCH$_3$); $^{13}C$ NMR (75 MHz, CDCl$_3$): $\delta = 160.0$ (2C), 132.8 (4C), 128.6 (2C), 114.7 (4C), 55.5 (2C); IR (ATR): $\nu = 2833, 1241, 608$ cm$^{-1}$; MS (EI) $m/z$ (%): 278 (M$^+$, 64), 139 (100), 125 (11), 96 (10).

2-((phenylthio)methyl)tetrahydro-2H-pyran (30c). Yellow oil; $R_f = 0.67$ (hexane/ethyl acetate: 4:1); $t_r = 12.9$; $^1H$ NMR (300 MHz, CDCl$_3$): $\delta = 7.40-7.30$ (m, 2H, ArH), 7.30-7.25 (m, 2H, ArH), 7.20-7.10 (m, 1H, ArH), 4.02 (ddd, $J = 11.3, 4.0, 2.0$ Hz, 1H, CHO), 3.50-3.35 (m, 2H, CH$_2$O), 3.09 (dd, $J = 13.2, 6.6$ Hz, 1H, HHCHS), 2.93 (dd, $J = 13.2, 5.8$ Hz, 1H, HHCHS), 1.90-1.70 (m, 2H, CH$_2$Cy), 1.65-1.45 (m, 3H, CH$_2$Cy), 1.45-1.25 (m, 1H, CH$_3$Cy); $^{13}C$ NMR (75 MHz, CDCl$_3$): $\delta = 136.7, 128.9$ (2C), 128.8 (2C), 125.8, 76.3, 68.7, 39.5, 31.2, 25.8, 23.2; IR (ATR): $\nu = 2933, 1088, 689$ cm$^{-1}$; MS (EI) $m/z$ (%): 208 (M$^+$, 40), 124 (28), 85 (100), 67 (17), 57 (15).

2-((phenylthio)methyl)tetrahydrofuran (30d). Yellow oil; $R_f = 0.50$ (hexane/ethyl acetate: 4:1); $t_r = 12.3$; $^1H$ NMR (300 MHz, CDCl$_3$): $\delta = 7.45-7.35$ (m, 2H, ArH), 7.35-7.25 (m, 2H, ArH), 7.20-7.10 (m, 1H, ArH), 4.10-4.00 (m, 1H, CHO), 3.95-3.85 (m, 1H, HCHO), 3.80-3.70 (m, 1H, HCHO), 3.15 (ddd, $J = 13.0, 5.8$ Hz, 1H, HHCHS), 2.97 (dd, $J = 13.0, 6.8$ Hz, 1H, HHCHS), 2.10-2.00 (m, 2H, CH$_2$CH$_2$O), 2.00-1.80 (m, 1H, HHCHO), 1.75-1.60 (m, 1H, HCHCHO); $^{13}C$ NMR (75 MHz, CDCl$_3$): $\delta = 136.5, 129.2$ (2C), 126.0, 77.7, 68.4, 39.0, 31.0, 25.9; IR (ATR): $\nu = 2865, 1053, 690$ cm$^{-1}$; MS (EI) $m/z$ (%): 194 (M$^+$, 39), 124 (26), 123 (11), 71 (100).

5-((phenylthio)methyl)dihydrofuran-2-(3H)-one (30e). Yellow oil; $R_f = 0.50$ (hexane/ethyl acetate: 1:1); $t_r = 14.4$; $^1H$ NMR (300 MHz, CDCl$_3$): $\delta = 7.45-7.35$ (m, 2H, ArH), 7.35-7.25 (m, 2H, ArH), 7.25-7.15 (m, 1H, ArH), 4.60 (ddd, $J = 14.1, 7.2, 5.0$ Hz, 1H, CHO), 3.32 (dd, $J = 13.0, 5.0$ Hz, 1H, HHCHS), 3.04 (dd, $J = 13.9, 7.4$ Hz, 1H, CHO).

HCHS), 2.65-2.45 (m, 2H, CH₂CO), 2.45-2.30 (m, 1H, HCHCH), 2.10-1.90 (m, 1H, HCHCH); ¹³C NMR (75 MHz, CDCl₃): δ = 176.5, 134.7, 130.1 (2C), 129.1 (2C), 126.9, 78.5, 38.5, 28.4, 26.9; IR (ATR): ν = 1767, 1168, 690 cm⁻¹; MS (EI) m/z (%): 209 (M⁺+1, 13), 208 (M⁺, 97), 124 (24), 123 (100), 110 (17), 109 (11), 85 (84), 77 (12), 51 (10).

4.4. SYNTHESIS OF TRIARYLBISMUTHINES

For commercially available organomagnesium reagents, a solution of BiCl₃ in dry THF (1 M) was added dropwise over a solution of ArMgBr in THF or Et₂O (1 M) under argon atmosphere with magnetic stirring. Once the addition was completed, the was heated to reflux for 12 h. Then, the reaction was allowed to reach room temperature and was slowly poured over a cold solution of NH₄Cl (sat. aq.). The aqueous solution was extracted with Et₂O (3 x 15 mL). The combined organic phases were dried over MgSO₄ and the solvent was removed under reduced pressure.349

For non-commercially available organomagnesium reagents, the corresponding aryl iodide (6.2 mmol) was dissolved in dry THF and cooled to -78 °C in an acetone bath. A n-butyllithium solution (2.5 M, 6.2 mmol) was added dropwise and the mixture was stirred at that temperature for 1 h. Then, a solution of BiCl₃ (2 mmol) in dry THF was added dropwise and the mixture was slowly allowed to reach room temperature. The corresponding mixture was stirred overnight at rt and then quenched with sat. aq, NaHCO₃. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers washed with H₂O and brine. The organic layer was dried over MgSO₄, filtered and reduced under reduced pressure. Ar₃Bi was usually purified by recrystallization from hot EtOH or by flash chromatography using a mixture of EtOAc and hexanes.350

4.5. SYNTHESIS OF SULFONAMIDES

A solution of Ar₃Bi (0.2 mmol), sodium metabisulfite (1.32 mmol), CuCl (0.006 mmol) and the corresponding nitrocompound (1.2 mmol) in 1.5 mL of DES

was stirred for 24 h at 80 °C. Once the reaction was completed, water was added to dissolve the DES phase. That aqueous suspension was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products 33. Alternatively, products could be retrieved by quenching the reaction mixture with NaHCO₃ and filtering the suspension. The filtrate was rinsed with distilled water to afford products 33 in high purity, although with lower yields than in the previous method due to the slight solubility of sulfonamides in water:

**N-phenylbenzenesulfonylamide (33a)**: Cream solid; m.p. 101-103 °C; Rf = 0.63 (hexane/ethyl acetate: 1/1); tR = 15.0; 1H NMR (400 MHz, CDCl₃): δ = 7.85-7.80 (m, 2H, ArH), 7.55-7.50 (m, 1H, NH), 7.45-7.40 (m, 2H, ArH), 7.30-7.20 (m, 3H, ArH); 13C NMR (101 MHz, CDCl₃): δ = 139.0, 136.5, 133.1, 129.4 (2C), 129.2 (2C), 127.3 (2C), 125.5, 121.8 (2C); IR (ATR): v = 3204, 1302, 1151, 723 cm⁻¹; MS (EI) m/z (%): 234 (M⁺+1, 12), 233 (M⁺, 86), 168 (40), 141 (24), 93 (12), 92 (100), 77 (51), 65 (33).

**N-(p-tolyl)benzenesulfonylamide (33b)**: White solid; m.p. 101-103 °C; Rf = 0.23 (hexane/ethyl acetate: 4/1); tR = 15.8; 1H NMR (300 MHz, CDCl₃): δ = 7.80-7.75 (m, 2H, ArH), 7.55-7.45 (m, 1H, ArH), 7.45-7.35 (m, 2H, ArH), 7.24 (br s, 1H, NH), 7.05-6.95 (m, 4H, ArH), 2.25 (s, 3H, CH₃); 13C NMR (101 MHz, CDCl₃): δ = 139.1, 135.5, 133.8, 133.0, 129.9 (2C), 129.1 (2C), 127.4 (2C), 122.4 (2C); 20.9; IR (ATR): v = 3256, 1328, 1159, 687 cm⁻¹; MS (EI) m/z (%): 247 (M⁺+57), 106 (100), 79 / 18, 77 (36), 51 (10).

