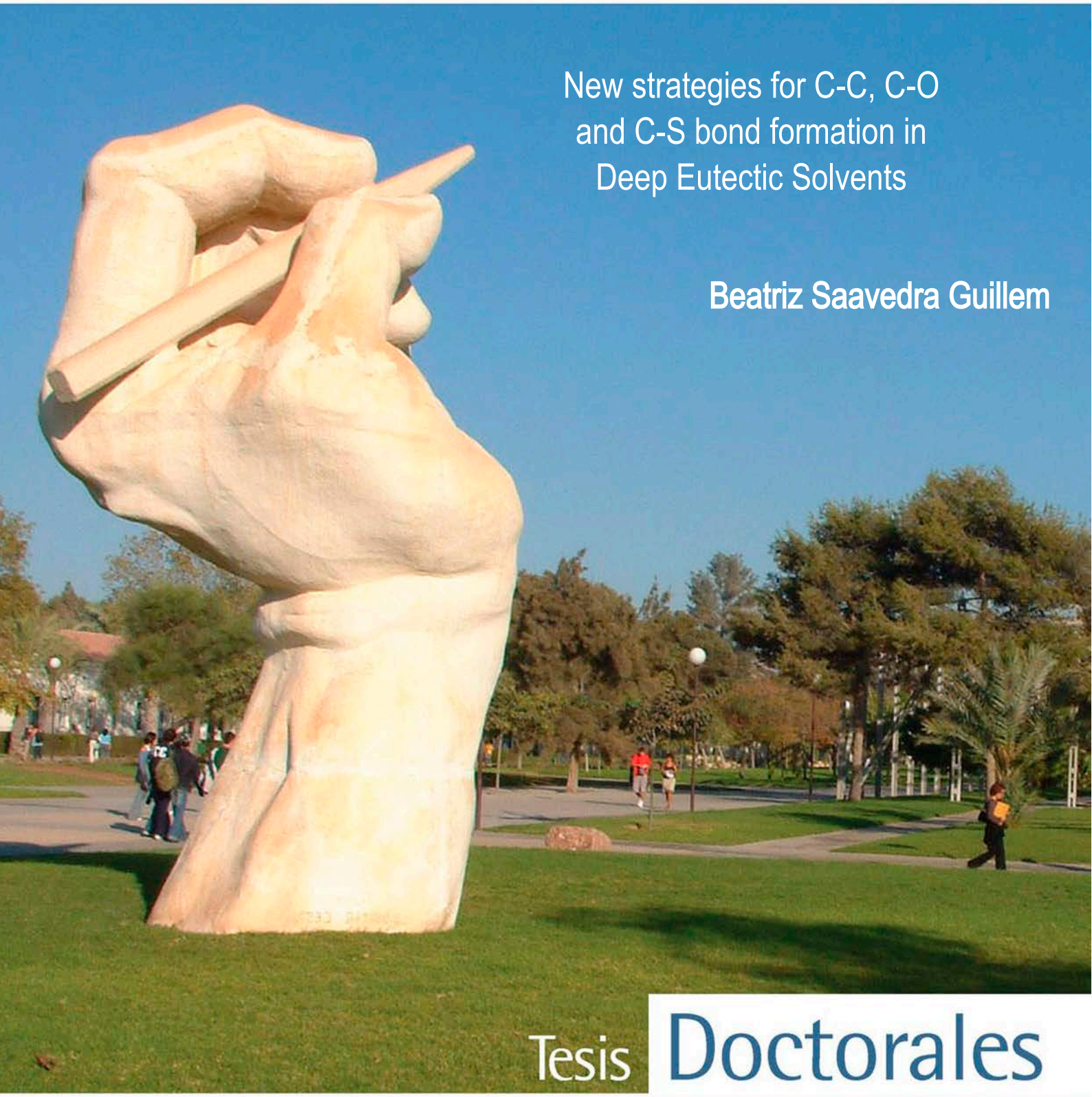
New strategies for C-C, C-O and C-S bond formation in Deep Eutectic Solvents

Beatriz Saavedra Guillem



Universitat d'Alacant
Universidad de Alicante

Instituto de Síntesis Orgánica (ISO)

Facultad de Ciencias

New strategies for C-C, C-O and C-S bond formation in Deep Eutectic Solvents

Manuscript thesis submitted to apply for PhD Degree with International Mention at the University of Alicante by:

BEATRIZ SAAVEDRA GUILLEM

Alicante, 18th June 2021

Doctoral Programme: Organic Synthesis

Scientific advisor:

Diego J. Ramón

PROLOGUE

Part of the results reported in this thesis have already been published:[†]

"Impregnated palladium on magnetite as a water compatible catalyst for the cycloisomerization of alkynoic acid derivatives" B. Saavedra, J. M. Pérez, M. J. Rodríguez-Álvarez, J. García-Álvarez, D. J. Ramón, *Green Chem*. **2018**, *20*, 2151-2157.

"Mezclas eutécticas como alternativa sostenible a los disolventes convencionales en Química Orgánica" D. A. Alonso, A. Baeza, R. Chinchilla, C. Gómez, G. Guillena, X. Marset, I. M. Pastor, D. J. Ramón, D. Ros-Ñíguez, B. Saavedra, *An. Quím.* **2018***, 114,* 79-87.

"A bipyridine-palladium derivative as general pre-catalyst for cross-coupling reactions in Deep Eutectic Solvents" B. Saavedra, N. González-Gallardo, A. Meli, D. J. Ramón, *Adv. Synth. Catal*. **2019**, *361*, 3868-3879.

"Palladium mesoionic carbene pre-catalyst for general cross-coupling transformations in Deep Eutectic Solvents" X. Marset, B. Saavedra, N. González-Gallardo, A. Beaton, M. M. León, R. Luna, D. J. Ramón, G. Guillena, *Front. Chem*. **2019**, *7*, 700-(+6).

"Multicomponent synthesis of sulfones and sulfides from triarylbismuthines and sodium metabisulfite in Deep Eutectic Solvents" B. Saavedra, X. Marset, G. Guillena, D. J. Ramón, *Eur. J. Org. Chem*. **2020**, 3462-3467.

"Deep Eutectic Solvent as sustainable medium for C-C bond formation *via* multicomponent radical conjugate additions" B. Saavedra, D. J. Ramón, Submitted.