**N-(4-methoxyphenyl)benzenesulfonylamide (33c)**: Brown solid; m.p. 87-89 °C; Rf = 0.63 (hexane/ethyl acetate: 1/1); tR = 16.9; 1H NMR (300 MHz, CDCl₃): δ = 7.75-7.70 (m, 2H, ArH), 7.60-7.50 (m, 1H, ArH), 7.45-7.40 (m, 2H, ArH), 7.05-6.95 (m, 2H, ArH), 6.86 (s, 1H, NH), 6.80-6.70 (m, 2H, ArH), 3.74 (s, 3H, OCH₃); 13C NMR

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(101 MHz, CDCl₃): δ = 158.1, 139.0, 133.0, 129.1 (2C), 128.9, 127.4 (2C), 125.6 (2C), 114.5 (2C), 55.5; IR (ATR): ν = 3259, 1508, 1326, 1155 cm⁻¹; MS (El) m/z (%): 263 (M⁺, 22), 122 (100).

N-(4-aminophenyl)benzenesulfonamide (33d):³⁵³ White solid; m.p. 168-170 °C; Rᵣ = 0.30 (hexane/ethyl acetate: 1/1); tᵣ = 13.4; ¹H NMR (400 MHz, DMSO-d₆): δ = 9.48 (s, 1H, NH), 7.65-7.60 (m, 2H, ArH), 7.60-7.50 (m, 2H, ArH), 6.70-6.65 (m, 2H, ArH), 6.45-6.35 (m, 2H, ArH), 5.15 (br s, 2H, NH₂); ¹³C NMR (101 MHz, DMSO-d₆): δ = 146.1, 139.7, 132.4, 128.9 (2C), 126.7 (2C), 125.5, 124.6 (2C), 114.2 (2C); IR (ATR): ν = 3395, 1653, 1260, 1160 cm⁻¹; MS (El) m/z (%): 248 (M⁺, 15), 107 (100), 80 (13).

N-(4-hydroxyphenyl)benzenesulfonamide (33e):³⁵⁴ White solid; m.p. 156-158 °C; Rᵣ = 0.40 (hexane/ethyl acetate: 1/1); tᵣ = 18.0; ¹H NMR (300 MHz, DMSO-d₆): δ = 9.73 (br s, 1H, NH), 9.31 (br s, 1H, OH), 7.70-7.65 (m, 2H, ArH), 6.60-6.45 (m, 3H, ArH), 6.85-6.75 (m, 2H, ArH), 6.65-6.55 (m, 2H, ArH); ¹³C NMR (101 MHz, DMSO-d₆): δ = 154.9, 139.5, 132.6, 129.0 (2C), 128.4, 126.7 (2C), 124.1 (2C), 115.5 (2C); IR (ATR): ν = 3243, 1320, 1190, 686 cm⁻¹; MS (El) m/z (%): 249 (M⁺, 36), 108 (100), 81 (15), 77 (14).

N-(4-chlorophenyl)benzenesulfonamide (33f):³⁵⁵ White solid; m.p. 116-118 °C; Rᵣ = 0.57 (hexane/ethyl acetate: 1/1); tᵣ = 16.4; ¹H NMR (300 MHz, CDCl₃): δ = 7.81 (ddd, J = 7.1, 3.1, 1.8 Hz, 2H, ArH), 7.60-7.50 (m, 2H, ArH + NH), 7.50-7.40 (m, 2H, ArH), 7.20-7.15 (M, 2H, ArH), 7.10-7.00 (M, 2H, ArH); ¹³C NMR (101 MHz, CDCl₃): δ = 138.7, 135.1, 133.4, 131.1, 129.5 (2C), 129.3 (2C), 127.3 (2C), 123.1 (2C); IR (ATR): ν = 3241, 1374, 1160, 688 cm⁻¹; MS (El) m/z (%): 269 (M⁺ Cl³⁷, 27), 267 (M⁺ Cl³⁵, 71), 141 (15), 128 (33), 126 (100), 101 (10), 99 (28), 77 (40), 51 (16).

**N-(4-acetylphenyl)benzenesulfonamide (33g)**: Brown solid; m.p. 125-127 °C; $R_t = 0.43$ (hexane/ethyl acetate: 1/1); $t_r = 18.2$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.90$-$7.80$ (m, 4H, ArH), 7.63 (s, 1H, NH), 7.60-$7.55$ (m, 1H, ArH), 7.50-$7.45$ (m, 2H, ArH), 7.25-$7.15$ (m, 2H, ArH), 2.53 (s, 3H, CH$_3$CO); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 197.1, 141.2, 138.9, 133.6, 133.5, 130.1 (2C), 129.4 (2C), 127.3 (2C), 119.2 (2C), 26.6; IR (ATR): $\nu = 3347, 1429, 1129, 695$ cm$^{-1}$; MS (EI) $m/z$ (%): 275 (M$^+$, 53), 261 (15), 260 (100), 119 (12), 77 (38).

**N-(3-chlorophenyl)benzenesulfonamide (33h)**: White solid; m.p. 114-116 °C; $R_t = 0.67$ (hexane/ethyl acetate: 1/1); $t_r = 16.22$ min. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.90$-$7.85$ (m, 2H, ArH), 7.74 (s, 1H, NH), 7.60-$7.55$ (m, 1H, ArH), 7.50-$7.45$ (m, 2H, ArH), 7.20-$7.10$ (m, 2H, ArH), 7.10-$7.00$ (m, 2H, ArH); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 138.6, 137.9, 135.0, 133.5, 130.4, 129.3 (2C), 127.3 (2C), 125.4, 121.1, 119.1; IR (ATR): $\nu = 3195, 1312, 1152, 683$ cm$^{-1}$; MS (EI) $m/z$ (%): 269 (M$^+$ Cl$^-$, 21), 267 (M$^+$ Cl$^-$, 57), 203 (12), 202 (17), 168 (25), 167 (11), 141 (59), 126 (25), 99 (24), 91 (11), 78 (11), 77 (100).

**N,N-(1,3-phenylene)dibenzenesulfonamide (33i)**: White solid; m.p. 162-165 °C; $R_t = 0.37$ (hexane/ethyl acetate: 1/1); $t_r = 16.03$ min. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta = 10.30$ (s, 2H, 2xNH), 7.70-$7.65$ (m, 4H, ArH), 7.60 ($ap$ t, $J = 7.4$ Hz, 2H, ArH), 7.51 ($ap$ t, $J = 7.6$ Hz, 4H, ArH), 7.11 (t, $J = 1.0$ Hz, 1H, ArH), 7.02 (t, $J = 8.1$ Hz, 1H, ArH), 6.69 (dd, $J = 8.1$, 1.9 Hz, 2H, ArH); $^{13}$C NMR (101 MHz, DMSO-d$_6$): $\delta =$ 139.3 (2C), 138.5 (2C), 132.9 (2C), 129.8, 129.2 (4C), 126.6 (4C), 115.2 (2C), 110.8; IR (ATR): $\nu = 3404, 1324, 1152, 688$ cm$^{-1}$; MS (DIP) $m/z$ (%): 388 (M$^+$, 43), 183 (100), 182 (35), 181 (11), 167 (19), 166 (59), 156 (26), 141 (13), 125 (15), 105 (15), 79 (14), 78 (17), 77 (83), 51 (18); HRMS calcd. (%) for C$_{18}$H$_{16}$N$_2$O$_4$S$_2$: 388.0551; found: 388.0549.

**N-(2-chlorophenyl)benzenesulfonamide (33j)**: White solid; m.p. 146-148 °C; $R_t = 0.63$ (hexane/ethyl acetate: 1/1); $t_r = 15.2$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 7.80-$7.75$ (m, 2H, ArH), 7.67 (dd, $J = 8.5$, 1.5 Hz, 1H, ArH), 7.60-$7.50$ (m, 1H, ArH), 7.45-$7.40$ (m, 2H, ArH), 7.30-$7.20$ (m, 2H, ArH), 7.10-$7.05$ (m, 1H, ArH), 7.00 (s, 1H, NH); $^{13}$C NMR (101

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MHz, CDCl₃): δ = 139.0, 133.4, 129.5, 129.2 (2C), 128.1 (2C), 127.4 (2C), 126.2, 125.4, 122.8; IR (ATR): ν = 3247, 1332, 1157 cm⁻¹; MS (El) m/z (%): 269 (M⁺ Cl⁺, 32), 267 (M⁺ Cl₁, 96), 168 (13), 167 (18), 141 (54), 128 (33), 126 (100), 102 (15), 99 (45), 90 (11), 77 (87), 63 (12).

N-(2-bromophenyl)benzenesulfonamide (33k) ¹⁴² White solid; m.p. 113-115 °C; Rᵣ = 0.43 (hexane/ethyl acetate: 7/3); tᵣ = 16.1; ¹H NMR (300 MHz, CDCl₃): δ = 7.80-7.75 (m, 2H, ArH), 7.68 (dd, J = 8.2, 1.5 Hz, 1H, ArH), 7.60-7.50 (m, 1H, ArH), 7.45-7.35 (m, 3H, ArH), 7.28 (ddd, J = 8.2, 7.5, 1.5 Hz, 1H, ArH), 6.99 (br s, 1H, NH), 6.98 (ddd, J = 8.0, 7.5, 1.5 Hz, 1H, ArH); ¹³C NMR (101 MHz, CDCl₃): δ = 138.9, 134.7, 133.4, 132.7, 129.2 (2C), 128.7, 127.4 (2C), 126.6, 123.1, 116.1; IR (ATR): ν = 1333, 1159, 722 cm⁻¹; MS (El) m/z (%): 314 (M⁺ Br⁺ + 1, 14), 313 (M⁺ Br⁺, 98), 312 (M⁺ Br⁺ + 1, 13), 311 (M⁺ Br⁺, 95), 172 (98), 170 (100), 145 (13), 143 (17), 141 (58), 125 (29), 91 (86), 90 (13), 77 (96), 65 (10), 64 (19), 63 (22), 51 (31).

N-(naphtalen-2-yl)benzenesulfonamide (331) ¹⁴⁵ White solid; m.p. 96-98 °C; Rᵣ = 0.63 (hexane/ethyl acetate: 1/1); tᵣ = 18.8; ¹H NMR (300 MHz, CDCl₃): δ = 7.90-7.80 (m, 2H, ArH), 7.75-7.65 (m, 3H, ArH), 7.58 (br s, 1H, NH), 7.56 (d, J = 2.2 Hz, 1H, ArH), 7.50-7.35 (m, 5H, ArH), 7.25 (dd, J = 8.9, 2.2 Hz, 1H, ArH); ¹³C NMR (101 MHz, CDCl₃): δ = 139.0, 134.1, 133.7, 133.2, 131.2, 129.5, 129.2 (2C), 127.7, 127.6, 127.4 (2C), 126.8, 125.6, 121.2, 118.6; IR (ATR): ν = 3189, 1321, 1148, 648 cm⁻¹; MS (El) m/z (%): 283 (M⁺, 51), 142 (72), 115 (100), 110 (11), 77 (16).

N-cyclohexylbenzenesulfonamide (33m) ¹⁴⁶ White solid; m.p. 81-83 °C; Rᵣ = 0.67 (hexane/ethyl acetate: 1/1); tᵣ = 14.8; ¹H NMR (300 MHz, CDCl₃): δ = 7.95-7.85 (m, 2H, ArH), 7.60-7.50 (m, 3H, ArH), 4.46 (d, J = 6.3 Hz, 1H, CH/NH), 3.17 (br s, 1H, NH), 1.80-1.75 (m, 2H, CH₂/CH₂), 1.70-1.60 (m, 2H, CH₂/Cy), 1.65-1.50 (m, 1H, CH₂/Cy), 1.30-1.10 (m, 5H, CH₂/Cy); ¹³C NMR (101 MHz, CDCl₃): δ = 141.6, 132.6, 129.2 (2C), 127.0 (2C), 52.8, 34.1 (2C), 25.3, 24.8; IR (ATR): ν = 3278, 2929, 1707.

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1322, 1159 cm<sup>-1</sup>; MS (EI) <sup>m/z</sup>: 239 (M<sup>+</sup>, 32), 197 (12), 196 (100), 141 (44), 98 (15), 77 (46).

4-methyl-N-phenylbenzenesulfonamide (33n)<sup>359</sup> White solid; m.p. 98-100 °C; R<sub>f</sub> = 0.37 (hexane/ethyl acetate: 1/1); t<sub>r</sub> = 16.0; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.70-7.60 (m, 2H, ArH), 7.30-7.20 (m, 5H, ArH + NH), 7.15-7.05 (m, 3H, ArH), 2.37 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 144.0, 136.7, 136.3, 129.8 (2C), 129.4 (2C), 127.4 (2C), 125.5, 121.7 (2C), 21.7; IR (ATR): ν = 3236, 1335, 1153, 753 cm<sup>-1</sup>; MS (EI) <sup>m/z</sup>: 248 (M<sup>+</sup> + 1, 11), 247 (M<sup>+</sup>, 69), 182 (22), 168 (14), 155 (47), 92 (55), 91 (100), 65 (41).

N-phenylnaphtalene-1-sulfonamide (33o)<sup>359</sup> White solid; m.p. 149-151 °C; R<sub>f</sub> = 0.43 (hexane/ethyl acetate: 7/3); t<sub>r</sub> = 20.6; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.76 (dd, J = 8.7, 0.7 Hz, 1H, ArH), 8.04 (d, J = 8.3 Hz, 1H, ArH), 7.94 (d, J = 8.1 Hz, 1H, ArH), 7.68 (ddd, J = 8.6, 7.0, 1.1 Hz, 1H, ArH), 7.61 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H, ArH), 7.46 (dd, J = 8.1, 7.5 Hz, 1H, ArH), 7.22 (s, 1H, NH), 7.15-7.10 (m, 2H, ArH), 7.05-7.00 (m, 1H, ArH), 7.00-6.95 (m, 2H, ArH); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 136.4, 134.8, 134.3, 134.1, 130.5, 129.3 (3C), 128.7, 128.3, 127.0, 125.4, 124.3, 124.2, 121.7 (2C); IR (ATR): ν = 3234, 1322, 1160, 692 cm<sup>-1</sup>; MS (EI) <sup>m/z</sup>: 283 (M<sup>+</sup>, 29), 219 (16), 218 (56), 217 (15), 128 (20), 127 (100), 92 (14).

4-methoxy-N-phenylbenzenesulfonamide (33p)<sup>359</sup> White solid; m.p. 105-107 °C; R<sub>f</sub> = 0.60 (hexane/ethyl acetate: 1/1); t<sub>r</sub> = 17.3; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.72 (d, J = 8.6 Hz, 2H, ArH), 7.22 (ap t, J = 7.6 Hz, 2H, ArH), 7.15-7.05 (m, 3H, ArH), 6.87 (d, J = 8.6 Hz, 2H, ArH), 3.81 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 163.2, 136.8, 130.7, 129.6 (2C), 129.4 (2C), 125.3, 121.7 (2C), 114.3 (2C), 55.7; IR (ATR): ν = 3255, 1336, 1152, 695 cm<sup>-1</sup>; MS (EI) <sup>m/z</sup>: 263 (M<sup>+</sup>, 61), 171 (100), 123 (21), 107 (50), 92 (35), 77 (32), 65 (20), 64 (12).

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**3,4,5-trimethoxy-N-phenylbenzenesulfonamide (33q):** White solid; m.p. 121-123 °C; Rf = 0.50 (hexane/ethyl acetate: 1/1); t1 = 20.4; 1H NMR (400 MHz, CDCl3): δ = 7.51 (s, 1H, NH), 7.30-7.20 (m, 2H, ArH), 7.15-7.10 (m, 3H, ArH), 7.01 (s, 2H, ArH), 3.84 (s, 3H, OCH3), 3.74 (s, 6H, 2xOCH3); 13C NMR (101 MHz, CDCl3): δ = 153.2 (2C), 141.8, 136.7, 133.4, 129.4 (2C), 125.7, 122.1 (2C), 104.6 (2C), 61.0, 56.4 (2C); IR (ATR): ν = 3259, 1312, 1148, 1125 cm⁻¹; MS (EI) m/z (%): 324 (M+ + 1, 14), 323 (M+, 81), 244 (11), 231 (19), 183 (25), 168 (14), 167 (100), 137 (13), 109 (11), 92 (15), 81 (11), 77 (12), 66 (12), 65 (14). HRMS calcd. (%) for C15H17NO3S: 323.0827; found: 323.0824.

**4-(dimethylamo-N-phenylbenzenesulfonamide (33r):** White solid; m.p. 172-174 °C; Rf = 0.27 (hexane/ethyl acetate: 7/1); t1 = 20.5; 1H NMR (300 MHz, CDCl3): δ = 7.65-7.55 (m, 2H, ArH), 7.25-7.20 (m, 2H, ArH), 7.10-7.00 (m, 3H, ArH), 6.72 (s, 1H, NH), 6.60-6.55 (m, 2H, ArH), 3.00 (s, 3H, OMe), 3.84 (s, 6H, 2xOCH3); 13C NMR (101 MHz, CDCl3): δ = 153.0, 137.3, 129.3 (2C), 129.2 (2C), 124.9, 124.5, 121.3 (2C), 111.0 (2C), 40.2 (2C); IR (ATR): ν = 3253, 1315, 1137, 1090 cm⁻¹; MS (EI) m/z (%): 277 (M+ + 1, 13), 276 (M+, 70), 184 (67), 136 (100), 120 (69), 119 (11), 105 (16), 104 (16), 91 (11), 77 (20), 65 (14), 64 (18); HRMS calcd. (%) for C14H13N3O3S: 276.9032; found: 276.0942.