"Indium mediated Barbier allylation of carbonyl compounds in Deep Eutectic Solvents" N. González-Gallardo, B. Saavedra, G. Guillena, D. J. Ramón, to be Submitted.

"Environmentally friendly ruthenium catalyzed C-H activation in Deep Eutectic Solvents" B. Saavedra, D. J. Ramón, Manuscript in preparation.

"Enantioselective Aldol reaction in environmentally friendly eutectogels based on L-amino acids and Deep Eutectic Solvents" B. Saavedra, A. Meli, F. D'Anna, D. J. Ramón, Manuscript in preparation.

[†] This research has been generously supported by the Spanish Ministerio de Economía y Competitividad (CTQ2015-66624-P9 and PGC2018-096616-B-I00), the University of Alicante (VIGROB-316FI) and the Generalitat Valenciana (ACIF-2017-211 fellowship for Beatriz Saavedra).

RESUMEN
SUMMARY
RESUM

La presente memoria se centra en el desarrollo de metodologías sostenibles utilizando disolventes respetuosos con el medio ambiente, tales como las mezclas eutécticas (DESs en inglés), para llevar a cabo reacciones de gran interés en Química Orgánica.

En el Primer Capítulo se describen varias metodologías para la formación de enlaces C-C a través de la adición de haluros alílicos a cetonas mediada por indio metálico, reacciones de acoplamiento cruzado, activación de enlaces C-H catalizada por rutenio, adición radicalaria de olefinas y la reacción aldólica enantioselectiva.

En el Segundo Capítulo se describe un protocolo para la formación de enlaces C-O, más concretamente, para la cicloisomerización de ácidos alquinoicos y derivados. Para ello, se empleó un catalizador heterogéneo de paladio fácilmente reciclable.

Finalmente, el Tercer Capítulo se basa en la formación de enlaces C-S mediante reacciones multicomponente. Este protocolo utiliza metabisulfito sódico y triarilbismuto para la síntesis de sulfonas, disulfuros y sulfuros, en mezclas eutécticas y sin necesidad de catalizador.

The aim of this PhD thesis is to develop sustainable methodologies using environmentally friendly solvents such as Deep Eutectic Solvents, also known as DESs.

In the First Chapter different methodologies for the C-C bond construction are described, including the indium mediated addition of allyl halides to ketones, cross-coupling reactions, ruthenium catalyzed C-H activation, radical conjugate additions of olefins, and enantioselective aldol reaction.

In the Second Chapter a protocol for the C-O bond formation is described. Specifically, the cycloisomerization of alkynoic acids and derivatives. For that, a heterogeneous and easily recyclable palladium catalyst was employed.

Finally, the Third Chapter is based on the C-S bond formation through multicomponent reactions using sodium metabisulfite and triarylbismuthines for the synthesis of sulfones, disulfides and sulfides, without the use of a catalyst, in DESs.

La present memòria es centra en el desenvolupament de metodologies sostenibles utilitzant dissolvents respectuosos amb el medi ambient, com poden ser les mescles eutèctiques (DESs en anglès) per a dur a terme reaccions de gran interès en Química Orgànica.

En el Primer Capítol es descriuen varies metodologies per a la formació d'enllaços C-C mitjançant l'addició de halurs metàl·lics a cetones catalitzada per indi metàl·lic, reaccions d'acoblament creuat, activació d'enllaços C-H catalitzada per ruteni, l'addició radicalària d'olefines i la reacció aldòlica enantioselectiva.

En el Segon Capítol es descriu un protocol per a la formació d'enllaços C-O, més concretament, per a la cicloisomerització d'àcids alquinòics i derivats. En aquest cas, es va utilitzar un catalitzador heterogeni de pal·ladi fàcilment reciclable.

Finalment, el Tercer Capítol es basa en la formació d'enllaços C-S mitjançant reaccions multicomponent. La metodologia utilitza metabisulfit sòdic i compostos de triarilbismut per a la síntesi de sulfones, disulfurs i sulfurs en mescles eutèctiques sense l'ús de catalitzadors.

PREFACE

Over the last few years, the research of the Organic Chemistry Department at the University of Alicante has been focused on developing methodologies that are in alignment with the Green Chemistry Principles.

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

Since their recent discovery at the beginning of this century, the application of these eutectic mixtures has been described in several research areas. However, their use in Organic Synthesis has not been exploited. In particular, very few reports of metal-catalyzed processes using these solvents were found throughout the literature.

The use of DESs as reaction medium could improve the sustainability of traditional organic transformations and lead the way to the discovery of novel methodologies and reactions for the synthesis of compounds with high added value.

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

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

I. GENERAL INTRODUCTION

II. RESULTS

CHAPTER I: "C-C Bond Formation Reactions"

CHAPTER II: "C-O Bond Formation Reactions"

CHAPTER III: "C-S Bond Formation Reactions"

III. EXPERIMENTAL PART

IV. CONCLUSIONS

V. BIOGRAPHY

VI. ACKNOWLEDGEMENTS

VII. INDEX

VIII. ABBREVIATION LIST

IX. EPILOGUE

GENERAL INTRODUCTION

SUSTAINABILITY

Concerns about the environmental impact, resulting from human economic activity, have become ubiquitous in nature, with the emerging consequences increasing in all areas, including the appearance of new zoonotic diseases.[1] For this reason, sustainability has become a priority in our society and therefore, there is a growing need to develop new environmentally friendly processes for the chemical industry.

In this context, the concept of Green Chemistry emerged as a new trend, based on the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances within the design, manufacture and applications of chemical products. The term was enshrined in a set of 12 principles at the beginning of the 1990s by different authors, as designing rules to help chemists in their research toward sustainability (Figure 1).[2]

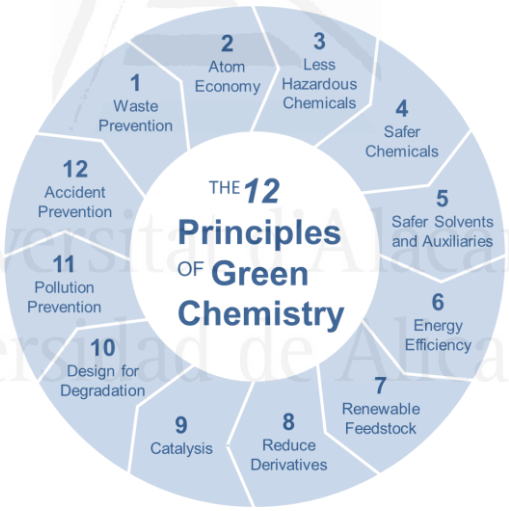


Figure 1. The 12 principles of Green Chemistry.