**4-fluoro-N-phenylbenzenesulfonamide (33s):** White solid; m.p. 106-108 °C; Rf = 0.47 (hexane/ethyl acetate: 7/1); t1 = 16.0 min; 1H NMR (300 MHz, CDCl3): δ = 7.85-7.75 (m, 2H, ArH), 7.30-7.20 (m, 3H, ArH + NH), 7.25-7.05 (m, 5H, ArH); 13C NMR (101 MHz, CDCl3): δ = 165.4 (d, J = 255.4 Hz), 136.3, 135.0 (d, J = 3.3 Hz), 130.1 (d, J = 9.5 Hz, 2C), 129.5 (2C), 125.8, 122.0 (2C), 116.4 (d, J = 22.6 Hz, 2C); IR (ATR): ν = 1334, 1149, 840 cm⁻¹; MS (EI) m/z (%): 251 (M+, 64), 186 (21), 159 (18), 95 (33), 92 (100), 75 (12), 65 (33).

**4-bromo-N-phenylbenzenesulfonamide (33t):** White solid; m.p. 106-109 °C; Rf = 0.57 (hexane/ethyl acetate: 1/1); t1 = 16.9; 1H NMR (300 MHz, CDCl3): δ = 7.70-7.60 (m, 2H, ArH), 7.55-7.50 (m, 2H, ArH), 7.40 (s, 1H, NH), 7.30-7.20 (m, 2H, ArH), 7.15-7.05 (m, 3H, ArH); 13C NMR (101 MHz, CDCl3): δ = 138.0, 136.2, 132.5 (2C), 129.6 (2C), 128.9 (2C), 128.2, 125.9, 121.9 (2C); IR (ATR): ν = 3250, 1335, 1155,
Experimental Part

741 cm⁻¹; MS (EI) m/z (%): 313 (M⁺ Br²¹, 32), 311 (M⁺ Br²⁹, 31), 220 (12), 218 (11), 168 (21), 157 (19), 155 (19), 92 (100), 76 (11), 75 (11), 65 (32).

N-phenyl-2-(trifluoromethyl)benzenesulfonamide (33u): White solid; m.p. 97-99 °C; Rf = 0.37 (hexane/ethyl acetate: 7/3); t₀ = 15.9; ¹H NMR (400 MHz, CDCl₃): δ = 8.00 (d, J = 7.9 Hz, 1H, ArH), 7.87 (d, J = 7.6 Hz, 1H, ArH), 7.64 (t, J = 7.6 Hz, 1H, ArH), 7.56 (td, J = 7.9, 0.8 Hz, 1H, ArH), 7.25–7.20 (m, 2H, ArH), 7.15–7.10 (m, 1H, ArH), 7.10–7.00 (m, 2H, ArH), 6.75 (s, 1H, NH); ¹³C NMR (101 MHz, CDCl₃): δ = 137.3, 125.7, 133.2, 132.6, 132.3, 129.5 (2C), 128.6 (q, J = 6.3 Hz, 1H, ArH), 127.8 (q, J = 32.9 Hz, 1H, ArH), 126.1, 123.1 (q, J = 273.8 Hz, 1H, ArH), 122.32 (2C); IR (ATR): v = 3278, 1497, 1352, 1160 cm⁻¹; MS (EI) m/z (%): 301 (M⁺, 53), 207 (15), 145 (31), 92 (100), 65 (37); HRMS calcd. (%) for C₁₃H₁₀F₃NO₂S: 301.0384; found: 301.0381.

N-phenyl-3-(trifluoromethyl)benzenesulfonamide (33v): White solid; m.p. 79-81 °C; Rf = 0.43 (hexane/ethyl acetate: 7/3); t₀ = 15.6; ¹H NMR (400 MHz, CDCl₃): δ = 8.04 (s, 1H, NH), 7.96 (d, J = 7.9 Hz, 1H, ArH), 7.78 (d, J = 7.9 Hz, 1H, ArH), 7.58 (t, J = 7.9 Hz, 1H, ArH), 7.30–7.25 (m, 3H, ArH), 7.20–7.15 (m, 1H, ArH), 7.10–7.05 (m, 2H, ArH); ¹³C NMR (101 MHz, CDCl₃): δ = 140.2, 135.8, 131.8 (q, J = 33.5 Hz, 1H, ArH), 130.5, 130.0, 129.8 (q, J = 6.6 Hz, 1H, ArH), 129.6 (2C), 126.2, 124.2 (q, J = 7.2 Hz, 1H, ArH), 122.3 (2C), 120.45 (q, J = 272.9 Hz, 1H, ArH); IR (ATR): v = 3231, 1322, 1165, 1155 cm⁻¹; MS (EI) m/z (%): 301 (M⁺, 52), 145 (22), 92 (100), 65 (28); HRMS calcd. (%) for C₁₃H₁₀F₃NO₂S: 301.0384; found: 301.0382.

N-(2-benzoyl-4-chlorophenyl)-4-methylbenzenesulfonamide (33x): Yellow solid; m.p. 114-116 °C; Rf = 0.53 (hexane/ethyl acetate: 7/1); t₀ = 28.1; ¹H NMR (400 MHz, CDCl₃): δ = 9.69 (s, 1H, NH), 7.76 (d, J = 8.8 Hz, 1H, ArH), 7.65–7.55 (m, 1H, ArH), 7.53 (d, J = 8.3 Hz, 2H, ArH), 7.48 (dd, J = 8.8, 2.5 Hz, 1H, ArH), 7.45–7.40 (m, 2H), 7.40–7.35 (m, 2H), 7.32 (d, J = 2.5 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H, ArH), 2.22 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 197.1, 144.1, 137.4, 136.9, 135.6, 133.6, 133.3, 132.3, 130.0 (2C), 129.8 (2C), 129.4, 128.4 (2C), 128.0, 127.3 (2C), 125.2, 21.5; IR (ATR): v = 3265, 1636, 1379, 1183 cm⁻¹; HRMS calcd. (%) for C₂₃H₁₉ClF₂NO₂S: 401.0921; found: 401.0922.

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MS (EI) m/z (%): 387 (M+ Cl<sup>37</sup>, 29), 385 (M+ Cl<sup>35</sup>, 29), 232 (33), 230 (100), 195 (54), 167 (24), 166 (14), 155 (15), 139 (12), 91 (66), 77 (21).

4.6. CATALYST-FREE SYNTHESIS OF SULFONES AND ARYL SULFIDES

**General procedure for the catalyst-free synthesis of sulfones:** A solution of Ar<sub>3</sub>Bi (0.2 mmol), sodium metabisulfite (1.32 mmol), and the corresponding electrophile (1.2 mmol) in 1.5 mL of DES was stirred for 5 h at 80 °C. Once the reaction was completed, water was added to dissolve the DES phase. That aqueous suspension was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products 29.

**General procedure for the catalyst-free synthesis of aryl sulfides:** A solution of Ar<sub>3</sub>Bi (0.2 mmol), sodium metabisulfite (1.32 mmol) in 1.5 mL of DES was stirred for 5 h at 80 °C. Then, I<sub>2</sub> (1.2 mmol) was added and the reaction was stirred for 20 minutes, before the corresponding pro-nucleophile was added (1.2 mmol). This final mixture was stirred at 80 °C for 5 additional hours. Once the reaction was completed, water was added to dissolve the DES phase. That aqueous suspension was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products 30.
CONCLUSIONS
Conclusions

From the results of this study, it can be concluded that Deep Eutectic Solvents can be employed as reaction mixtures to carry out traditional and novel organic transformations.

Furthermore, the rational design of DES-compatible pre-catalysts could improve the results obtained compared to traditional pre-catalysts, and, in some cases, exceed those obtained with common VOC solvents.

The cross-dehydrogenative coupling of tetrahydroisoquinolines could be accomplished using a highly-recyclable catalytic system, producing water as the only by-product.

Traditional palladium catalysed C-C cross-coupling reactions could also be performed in DES using different types of palladium complexes.

Efficient multicomponent C-S bond formation cross-coupling reactions proceeded smoothly in DES, while it was proven that a solvent design “à la carte” for a certain reaction could be performed.
I was born in Alcoi (Alacant) on 15\textsuperscript{th} December 1992.

I conducted my primary studies at school "Esclavas SCJ" and secondary ones at I.E.S. "Cotes Baixes" in Alcoi (Alacant).

During 2010-2014, I underwent the degree in Chemistry studies on the Science Faculty at the University of Alicante.

In September 2014 I joined the research group of Prof. Ramón at the Organic Chemistry Department of the University of Alicante, where I performed the Master in Medicinal Chemistry.

Since 2015 to the present, I have been working in my Doctoral Thesis. Part of results are presented this manuscript.

Since November 2016, I hold a predoctoral grant from Generalitat Valenciana (GVA).

From 17\textsuperscript{th} July 2017 to 17\textsuperscript{th} October 2017, I performed an internship at prestigious research group of Prof. Dr. Alan Armstrong, at the Imperial College of London, working in the development of small molecule inhibitors of RscBCD/AddAB.
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ABBREVIATION LIST
Abbreviation List

AcChCl: acetylcholine chloride
AES: auger electron spectroscopy
CDC: cross-dehydrogenative coupling
DABSO: 1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DABCO: 1,4-Diazabicyclo[2.2.2]octane
DES: deep eutectic solvent
DFT: density functional theory
ChCl: choline chloride
DMU: N,N’-dimethylurea
DOS: diversity-oriented synthesis
DSC: differential-scanning calorimetry
GC: gas chromatography
HBD: hydrogen-bond donor
HBA: hydrogen-bond acceptor
HPLC: high-performance liquid chromatography
IL: ionic liquid
ICP: inductively coupled plasma
IR: infrared
LMM: low-melting mixture
LB: Luria Bertani
MS: mass spectroscopy
MCR: multicomponent reaction
MBFT: multiple bond-forming transformation
MW: microwave
NMR: nuclear magnetic resonance
NP: nanoparticle
NC: nanocrystal
SET: single-electron transfer
SANDALS: small angle neutron diffractometer for amorphous/liquid samples
TPPTS: triphenylphosphine-3,3',3''-trisulfonic acid trisodium salt
THIQ: 1,2,3,4-tetrahydroisoquinoline
(HR)TEM: (high-resolution) transition electron microscopy
TBAB: tetrabutylammonium bromide
TON: turnover number
TEMPO: 2,2,6,6-tetramethylpiperidine 1-oxyl
Tg: glass transition temperature
VOC: volatile organic compound
XPS: X-ray photoelectron microscopy
XRF: X-ray fluorescence
EPILOGUE
Desde el Neolítico, la historia de la humanidad se ha caracterizado por la explotación de los recursos naturales en beneficio propio. Sin embargo, a partir de la Revolución Industrial, en el siglo XVIII, esta situación se vio incrementada hasta llegar a ser insostenible. Las consecuencias que esta situación ha provocado en el medio ambiente son tan acentuadas que incluso se ha propuesto una nueva era geológica, el Antropoceno.

Esta situación ha generado problemas tales como el cambio climático, haciendo despertar la conciencia de nuestra propia insostenibilidad. La producción industrial necesita volverse más eficiente (tanto desde un punto de vista de productividad, como ecológico), para conseguir satisfacer las necesidades de consumo actuales. Esta nueva tendencia hacia un desarrollo sostenible es aplicable a muchos aspectos de la vida moderna, no siendo la industria química una excepción.

En 1991, el profesor Paul T. Anastas propuso el concepto de “Green Chemistry” (o Química Sostenible), recogiendo 12 principios básicos que todo proceso químico debería seguir de forma ideal. A pesar de que cumplir todos estos principios puede resultar inabordable desde el punto de vista práctico, algunos de estos aspectos deben ser tratados de forma urgente. Entre ellos, y dada la crisis derivada de la escasez de las fuentes fósiles, destaca el uso de materias primas renovables.

Al aplicar estos principios a la Química Orgánica, y más concretamente a la industria farmacéutica, se identifica rápidamente un problema en el uso de disolventes orgánicos volátiles. La industria farmacéutica, así como las relacionadas con ella, son el motor principal de la investigación en Síntesis Orgánica. No obstante, la mayoría de las transformaciones orgánicas que han sido desarrolladas tradicionalmente, requieren de un disolvente orgánico derivado del petróleo. Además de proceder de fuentes no renovables, estos disolventes son, en general, volátiles, inflamables, no biodegradables y tóxicos para el ser humano y el medio ambiente. Si se tiene en cuenta que dichos disolventes representan alrededor del 80% de la masa no acuosa que se emplea en la industria farmacéutica, resulta evidente la insostenibilidad que reside en su empleo.

Otro de los aspectos que potencia la Química Sostenible es el empleo de catalizadores. Las transformaciones más eficientes suelen estar catalizadas por complejos organometálicos. Sin embargo, el uso eficiente de estos catalizadores
requiere normalmente del empleo de disolventes que confieran estabilidad a los posibles intermedios y estados de transición. Es por esto que la búsqueda de disolventes biorenovables y el desarrollo de catalizadores compatibles con los mismos son temas a ser tratados con urgencia.

En respuesta a este problema, son varias las alternativas planteadas, entre ellas el uso de disolventes fluorados, fluidos super críticos, disolventes derivados de biomasa o incluso agua. A pesar de las obvias ventajas de estos medios de reacción respecto a los disolventes orgánicos volátiles tradicionales, cada uno de ellos sigue presentando claras desventajas en su aplicación, como pueden ser la baja solubilidad de compuestos orgánicos, la capacidad de hidrolizar reactivos (en el caso del agua), el elevado precio y la persistencia en la atmósfera de los disolventes fluorados, la dificultad de trabajar con fluidos super críticos (junto a la baja solubilidad que presentan muchos compuestos en ellos), así como las limitaciones impuestas por la naturaleza a la hora de modular las propiedades de los disolventes provenientes de biomasa.

Algo más sofisticados son los líquidos iónicos, disolventes compuestos por un catión, como por ejemplo imidazolio, y un anión poco coordinante con baja nucleofilia. Estos líquidos iónicos se han postulado como una de las mejores alternativas a los VOC (Volatile Organic Compounds en terminología inglesa), puesto que poseen una presión de vapor despreciable, no son inflamables, son estables a altas temperaturas y son inmiscibles en muchos disolventes orgánicos. Sin embargo, siguen presentando desventajas como su baja estabilidad en agua, la necesidad de emplear disolventes orgánicos al terminar la reacción y especialmente la baja economía atómica que conlleva su producción, lo cual conduce a su vez a que estos líquidos iónicos posean un precio elevado, todo ello sin olvidar su elevada toxicidad medioambiental.

A pesar de que hasta la fecha no se ha establecido la alternativa ideal a los VOC, recientemente se ha empezado a evaluar un nuevo medio de reacción con resultados muy prometedores. Se trata de los DESs (siglas que corresponden a Deep Eutectic Solvents en inglés), los cuales pueden definirse como mezclas eutécticas de dos componentes que en proporción adecuada, experimentan un cambio de fase de sólido a líquido a una temperatura concreta, la cual es muy inferior a la de las temperaturas de fusión de sus componentes por separado.
A pesar de que las mezclas eutécticas son conocidas desde hace décadas, no fue hasta principios del presente siglo cuando empezaron a utilizarse como posibles medios de reacción. Estos DES, formados normalmente por mezclas de ácidos y bases de Lewis o Bronsted pueden contener una gran variedad de especies iónicas, dotándole de unas propiedades únicas frente a los disolventes tradicionales, que les permiten llevar a cabo reacciones de muy diversa índole. Además de mantener muchas de las ventajas de los líquidos iónicos, tales como su prácticamente nula presión de vapor y baja inflamabilidad, los DESs poseen una clara ventaja, y es que la mayoría de los componentes que forman estas mezclas proceden de fuentes renovables. Es el caso del cloruro de colina, uno de los componentes más empleados en la formación de DESs que se produce a gran escala industrialmente en un proceso simple y de gran eficacia atómica, y es empleado como aditivo en alimento de aves para estimular su crecimiento. Otros de los componentes más empleados tienen también su origen en la naturaleza, como son ciertos aminoácidos, urea, resorcínol, ácidos carboxílicos naturales o diferentes políolos. Puesto que todos los átomos de los componentes iniciales se incorporan en la mezcla final, la economía atómica del proceso de formación de los DES es máxima, lo cual unido a la baja toxicidad y elevada biodegradabilidad de las mezclas, convierten a estos disolventes en una alternativa sostenible, al minimizar el impacto ecológico.

Además, cabe destacar que, debido a la elevada solubilidad de los DES en agua, la adición de la misma al medio de reacción una vez ésta ha terminado, permite la disolución de la mezcla eutéctica, de tal forma que los productos orgánicos precipitan en forma de sólidos o se mantienen en una fase líquida insoluble en agua y, por tanto, claramente separada. Por ello, las extracciones con disolventes orgánicos pueden ser obviadas, y la posible recuperación del DES se consigue fácilmente mediante la evaporación del agua.