[1] Naicker, P. R. *Arch. Clin. Microbiol.* **2011**, *2*, 1-5.

[2] a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998; b) Sheldon, R. A.; Arends, I.; Hanefeld, U. *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, 2007; c) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301-312; d) Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437-1451.

Individually, these principles were not new, but what was revolutionary was grouping them together as a guide for the design of processes with less environmental impact.

One major challenge faced in Green Chemistry is the evaluation of the sustainability of chemical processes. Therefore, different metrics that quantify the environmental impact are needed to compare processes and products on the basis of their greenness.[3] The most widely accepted metrics are atom economy[4] and the *E* factor.[5] Atom economy is calculated by dividing the molecular weight of the product by the total sum of the molecular weights of all substances formed in the stoichiometric equation, expressed as a percentage. This metric assumes the use of exact stoichiometric quantities of the starting materials and chemical yields of 100%, and disregards substances which do not appear in the stoichiometric reaction (*e.g.* solvents, work-up chemicals). In contrast, the *E* factor, is defined as the mass ratio of waste to desired product. Unlike atom economy, the *E* factor takes into account the product yield and waste from all the auxiliary substances and also, the *E* factor can be applied to a multi-step procedure facilitating the evaluation of the whole process.

$$\text{Atom economy} = \frac{\text{MW product}}{\sum \text{MW reactants}} \cdot 100$$

$$E \text{ factor} = \frac{\text{mass of total waste}}{\text{mass of product}}$$

Figure 2. Atom economy and *E* factor equations.

Today's chemical sector follows a linear path (Figure 3, left), take-make-dispose, in which feedstocks are pushed through a production chain that relies on product manufacture for only its intended use and finally, the disposal of the product as waste (often toxic, persistent and bioaccumulative).

Within our linear economy, Green Chemistry has allowed the optimization of chemical processes, leading to production systems with lower environmental impact. This has laid the groundwork for a sustainable culture in the chemical industry. However, further steps need to be taken toward sustainability. The new generation of production systems should

[3] Sheldon, R. A. *ACS Sustainable Chem. Eng.* **2018**, *6*, 32-48.
[4] Trost, B. M. *Science* **1991**, *254*, 1471-1477.
[5] a) Sheldon, R. A. *Chem. Ind. (London)* **1992**, 903-906; b) Sheldon, R. A. *Green Chem.* **2017**, *19*, 18-43.

gradually evolve to a circular economy (Figure 3, right), preserving the efficiency of functionality while reducing or eliminating waste. This approach aims to keep products, components and materials at their highest utility and value at all times, expanding the scope of sustainability to the entire process. It promotes, in particular, the use of renewable sources and highlights the importance of the design of novel chemical reactions to reuse and recycle chemicals, as well as, their energy consumption.[6]

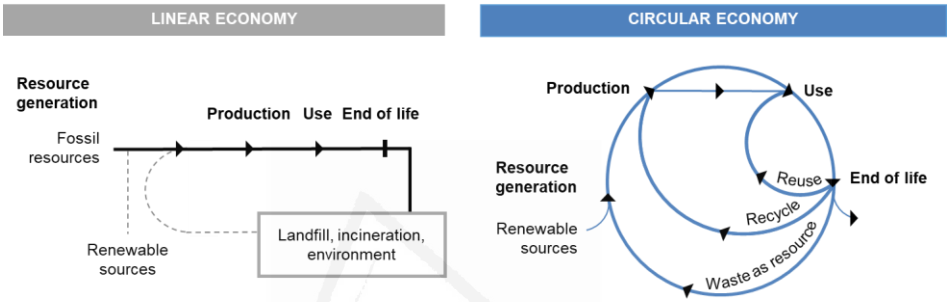


Figure 3. A comprehensive illustration of economic systems.

ALTERNATIVE SOLVENTS

Solvents are often accountable for the vast majority of mass in synthesis and processes. Many conventional solvents are harmful, toxic, environmentally damaging, and their volatility contributes to air, water and land pollution. Particularly, it has been estimated that solvents constitute about 80-90% of the total mass of chemicals involved in pharmaceutical manufacturing.[7] In an effort to address these shortcomings, several alternative solvents have emerged over the last few years.[8]

From a strict sustainability point of view, the most evident solution is the complete elimination of solvents. Many solvent-free processes can be found in the literature.[9] These reactions have a high reaction rate and an easier purification, but the absence of solvent is

[6] a) Keijer, T.; Bakker, V.; Slootweg, J. C. *Nat. Chem.* **2019**, *11*, 190-195; b) Zimmerman, J. B.; Anastas, P. T.; Erythropel, H. C.; Leitner, W. *Science* **2020**, *367*, 397-400.
[7] Constable, D. J. C.; Jiménez-González, C.; Henderson, R. K. *Org. Process Res. Dev.* **2007**, *11*, 133-137.
[8] Sheldon, R. A. *Green Chem.* **2005**, *7*, 267-278.
[9] a) Metzger, J. O. *Angew. Chem. Int. Ed.* **1998**, *37*, 2975-2978; Varma, R. *Green Chem.* **1999**, *1*, 43-55; b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025-1074.

not widely applicable to all chemical reactions. In general, solvents are often essential to ease heating processes and mass transfer within the reaction, assuming fast and safe conversions, preventing the formation of unwanted side-products by dilution and stabilizing transition metal states. Consequently, many efforts have been devoted to finding alternative sustainable media.