Por otro lado, debido a sus propiedades físicas, los DES son capaces de disolver gran variedad de compuestos, tanto orgánicos como inorgánicos, permitiendo diseñar procesos catalíticos más efectivos. Si bien su elevada viscosidad puede parecer un problema, una adecuada selección de los componentes de la mezcla eutéctica permite la modulación selectiva de las propiedades de la misma, por lo que su empleo es factible incluso a escala industrial.

Este tipo de disolventes eutécticos ha ido creciendo en popularidad en los últimos quince años. Inicialmente los DESs encontraron su aplicación en campos
como el procesado de metales o en técnicas de separación en combinación con otros disolventes. No obstante, su empleo en diversos campos, como son la biotecnología, la química analítica o procesos de polimerización ya han sido explorados. Su aplicación como medios de reacción en síntesis orgánica se encuentra en cierres, a pesar de que ya existen ejemplos de reacciones llevadas a cabo en DES como disolventes. Algunos de estas mezclas eutécticas han probado su efectividad como disolventes y catalizadores al mismo tiempo. Cuidadosamente el componente que conforman el DES pueden aprovechar sus propiedades ácido/base para emplearlos como organocatalizadores en determinadas reacciones, tales como condensaciones. En ciertas ocasiones, alguno de los componentes del eutéctico actúa a la vez como reactivo. Es el caso de la reacción de Beginelli llevada a cabo en la mezcla ácido 1-(+)-tartárico y dimetilurea, en el que una molécula de dimetilurea se incorpora en el producto final.

![Diagrama de reacción](attachment:image.png)

En otras ocasiones los DESs son únicamente el medio de reacción, llevándose a cabo reacciones en las que no se necesita catalizador o se añade un catalizador externo a la propia mezcla eutéctica. Es el caso del empleo de catalizadores metálicos. No obstante, comparado con los campos anteriores, éste no ha sido explorado en profundidad. Cuando se inició el desarrollo experimental de la presente tesis, a penas unas pocas reacciones catalizadas por metales habían sido descritas en DES como medios de reacción. Entre ellas se encontraban reacciones como cicloadiciones tipo click catalizadas por CuI, la reacción de Tsuji-Trost o la aminocarbonilación de yoduros de arilo.

Por todo esto, las propiedades únicas de los DESs, su seguridad y biorenovabilidad, unidas a las posibilidades de reciclado y reutilización, convierten a esta clase de medios de reacción en una alternativa sostenible y extremadamente prometedora a los perniciosos disolventes orgánicos volátiles; habiendo probado ya que su aplicación en síntesis orgánica no es solo posible, sino que puede resultar muy ventajosa en combinación con el desarrollo de nuevos catalizadores organometálicos. Sin embargo, se trata de un campo que se encuentra
en sus albores y requiere de un amplio estudio que permita explotar sus ventajas, facilitando así su incorporación al mundo industrial.

En este contexto se decidió desarrollar metodologías para llevar a cabo reacciones de acoplamiento en DESs. Una de las estrategias sintéticas que más atención suscita en Síntesis Orgánica es la formación de enlaces C-C a través de la activación del enlace C-H. El acoplamiento cruzado oxidativo de dos enlaces C-H (pro-nucleófilo y pro-electrófilo) permite la síntesis de una gran variedad de compuestos sin necesidad de una funcionalización previa, dando lugar a rutas sintéticas con menor número de pasos y mayor eficiencia.

Una de las variantes de este tipo de reacción, es la oxidación catalítica de enlaces C-H sp³ adyacentes a nitrógeno, la cual genera iminas o cationes imínio, capaces de reaccionar con nucleófilos para generar un enlace C-C. Se trata, por tanto, de una metodología interesante para la funcionalización de aminas.

En concreto, esta estrategia se ha empleado para derivatizar tetrahidroisoquinolinas, un tipo de estructuras que se encuentran en numerosos compuestos naturales y poseen crecientes aplicaciones en el campo de la farmacología. En concreto, las alquínil-tetrahidroisoquinolinas son ligandos potenciales para los receptores dopaminérgicos D₃, convirtiéndolas en posibles fármacos en tratamientos psiquiátricos y neurológicos.

Existen diferentes variantes en la bibliografía para llevar a cabo esta reacción. En primer lugar, cabe destacar las metodologías que emplean procesos fotoredox, normalmente irradiando la mezcla de reacción con luz visible y catalizadores metálicos de elevado precio basados, principalmente, en iridio y rutenio. Por otro lado, se han desarrollado metodologías que no involucran fotocatalización, en las que, sin embargo, se emplean otro tipo de metales como vanadio, en combinación de un oxidante. A pesar del gran interés de este tipo de reacción, la necesidad de emplear este tipo de oxidantes en cantidades estequiométricas es poco deseable. Por tanto, se decidió desarrollar una metodología sostenible para llevar a cabo este tipo de acoplamiento. Para ello, se eligieron las mezclas cetéicas como medios de reacción y se pensó en particulares de óxido de cobre impregnadas sobre magnetita como catalizador reciclable. En este caso, se esperaba que el oxígeno atmosférico fuera capaz de reoxidar al catalizador, evitando así el uso de oxidantes adicionales, de tal forma que el único subproducto de la reacción sería H₂O.
Además, el uso del catalizador soportado sobre magnetita permitiría llevar a cabo el reciclado del catalizador aprovechando sus propiedades paramagnéticas.

Para demostrar la utilidad de los catalizadores soportados en magnetita en la activación del enlace C-H en alfa a nitrógeno, se procedió a optimizar las condiciones de reacción; realizando un screening con diferentes especies metálicas soportadas y ajustando disolvente, temperatura y tiempo de reacción. Para ello, se eligió la reacción entre el 2-(4-fluorofenil)-1,2,3,4-tetrahidroisoquinolina y el fenilacetileno como modelo a estudiar. En primer lugar, se buscó el disolvente más adecuado para llevar a cabo esta reacción. Puesto que la reacción se llevó a cabo bajo condiciones aeróbicas, se observó un único subproducto (además del agua), la oxidación de la tetrahidroisoquinolina a la lactama correspondiente.

Entre los DES empleados, los mejores resultados se obtuvieron empleando la mezcla cloruro de colina:etilenglicol (1:2). A continuación, se modificó la cantidad de catalizador, pudiendo observarse que la conversión no se veía resentida al reducir a la mitad la carga del metal (0.91 mol%), pero sí al reducirlo por debajo de dicha cantidad (0.37 mol%). Por otro lado, al doblar la cantidad de catalizador sí que se mejoraron los resultados notablemente (3.64 mol%). Cuando en lugar de emplear 2 equivalentes del alquino se añadió únicamente uno, el rendimiento disminuyó, mientras que aumentar hasta 5 equivalentes no generó mejora alguna.

En cuanto a la temperatura, cuando se llevó a cabo la reacción sin calentar, ésta se ralentizó, por lo que se incrementó el tiempo de reacción hasta los 7 días, pero se obtuvo un 99% de conversión al producto deseado y no se observó la formación de subproducto. Curiosamente, calentar a 100 °C conllevó un peor rendimiento. El empleo de disolventes de uso corriente en Síntesis Orgánica ofreció rendimientos inferiores a los obtenidos en DES.

Habiendo esclarecido las mejores condiciones de reacción, se procedió a analizar la reactividad de diferentes sustratos. En primer lugar, se modificó el sustituyente del nitrógeno de la tetrahidroisoquinolina, sin modificar el fenilacetileno como pro-nucleófilo. La reacción tuvo lugar tanto con anillos que contienen grupos electrón-atrayentes, como con grupos que ceden densidad electrónica. Por otro lado, cuando se introdujo un grupo tosiló como sustituyente del nitrógeno la reacción no tuvo lugar.
A continuación, se probó la reactividad de diferentes pro-nucleófilos, empezando por diversos alquinos. De nuevo, quedó patente la validez del método tanto para alquinos pobres en densidad electrónica, como ricos. Por otro lado, la sustitución del grupo aromático por uno alifático o uno olefinico no impidió que la reacción tuviese lugar. Del mismo modo, se estudiaron otros posibles pro-nucleófilos, tales como nitrocompuestos, sililenol éteres o compuestos carbonílicos, entre otros.

![Reacción química](image)

Además, se llevó a cabo el estudio de la reciclabilidad del proceso. Se eliminó el disolvente y los productos de reacción mediante su disolución en agua, recuperando así el catalizador de forma sencilla gracias a sus propiedades magnéticas. Dicho catalizador recuperado fue empleado en posteriores ciclos. Desafortunadamente, el rendimiento de la reacción empezó a verse afectado a partir del tercer ciclo, por lo que no se pudo llevar a cabo un reciclado efectivo. Sin embargo, puesto que el DES empleado no es soluble en disolventes orgánicos, se diseñó otra estrategia. En este caso, una vez completada la reacción se añadió ciclopentilmetil éter y se extrajeron los productos de reacción, así como posibles subproductos y reactivos de partida. De esta forma, en el recipiente de reacción quedaron el disolvente eutéctico y el catalizador, los cuales se emplearon en nuevos ciclos de reacción mediante la adición de reactivos de partida frescos. De esta forma, el medio de reacción y el catalizador se utilizaron 10 veces consecutivas sin afectar negativamente al rendimiento de la reacción.
Finalmente se analizó el catalizador tras haber sido recuperado de la mezcla de reacción. Se encontró que el tamaño de partícula promedio disminuyó ligeramente. Al mismo tiempo se detectó cierto lixiviado del cobre soportado hacia el medio de reacción, lo cual explicó por qué el reciclado del DES y catalizador fue más efectivo que cuando se recicló únicamente el catalizador.

En vista de los resultados obtenidos, se decidió enfocar el estudio en el desarrollo de catalizadores organometálicos homogéneos. Puesto que la naturaleza de las mezclas eutécticas puede parecer incompatible con este tipo de catalizadores, se pensó en sintetizar un catalizador de paladio tipo pinza. Estos complejos organometálicos presentan, de forma general, alta estabilidad y han demostrado aplicaciones muy interesantes en Síntesis Orgánica.

Por ello, se inició el estudio sintetizando un complejo de paladio tipo pinza en tres pasos de reacción. En primer lugar, se hizo reaccionar 1,3-bis(clorometil)benceno con un exceso de dimetil amina. A continuación, se llevó a cabo una desprotonación bajo condiciones termodinámicas empleando n-BuLi como base, para añadir a continuación I$_2$ dando el correspondiente yoduro de arilo. Finalmente se hizo reaccionar el producto anterior con un precursor de Pd (0) para generar el complejo deseado.
Una vez obtenido el complejo se probó su actividad catalítica en diferentes reacciones, obteniendo buenos resultados en la reacción de acoplamiento cruzado tipo Hiyama. En comparación con otras reacciones de acoplamiento que utilizan paladio como catalizador, la reacción de acoplamiento cruzado de Hiyama adquiere importancia en el ámbito de la Química Verde ya que es manera de formar enlaces C–C utilizando reactivos de organosilicio, los cuales son, en general, muy estables frente al aire o la humedad, no tóxicos, medioambientalmente beninos y pueden adquirirse de manera asequible o ser fácilmente preparados. Por tanto, la reacción de acoplamiento cruzado de Hiyama ha pasado a convertirse en una alternativa medioambientalmente benigna frente a otras reacciones que emplean reactivos de boro, estano y zinc.

Durante el proceso de optimización de las condiciones de reacción se estudiaron una gran variedad de mezclas eutécticas. El mejor resultado fue el obtenido con la mezcla cloruro de colina y glicerol. No obstante, al probar la reacción empleando únicamente glicerol como disolvente, el rendimiento obtenido fue superior, por lo que la presencia del cloruro de colina parecía afectar negativamente a la reacción. Aún así, se decidió analizar el alcance de la reacción empleando tanto la mezcla de cloruro de colina y glicerol como glicerol puro como medios de reacción.

De esta forma, se comprobó que en la síntesis de biarilos, se obtuvieron mejores resultados empleando glicerol como disolvente. Sin embargo, los resultados fueron diferentes en el caso de introducir un grupo vinilo, obteniendo diferentes valores de rendimiento y selectividad en función del disolvente y sustrato.
La metodología pudo llevarse a cabo en escala de gramos. De esta forma, una vez completada la reacción se extrajo el producto de reacción empleando 2-MeTHF. Tras evaporar el disolvente se obtuvo el producto de reacción con un elevado nivel de pureza sin necesidad de realizar ningún paso extra de purificación. Además, se llevaron a cabo una serie de pruebas con la finalidad de determinar la especie catalíticamente activa, obteniéndose resultados que parecían indicar la formación de un intermedio de Pd (IV).

Finalmente se probaron otras reacciones de acoplamiento cruzado, tales como las reacciones de Suzuki, Heck o Sonogashira, pero los resultados obtenidos no fueron del todo satisfactorios.

Por este motivo se trató de mejorar la compatibilidad de los catalizadores con el medio de reacción, con el fin de mejorar su capacidad catalítica. Para ello se pensó en diseñar nuevos ligandos con los que formar complejos organometálicos capaces de integrarse en la estructura de los DES. Bajo este precepto, se prepararon fosfinas catiónicas a partir de derivados de 2-piridona mediante reacciones de arilación, seguidas por cloración y sustitución nucleófila aromática con la correspondiente fosfina, para, a continuación, formar el complejo a partir de un precursor metálico.
El ligando constituye una sal de piridinio, la cual es soluble en un medio tan polar como el de un DES. Además, al ser el contraión un cloruro, su integración en la estructura de DESs que contengan este mismo anión como parte de su estructura. Los nuevos ligandos fueron caracterizados por técnicas propias de Química Orgánica (resonancia magnética nuclear, espectrometría de masas, espectroscopia infrarroja, etc.), además de someterse a un estudio de complejación con diferentes fuentes de Pd mediante espectroscopia ultravioleta.

Dichos ligandos fueron ensayados junto con cloruro de paladio en la reacción de Suzuki-Miyaura en mezclas eutécticas, obteniendo buenos resultados. Bajo las mismas condiciones se probaron fosfinas no iónicas comercialmente asequibles, capaces de favorecer dicha reacción bajo condiciones tradicionales. Sin embargo, dichas fosfinas comerciales no produjeron una mejora en el rendimiento de la reacción, al contrario que las fosfinas catiónicas que sí lo mejoraron sustancialmente.

De esta forma se llevó a cabo la optimización de las condiciones de reacción hasta encontrar la mejor temperatura, carga de catalizador, disolvente (mezcla eutéctica), base y equivalentes de reactivos. Bajo estas condiciones optimizadas se analizó el alcance de la reacción, probando su eficacia para diferentes haluros de arilo, puesto que se obtuvieron buenos resultados tanto con anillos aromáticos ricos en electrones como en aquellos pobres. Únicamente 0.1 mol% de Pd fue empleado en el caso de emplear yoduros de arilo y 1 mol% para los correspondientes bromuros.

Del mismo modo, se analizó la eficacia del sistema catalítico desarrollado para otras reacciones de acoplamiento cruzado como son las de Sonogashira y Heck. De nuevo, en ambos casos se llevó a cabo un estudio de optimización de las condiciones de reacción y posteriormente se analizó el alcance de las mismas.

Por otro lado, aprovechando las características únicas de los disolventes eutécticos, se llevó a cabo el reciclado del catalizador, pudiéndose reutilizar tanto el disolvente como el catalizador hasta 5 ciclos sin una caída importante en el
rendimiento de la reacción para las reacciones de Suzuki y Sonogashira. De esta manera se puso de manifiesto que estos ligandos, basados en fosfinas catiónicas y diseñados de manera racional, poseen una gran capacidad catalítica junto con cloruro de paladio, pudiéndose trasladar los buenos resultados que se han obtenido en medios tradicionales en el campo de las reacciones de acoplamiento cruzado a mezclas eutécticas, las cuales constituyen una alternativa medioambientalmente benigna a los disolventes orgánicos volátiles y los problemas que derivan de ellos.

Una vez probada la capacidad de los DES como medios de reacción aptos para llevar a cabo reacciones de acoplamiento cruzado para la formación de enlaces C-C, se pasó a estudiar reacciones en las que primara la formación de enlaces carbono-heteroátomo. La presencia de heteroátomos resulta crucial en numerosos compuestos de interés para la industria farmacéutica, además de en el campo de ciencia de los materiales.

En concreto, la síntesis de sulfonas es un ejemplo en el que se carece de metodologías sostenibles. De forma general, las sulfonas se sintetizan mediante la oxidación de precursores en los que los enlaces C-S ya están preformados. Esta estrategia depende completamente de los precursores comercialmente asequibles y requiere del uso de oxidantes en cantidades estequiométricas que suelen generar subproductos nocivos. La incorporación de SO$_2$ en moléculas orgánicas es una transformación de gran interés. No obstante, el dióxido de azufre presenta una alta toxicidad. Además, su naturaleza gaseosa complica su empleo en metodologías sintéticas, requiriendo de un equipamiento muy específico. Es por esto que en los últimos años se han desarrollado alternativas al uso de SO$_2$, tales como el DABSO. Estos sustitutos liberan SO$_2$ de forma controlada en el medio de reacción, por lo que su uso es seguro y eficaz.