Water, the most abundant and innocuous substance on earth, seems to be an ideal alternative to organic solvents because it is an inexpensive solvent, readily available, non-toxic, completely safe and very attractive from both an economical and environmental point of view. The unique structure and physicochemical properties of water lead to particular interactions, like hydrophobic effects, that enhance the rate and the selectivity of a wide variety of organic reactions. The low solubility of oxygen in water facilitates air-sensitive transformations carried out in open air and also, the low solubility of organic compounds allows easier separation. Moreover, the use of water implies the elimination of protection-deprotection steps for certain compounds with acidic-hydrogen functional groups. In spite of these potential advantages, the inherently poor solubility of organic reagents, the facile decomposition of active species (*e.g.* catalysts) and the incompatibility of several organic functionalities due to hydrolysis, restricts the use of water as a universal solvent in organic synthesis, with the cost of possible water purification being nearly prohibitive.[10]

Supercritical fluids (SCFs) have been proved to be valuable alternatives to traditional organic solvents both in the industry and in academic research.[11] SCFs are generated by simultaneous heating and compression of the corresponding compound, above its critical point. The most employed are supercritical CO_2[12] (31.1 ^{o}C and 73.8 bar) and supercritical water[13] (374 ^{o}C and 220 bar). In the supercritical region, the fluid possess a combination of properties between the liquid and gas state. Typically, SCFs exhibit relatively high densities,

[10] a) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725-748; b) Simon, M.-O.; Li, C.-J. *Chem. Soc. Rev.* **2012**, *41*, 1415-1427; c) Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. *Chem. Rev.* **2018**, *118*, 679-746.
[11] a) Baiker, A. *Chem. Rev.* **1999**, *99*, 453-474; b) Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475-494; c) Jessop, P. G.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids*, John Wiley & Sons, 2008.
[12] Wells, S. L.; DeSimone, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 518-527.
[13] Savage, P. E. *Chem. Rev.* **1999**, *99*, 603-622.

low viscosities and high diffusivities, which offer a potential for increased reaction rates and a high solubility of gases. Also, their potential lies in the complete removal of the solvent by degassing the system. However, significant drawbacks such as the expensive and complex equipment along with a high power consumption, the low solubility of polar substances and the chemical reactivity of the solvent (incompatibility of supercritical CO_2 with amines due to carbamate formation), reveal the limitations in the applicability of the SCFs.

Many organic reactions have been carried out in pure and biphasic fluorous media. Perfluorinated liquids have unique properties for organic synthesis such as high hydrogen bond ability, low nucleophilicity and toxicity, non-flammability and non-polar character. These type of solvents might provide an attractive approach, except for their high cost and persistence in the environment, which reduces its attractiveness as sustainable solvents.[14]

Biomass and waste exhibit great potential for replacing fossil fuels in the production of bio-based solvents.[15] Terpenes are present in high concentration in essential oils and resins of a diverse range of biomass. These can be used directly as solvents (D-limonene and pinene isomers) or modified to produce more stable derivatives (*p*-cymene). Glycerol, a widely accepted sustainable solvent, can be obtained from biodiesel production (as by-product). Furthermore, the chemical or enzymatic hydrolysis of starch and cellulose produce glucose. Subsequent chemical transformations of glucose can provide a wide range of valuable products, which can be employed as solvents (*e.g.* γ-valerolactone, 2-methyltetrahydrofuran or cyrene). Other bio-based solvents, such as ethanol and ethyl lactate, are produced through fermentation processes of waste sugars. Also, reacting CO_2 with other compounds obtained from waste sources, can yield alternative solvents like cyclic carbonates. At present, bio-based solvents are produced at relatively small scales and, as a consequence, are more expensive than their petroleum-derived counterparts. All these facts,

[14] Ryu, I.; Matsubara, H.; Emnet, C.; Gladysz, J. A.; Takeuchi, S.; Nakamura, Y.; Curra, D. P. Fluorous Solvents, in *Green Reaction Media in Organic Synthesis* (Ed.: K. Mikami), Blackwell, Oxford, UK, 2005, pp. 59-124.

[15] a) Byrne, F.; Jin, S.; Sherwood, J.; McElroy, C. R.; Farmer, T. J.; Clark, J. H.; Hunt, A. J. (Ed.) *Bio-based solvents*, John Wiley & Sons Ltd., Hoboken, 2017; b) Clarke, C. J.; Tu, W.-C.; Levers, O.; Brohl, A.; Hallett, J. P. *Chem. Rev.* **2018**, *118*, 747-800.

combined with the lack of bio-based solvents with different polarity characteristics, limit their application as sustainable solvents in organic synthesis.

Some inert polymers, mainly polyethylene glycol (PEG) and polypropylene glycol (PPG), represent an alternative of volatile organic compounds (VOCs). Liquid polymers have the inherent advantage of negligible volatility but exhibit low solubility in water and their biodegradability decreases as their molecular weight increases.[16]

In this regard, ionic liquids (ILs)[17] are salts, typically containing a large organic cation and a small inorganic or organic anion, in which the ions are poorly coordinated, resulting in a melting temperature below 100 ^{o}C. The charge of the cation, as well as the charge of the anion, is delocalized through a large volume of the molecule by resonance, which prevents the formation of a stable crystal lattice. ILs are considered green solvents that exhibit characteristics such as non-volatility, low flammability, high chemical and thermal stabilities, remarkable solvating power and tuneable properties. However, it should be pointed out that some properties of ILs are incompatible with Green Chemistry standards due to most of them being toxic and persistent in the environment[18] and their synthesis requires a large number of steps, employing, in some cases, petroleum-derived chemicals, which results in high economical costs.

More recently, trying to overcome the aforementioned drawbacks of ILs, a new generation of solvents emerged. Deep eutectic solvents (DESs), were firstly described by Abbott at the beginning of this century.[19] The physical properties of DESs are similar to those of ILs, with the exception that DESs are generally made of non-toxic, cheap and sustainable

[16] a) Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64-82; b) Heldebrant, D. J.; Witt, H. N.; Walsh, S. M.; Ellis, T.; Rauscher, J.; Jessop, P. G. *Green Chem.* **2006**, *8*, 807-815.

[17] Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*, Wiley-VCH, Verlag, 2002; Hallett, J. P.; Welton, T. *Chem. Rev.* **2011**, *111*, 3508-3576.

[18] a) Thuy Pham, T. P.; Cho, C.-W.; Yun, Y.-S. *Water Res.* **2010**, *44*, 352-372; b) Egorova, K. S.; Ananikov, V. P. *ChemSusChem* **2014**, *7*, 336-360.

[19] a) Abbott, A. P.; Capper, G.; Davies, D. L.; Munro, H. L.; Rasheed, R. K.; Tambyrajah, V. *Chem. Commun.* **2001**, 2010-2011; b) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Chem. Commun.* **2003**, 70-71; c) Abbott, A. P.; Boothby, D.; Capper, G.; Davies, D. L.; Rasheed, R. K. *J. Am. Chem. Soc.* **2004**, *126*, 9142-9147.

compounds through a simple synthesis with 100% atom economy. All these factors, highlight the broad potential of DESs as a replacement for hazardous organic solvents.

The selection of a proper solvent is often difficult since it has to meet certain requirements such as chemical efficiency for the reaction, safety for human health and the environment, industrial constraints and cost. Therefore, solvents have been ranked in different guides depending on their environmental impact, safety and health characteristics.[20]

However, an important point to consider is whether these alternative solvents are truly sustainable alternatives. Although one solvent can enable a more sustainable process, its application may increase environmental impacts or negatively affect the cost of the process. Consequently, the solvent should be selected on a process-by-process basis and all solvent alternatives should be taken into consideration.

Deep Eutectic Solvents

Deep eutectic solvents (DESs) are systems formed by an eutectic mixture of two or more components, generally Lewis and Brønsted acids and bases, which can contain a variety of anionic and/or cationic species.[21] The resulting DES is characterized by a melting point much lower than its individual components (Figure 4). This significant decrease in the melting point stems from electrostatic and strong hydrogen bonding interactions, which serve to difficult the ability of the precursors to crystalize, giving rise to a liquid mixture close to room temperature. Although eutectic mixtures have been acknowledged for decades,[22] as well as their unusual reactivities near the eutectic point,[23] it was not until the beginning of this century that these mixtures started to become popular in the scientific community.[19]

[20] a) Prat, D.; Pardigon, O.; Flemming, H.-W.; Letestu, S.; Ducandas, V. r.; Isnard, P.; Guntrum, E.; Senac, T.; Ruisseau, S. p.; Cruciani, P. *Org. Process Res. Dev.* **2013**, *17*, 1517-1525; b) Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F. *Green Chem.* **2016**, *18*, 3879-3890; c) Diorazio, L. J.; Hose, D. R.; Adlington, N. K. *Org. Process Res. Dev.* **2016**, *20*, 760-773.
[21] a) Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jérôme, F. *Chem. Soc. Rev.* **2012**, *41*, 7108-7146; b) Smith, E. L.; Abbott, A. P.; Ryder, K. S. *Chem. Rev.* **2014**, *114*, 11060-11082; c) Ramón, D. J.; Guillena, G. *Deep Eutectic Solvents: Synthesis, Properties, and Applications*, John Wiley & Sons, 2020.
[22] Rastogi, R. P.; Bassi, P. S. *J. Phys. Chem.* **1964**, *68*, 2398-2406.
[23] Pincock, R. E. *Acc. Chem. Res.* **1969**, *2*, 97-103.

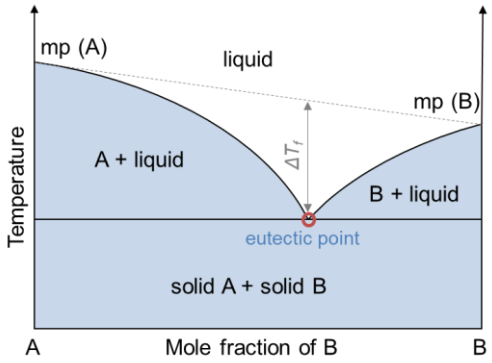


Figure 4. Phase diagram of a binary mixture.

DESs are largely classified depending on their composition and properties (Figure 5). DESs formed by metal halides and quaternary ammonium salts, type I, are usually more expensive and toxic than other type of DESs due to the use of anhydrous metal halides in their preparation. The limited range of non-hydrated metal halides with a suitable low melting point, can be increased by using hydrated metal halides (type II DESs). The relatively low cost of many hydrated metal salts coupled with their inherent air/moisture stability, generates a wide variety of low temperature eutectic mixtures.

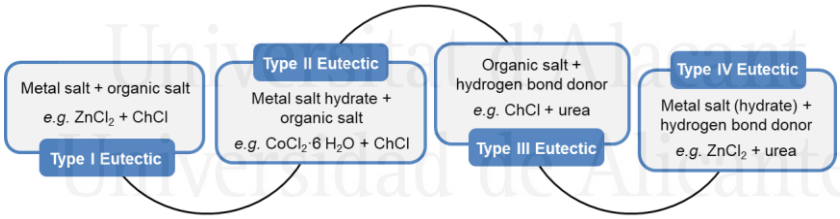


Figure 5. Schematic classification of different types of DESs.

Type III eutectics, formed by the combination of a hydrogen bond acceptor (HBA), typically a quaternary ammonium salt, and hydrogen bond donors (HBDs), are the most important DESs from a sustainable point of view. A wide range of inexpensive, safe, renewable and biodegradable components are capable of forming this type of eutectic mixtures, including natural products, such as organic acids, sugars and amino acids (Figure

6). In those cases, DESs are called natural deep eutectic solvents (NADESs).[24] Furthermore, it has been shown that different metal halides form eutectic mixtures in combination with HBDs (type IV DESs). Additionally, outside this classification, several non-ionic based DESs have been described such as hydrophobic DESs composed by long chain alcohols, carboxylic acids or ammonium derivatives.[25]

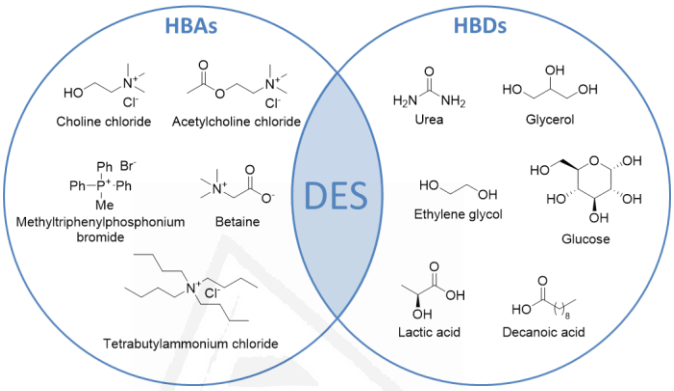


Figure 6. Molecular structures of HBDs and HBAs of type III DESs.