De esta manera, se llevó a cabo la síntesis multicomponente de sulfonas a partir de ácidos borónicos, metabisulfito de sodio y diferentes fuentes de alquilación catalizada por paladio. De nuevo, la fosfina catiónica empleada en las reacciones formación de enlaces C-C fue vital para obtener buenos resultados, ya que la reacción a penas tenía lugar en su ausencia. Esta estrategia permitió la síntesis de productos de relativa complejidad a partir de moléculas muy sencillas en un único paso de reacción. Esto fue posible gracias a las capacidades únicas del DES que permitieron solubilizar y activar tanto la fuente inorgánica de azufre, el ácido borónico, el reactivo de alquilación y el catalizador organometálico en un único medio.
Además, se comprobó que el benzenosulfínato de sodio (intermedio de reacción) fue capaz de reaccionar con una gran variedad de electrófilos, dando lugar a sulfonas heterosustituidas. Por otro lado, dicho intermedio se hizo reaccionar con yodo molecular, permitiendo, a continuación, la reacción con diferentes nucleófilos y fuentes radicalarias, dando acceso a una gran variedad de tioéteres sustituidos.

Con el fin de completar el estudio, se sintetizaron y caracterizaron nanopartículas de paladio de diferentes morfologías (cúbica, decádrica y octaédrica) y se probaron en la reacción estudiada anteriormente para determinar si las diferentes caras expuestas de las nanopartículas poseían diferente actividad catalítica. Además, dichos resultados se compararon con las nanopartículas generadas in situ en el medio de reacción a partir de cloruro de paladio (II) y la piridiniofosfina empleada.

Finalmente, siguiendo con el proyecto de formación de enlaces C-S mediante reacciones multicomponente, se desarrolló una nueva síntesis sostenible de sulfonamidas. Las sulfonamidas poseen numerosas aplicaciones en el campo de la industria farmacéutica. Sin embargo, los métodos para síntesis son limitados y a menudo han evolucionado en el último siglo. De forma general, se requiere el empleo de haluros de sulfonilo para hacer reaccionar con las correspondientes aminas. Este método requiere del uso de reactivos nocivos, los cuales no siempre son comercialmente asequibles y deben ser manipulados bajo condiciones anhidras debido a su inestabilidad frente a la humedad. En el caso de que estos haluros de sulfonilo deban ser preparados, es necesario el uso de cantidades estequiométricas de reactivos generalmente tóxicos que generan grandes cantidades de subproductos orgánicos.

Por ello, en base a la experiencia previa se decidió llevar a cabo la síntesis de sulfonamidas a partir de compuestos de triarilbismuto, nitrocompuestos y metabisulfito de sodio. La sustitución de los ácidos borónicos por compuestos de triarilbismuto contribuye a mejorar la sostenibilidad del proceso, puesto que estos derivados de Bi (III) han demostrado poseer una toxicidad muy baja, además de
tener la capacidad para transferir tres grupos arilo por cada molécula de reactivo de partida, lo cual mejora la economía atómica del proceso. Para llevar a cabo esta reacción se empleó cloruro de cobre como catalizador, siendo éste un metal más abundante (y por tanto asequible) que el paladio. De esta forma, la reacción entre el metabisulfito de sodio y los compuestos de triarilbismuto dan lugar a arilsulfinitos de sodio, liberando sulfito de sodio al medio. Dicho sulfito, puede generar bisulfito de sodio con la humedad contenida en el DES, reactivo que ha demostrado ser un reductor de diferentes grupos funcionales en Química Orgánica. Es por esto que se planteó la reacción del sulfinito formado in situ con nitrocompuestos, los cuales pudieron ser reducidos por el bisulfito de sodio en presencia del cloruro de cobre para dar lugar a los correspondientes sulfonamidas. Por tanto, esta síntesis cumple con la mayoría de los requisitos impuestos por la química sostenible, ya que hace uso del subproducto del primer paso de reacción como reactivo para llevar a cabo la etapa final de la reacción.

Durante la optimización de las condiciones de reacción se ideó una nueva mezcla eutéctica para ser empleada como disolvente. Puesto que dicho DES no había sido descrito previamente, se realizaron calorimetrías diferenciales de barrido a mezclas de los dos componentes que conforman el DES en diferentes proporciones. A partir de los resultados obtenidos, se pudo construir el diagrama de fases de la mezcla eutéctica, así como determinar la relación molar de los componentes en el punto eutéctico.

Con las condiciones optimizadas, se pasó a analizar el alcance de la reacción. En primer lugar, una gran variedad de nitrocompuestos se hizo reaccionar con trifenilbismuto, obteniendo buenos rendimientos de las correspondientes sulfonamidas sin que las variaciones en los sustituyentes de los anillos aromáticos unidos al grupo nitro afectasen demasiado al devenir de la reacción. De hecho, incluso nitrocompuestos alifáticos fueron compatibles con la metodología, aunque con rendimientos inferiores.

A continuación, se probaron diferentes compuestos de triarilbismuto. De nuevo, la reacción funcionó con rendimientos de moderados a muy buenos con diferentes sustituyentes, si bien es cierto que cuando los anillos poseían sustituyentes en orto, los rendimientos se vieron afectados negativamente. Cabe destacar que la síntesis de un compuesto con potencial actividad como fármaco anti-lepra pudo ser sintetizado en un único paso de reacción.
Además, la síntesis de sulfonas se llevó a cabo sin necesidad de emplear ningún catalizador metálico en la reacción. Esto fue posible gracias a la versatilidad del enlace C-Bi, en el cual la inserción de SO2 puede tener lugar fácilmente. Una vez formado el sulfinato correspondiente, la reacción con electrófilos para generar las sulfonas tiene lugar con facilidad. Del mismo modo, añadir yodo molecular seguido de un acceptor de radicales también dio como resultado los correspondientes sulfuros de arilo. Además de evitar el uso de catalizadores, estas últimas reacciones transcurren en tan solo 5 horas. El mecanismo de la reacción se elucidó a partir de ciertas pruebas mecanísticas.

Desde su descubrimiento, los DES han sido propuestos como disolventes sostenibles con una toxicidad muy baja. No obstante, existen pocos análisis exhaustivos de la toxicidad real de los DES. Además, se tiene a generalizar respecto a la baja toxicidad de las mezclas eutécticas en lugar de analizar pormenorizadamente cada una de ellas. Es por esto que, puesto que el DES empleado en el desarrollo de esta metodología no era conocido, se llevó a cabo un análisis de la toxicidad real del mismo.

Tras un análisis bibliográfico, se detectó que el método más comúnmente extendido para la evaluación de la toxicidad no mostraba resultados válidos. Dicho método se basa en la difusión de la sustancia a analizar desde un disco hacia el medio de cultivo. Sin embargo, la elevada viscosidad de los DES impide que se obtengan resultados que puedan ser considerados como válidos y reproducibles. Por ello, se llevó a cabo el estudio en disolución acuosa, monitorizando, no sólo el crecimiento celular, si no también parámetros como el pH de la disolución. De esta forma se encontró que el método de esterilización del DES previo a los ensayos afectaba en gran medida a los resultados, puesto que alguno de los componentes de la mezcla eutéctica puede sufrir hidrólisis, disminuyendo el pH de la disolución resultante. En estos casos, la toxicidad no se debe al propio DES si no a la acidez del medio de cultivo. Finalmente se encontró que el DES estudiado permitía el crecimiento de E. Coli en concentraciones de hasta 450 mM. Por tanto, puede concluirse que la toxicidad de esta mezcla eutéctica es reducida, especialmente se la compara con la mayoría de los disolventes orgánicos volátiles tradicionales.

Por tanto, de los resultados obtenidos durante el desarrollo de la presente tesis doctoral, se puede concluir que las mezclas eutécticas pueden ser empleadas como medios de reacción para llevar a cabo transformaciones orgánicas, tanto clásicas como novedosas.
Además, se ha demostrado que el diseño racional de pre-catalizadores compatibles con los DES puede mejorar los resultados obtenidos, si se comparan con pre-catalizadores tradicionales. De esta forma se puede incluso superar en algunos casos los resultados que se han obtenido de forma clásica en disolventes orgánicos volátiles.

Concretamente, el acoplamiento cruzado deshidrogenante de tetrahidroisoquinolinas pudo ser llevado a cabo empleando un sistema catalítico reciclablable, mediante una metodología que produce únicamente agua como subproducto de reacción.

Por otro lado, se probó que reacciones tradicionales de acoplamiento cruzado para la formación de enlaces C-C catalizadas por paladio pueden ser llevadas a cabo en DES, empleando diferentes complejos de paladio.

Finalmente, se ha desarrollado una metodología para la formación de enlaces C-S en DES, tanto para la síntesis de sulfonas como de sulfonamidas y compuestos derivados. Probando además que el diseño de disolventes “a la carta” para cada reacción es posible.