The interest in type III DESs increased considerably at industrial and academic level due to their interesting and unique properties. DESs are usually prepared by mixing the appropriate amount of the corresponding HBA and HBD, and heating the mixture until a colorless liquid is formed. Therefore, the synthetic procedure is very simple and environmentally benign with no waste production (*E* factor = 0) and a maximum atom economy. The number of DESs that can be synthesized from the available chemicals has no limitation, owing this to the large number of components that form DESs. Typically, DESs are composed of choline chloride (ChCl) or natural amino acids as HBAs and urea, natural carboxylic acids or polyalcohols as HBDs, hence, most of their components come from renewable sources.[26,24b] For example, ChCl is a cheap, biodegradable and non-toxic salt, used as additive in chicken food and it can be extracted from biomass or simply produced

[24] a) Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R. L.; Duarte, A. R. C. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1063-1071; b) Liu, Y.; Friesen, J. B.; McAlpine, J. B.; Lankin, D. C.; Chen, S.-N.; Pauli, G. F. *J. Nat. Prod.* **2018**, *81*, 679-690.

[25] Florindo, C.; Branco, L. C.; Marrucho, I. M. *ChemSusChem* **2019**, *12*, 1549-1559.

[26] Dai, Y.; van Spronsen, J.; Witkamp, G.-J.; Verpoorte, R.; Choi, Y. H. *Anal. Chim. Acta* **2013**, *766*, 61-68.

from triethylamine, hydrochloric acid and ethylene oxide in a simple and economic process.[27] Several studies reported very low toxicities[28] and a high biodegradability[29] of the DESs. However, these properties depend on the components of each DES. Moreover, the physicochemical and thermal properties of DESs can be easily tuned by varying the components and their ratios, leading to a specific design according to each particular application.[30]

The real structure of DESs is unknown, but many researchers sought to achieve a better understanding of their complex structure.[31] The typical ChCl:urea (1:2) eutectic mixture was initially understood as a type of complex in which the chloride anion was delocalized from the choline onto urea, forming a complex ion (Figure 7).[32]

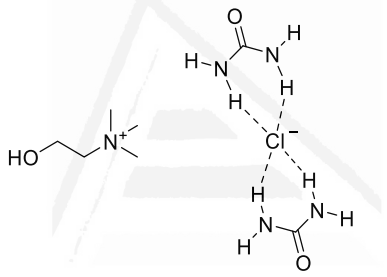


Figure 7. The initially proposed complex anion structure of ChCl:urea (1:2).

[27] Frauenkron, M.; Melder, J. P.; Ruider, G.; Rossbacher, R.; Höke, H. *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2001.

[28] a) Hayyan, M.; Hashim, M. A.; Hayyan, A.; Al-Saadi, M. A.; AlNashef, I. M.; Mirghani, M. E. S.; Saheed, O. K. *Chemosphere* **2013**, *90*, 2193-2195; b) Juneidi, I.; Hayyan, M.; Hashim, M. A. *RSC Adv.* **2015**, *5*, 83636-83647; c) Macario, I. P. E.; Jesus, F.; Pereira, J. L.; Ventura, S. P. M.; Goncalves, A. M. M.; Coutinho, J. A. P.; Goncalves, F. J. M. *Chemosphere* **2018**, *212*, 890-897.

[29] a) Radošević, K.; Cvjetko Bubalo, M.; Gaurina Srček, V.; Grgas, D.; Landeka Dragičević, T.; Radojčić Redovniković, I. *Ecotoxicol. Environ. Saf.* **2015**, *112*, 46-53; b) Zhao, B.-Y.; Xu, P.; Yang, F.-X.; Wu, H.; Zong, M.-H.; Lou, W.-Y. *ACS Sustainable Chem. Eng.* **2015**, *3*, 2746-2755.

[30] a) Jeong, K. M.; Lee, M. S.; Nam, M. W.; Zhao, J.; Jin, Y.; Lee, D.-K.; Kwon, S. W.; Jeong, J. H.; Lee, J. *J. Chromatogr. A* **2015**, *1424*, 10-17; b) Liu, X.; Fu, N.; Zhang, Q.; Cai, S.; Wang, Q.; Han, D.; Tang, B. *J. Chromatogr. Sci.* **2019**, *57*, 272-278.

[31] Kaur, S.; Kumari, M.; Kashyap, H. K. *J. Phys. Chem. B* **2020**, *124*, 10601-10616.

[32] Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Chem. Commun.* **2003**, 70-71.

Afterwards, the structural characteristics of different mixtures of choline chloride and urea were investigated by performing molecular dynamic (MD) simulations.[33] Surprisingly, this study showed that cation-anion interaction dominates when choline chloride was in excess, as in its crystalline structure, and *vice versa* when urea was in excess (mainly anion-urea interactions were observed). However, at the eutectic ratio, the cation-anion and anion-urea interactions energies are balanced. Hence, this was the first insight into evidence of a more complicated structure than the complex ion model, because alongside the choline chloride interaction, hydrogen bonding between chloride-urea and choline-urea (more modest interactions) were observed, and a balance of these interactions seems crucial to form this DES.

More recently, the first experimental study of the liquid structure of ChCl:urea (1:2), using neutron diffraction measurements at 303 K and atomistic modelling to refine the structure, was reported.[34] This excellent work revealed that the choline-chloride O-H···Cl bond is relatively strong and stable, and the interplay between this bond and the urea N-H···Cl, as well as, the urea-urea N-H···O bonding, defines the structure of the system. In other words, the bulk structure could be considered as a dynamic cage centered around the chloride, competitively coordinated between choline and urea H-bonds (Figure 8).

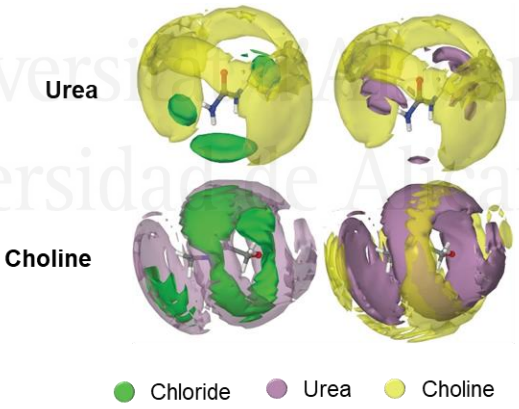


Figure 8. SDF plots showing the typical coordination of molecules in ChCl:urea (1:2).

[33] Sun, H.; Li, Y.; Wu, X.; Li, G. *J. Mol. Model.* **2013**, *19*, 2433-2441.
[34] Hammond, O. S.; Bowron, D. T.; Edler, K. J. *Green Chem.* **2016**, *18*, 2736-2744.

From the balance between electrostatics and H-bonding, chloride is strongly associated in a circular bond around the choline free hydroxyl group and ammonium moiety, but a secondary occupation of chloride anions can be observed in the positive charged choline methyl groups. Simultaneously, urea interacts with the chloride through its proximal and distal protons while it is associated with several other urea molecules. The spatial density function (SDF) plot of choline around urea shows that the interactions between these two species is not predominantly hydrogen bond driven. Choline molecules are radially around the C=O axis of urea molecule. This configuration allows choline to form strong H-bonds with chloride *via* its hydroxyl group and also, a weak hydrogen bond interaction with electronegative urea atoms.

The effect of water upon ChCl:urea (1:2) eutectic mixture, in different DES:water molar ratios has also been analyzed.[35] At low levels (≤ 1 water molar equivalent), water slightly contributes to the hydrogen bonding network and enhances the choline-urea interaction. Whereas higher concentrations of water, between 2 and 10 equivalents, DES clusters still exist but are separated by the diluent. At 15 molar water content, DES components are preferably solvated by water and consequently, the system becomes as DES aqueous solution. This explains the tolerance of hydrophilic DES toward hydration and trends in their physicochemical properties such as the reduction in viscosity with water.[36]

The structure and hydrogen bonding in ChCl:ethylene glycol (1:2) and ChCl:glycerol (1:2) is fundamentally different, with a much stronger self-interaction of polyol-polyol component, leading to stronger choline-chloride interactions in the structure and thus, weaker chloride intercalation.[37] Other phenol based eutectic mixtures were analyzed using concurrent synchrotron powder X-ray diffraction (XRD) and differential scanning calorimetry (DSC), revealing that the formation of many DESs may be due to the existence of highly metastable low melting point co-crystals.[38]

[35] Hammond, O. S.; Bowron, D. T.; Edler, K. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 9782-9785.
[36] Dai, Y.; Witkamp, G.-J.; Verpoorte, R.; Choi, Y. H. *Food Chem.* **2015**, *187*, 14-19.
[37] a) Stefanovic, R.; Ludwig, M.; Webber, G. B.; Atkin, R.; Page, A. J. *Phys. Chem. Chem. Phys.* **2017**, *19*, 3297-3306; b) Turner, A. H.; Holbrey, J. D. *Phys. Chem. Chem. Phys.* **2019**, *21*, 21782-21789.
[38] Hall, C. L.; Potticary, J.; Hamilton, V.; Gaisford, S.; Buanz, A.; Hall, S. R. *Chem. Commun.* **2020**, *56*, 10726-10729.

In contrast to traditional molecular solvents, which typically have a very homogeneous H-bonding character (O-H···O in water or alcohols), DESs contain many different H-bond types. The delicate balance of all these interactions, could be expected to increase the entropy of the system (highly disordered structure) and explain the eutectic point depression. Obviously, it is difficult to extend these conclusions to other DESs, but, higher understanding of DES structure can lead to new applications.

Applications of DESs

DESs have received a great interest in diverse fields due to their unique and adjustable properties for different applications, showing an exponential growth in the number of related publications over the last few years (Figure 9).

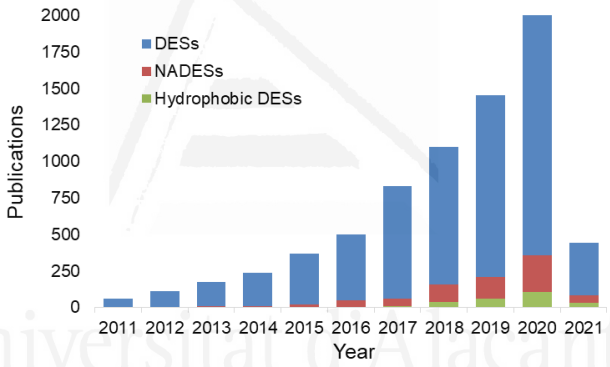


Figure 9. Publications in the field of DESs per year (updated February 2021, Scifinder).

The high solvation capacity of DESs has driven to its application in the extraction of a wide range of bioactive compounds such as phenolic compounds, polysaccharides and proteins, from a variety of material sources.[39] In this sense, DESs can be efficiently applied to the treatment of biomass, including dissolution of lignin, conversion of carbohydrates to furanic derivatives, extraction/purification of bio-based chemicals[40] and also, biodiesel production.[41] Additionally, the ionic nature of DESs leads to interesting solvent properties for

[39] a) Dai, Y.; van Spronsen, J.; Witkamp, G.-J.; Verpoorte, R.; Choi, Y. H. *Anal. Chim. Acta* **2013**, *766*, 61-68; b) Zainal-Abidin, M. H.; Hayyan, M.; Hayyan, A.; Jayakumar, N. S. *Anal. Chim. Acta* **2017**, *979*, 1-23.
[40] Vigier, K. D. O.; Chatel, G.; Jerome, F. *ChemCatChem* **2015**, *7*, 1250-1260.
[41] Tao, L.; Yuefeng, D.; Shucai, G.; Ji, C. *Chin. J. Chem. Eng.* **2010**, *18*, 322-327.

CO_2 and SO_2 capture and the conversion of the captured gases to other value-added compounds.[42] More recently, the tunability of DESs components arose to hydrophobic DESs.[43] Their immiscibility with water makes hydrophobic DESs potential alternatives for the extraction of diverse compounds from water.[44]

Alternatively, the preorganized supramolecular nature of DESs provides a soft template to guide the formation of nanostructured materials,[45] from metal nanoparticles (MNPs) or nanocrystals to nanosheets, as well as hierarchically porous carbons or supramolecular gels.[46] Otherwise, many DESs have been shown to be compatible with protein and nucleic acid biomolecules. For example, it was demonstrated that DNA was stable and retained its structural integrity after 6 months when stored in a DES, and that enzymatic peptide synthesis, nucleic acid replication and DNA/RNA architectures could be performed efficiently in DESs.[47] Another recent application of DESs is their use as a medium for evaporative crystal growth of pharmaceuticals with a morphological control, by utilizing a system where one of the components is inherently volatile, as for instance phenol.[48]

Moreover, the conductive properties of DESs make them an ideal medium for a wide range of electrochemical applications, namely MNPs or nanocrystals synthesis through electrodeposition,[49] and electropolishing of metal surfaces.[50]

[42] a) Yang, D.; Hou, M.; Ning, H.; Zhang, J.; Ma, J.; Yang, G.; Han, B. *Green Chem.* **2013**, *15*, 2261-2265; b) Sarmad, S.; Mikkola, J.-P.; Ji, X. *ChemSusChem* **2017**, *10*, 324-352; c) Wu, K.; Su, T.; Hao, D.; Liao, W.; Zhao, Y.; Ren, W.; Deng, C.; Lü, H. *Chem. Commun.* **2018**, *54*, 9579-9582; d) Long, G.; Yang, C.; Yang, X.; Zhao, T.; Liu, F.; Cao, J. *ACS Sustainable Chem. Eng.* **2020**, *8*, 2608-2613.

[43] van Osch, D. J. G. P.; Zubeir, L. F.; van den Bruinhorst, A.; Rocha, M. A. A.; Kroon, M. C. *Green Chem.* **2015**, *17*, 4518-4521.

[44] Lee, J.; Jung, D.; Park, K. *TrAC, Trends Anal. Chem.* **2019**, *118*, 853-868.

[45] Wagle, D. V.; Zhao, H.; Baker, G. A. *Acc. Chem. Res.* **2014**, *47*, 2299-2308.

[46] Ruiz-Olles, J.; Slavik, P.; Whitelaw, N. K.; Smith, D. K. *Angew. Chem. Int. Ed.* **2019**, *58*, 4173-4178.

[47] a) Mondal, D.; Sharma, M.; Mukesh, C.; Gupta, V.; Prasad, K. *Chem. Commun.* **2013**, *49*, 9606-9608; b) Guajardo, N.; Müller, C. R.; Schrebler, R.; Carlesi, C.; Domínguez de María, P. *ChemCatChem* **2016**, *8*, 1020-1027; c) Guajardo, N.; Domínguez de María, P. *ChemCatChem* **2019**, *11*, 3128-3137; d) Núñez-Pertíñez, S.; Wilks, T. R. *Front. Chem.* **2020**, *8*, 41.

[48] Potticary, J.; Hall, C.; Hamilton, V.; McCabe, J. F.; Hall, S. R. *Cryst. Growth Des.* **2020**, *20*, 2877-2884.

[49] a) Wei, L.; Fan, Y.-J.; Tian, N.; Zhou, Z.-Y.; Zhao, X.-Q.; Mao, B.-W.; Sun, S.-G. *J. Phys. Chem. C* **2012**, *116*, 2040-2044; b) Renjith, A.; Roy, A.; Lakshminarayanan, V. *J. Colloid Interface Sci.* **2014**, *426*, 270-279.

[50] Alrbaey, K.; Wimpenny, D. I.; Al-Barzinjy, A.; Moroz, A. *J. Mater. Eng. Perform.* **2016**, *25*, 2836-2846.

In the field of catalysis, DESs are starting to be used as reaction media in different chemical transformations ranging from organic transformations and metal-catalyzed organic reactions to polymerizations[51] and bio-catalyzed reactions.[52]

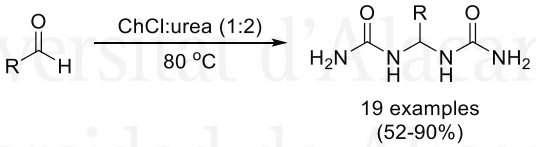
Organic synthesis in DESs

In recent years, the use of DESs as an alternative reaction media for carrying out synthetic transformations, instead of volatile organic compounds (VOCs), is becoming increasingly important.[53] These mixtures can act not only as innocuous solvents, but also as reagents and, in some cases as catalysts, owing this to their acidic or basic character.

In this section, various organic transformations are presented, highlighting the broad potential of DESs to provide plenty of opportunities for developing new and unexplored synthetic routes.

DESs as reagents

Urea derivatives are common constituents in different eutectic mixtures. In this context, aldehydes reacted with urea present in ChCl:urea (1:2) mixture, producing the corresponding geminal diureas (Scheme 1).[54]



Scheme 1. Synthesis of geminal diureas.

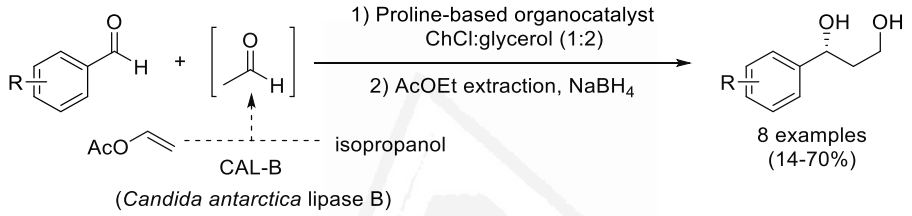
In this vein, a variety of dihydropyrimidinones were prepared from *N,N'*-dimethylurea (DMU), aldehydes and 1,3-dicarbonylic compounds in a DES formed by the same DMU and

[51] Gómez, A. V.; Biswas, A.; Tadini, C. C.; Furtado, R. F.; Alves, C. R.; Cheng, H. N. *J. Braz. Chem. Soc.* **2019**, *30*, 717-726.
[52] Pätzold, M.; Siebenhaller, S.; Kara, S.; Liese, A.; Syldatk, C.; Holtmann, D. *Trends Biotechnol.* **2019**, *37*, 943-959.
[53] a) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Guillena, G.; Pastor, I. M.; Ramón, D. J. *Eur. J. Org. Chem.* **2016**, 612-632; b) Liu, P.; Hao, J.-W.; Mo, L.-P.; Zhang, Z.-H. *RSC Adv.* **2015**, *5*, 48675-48704.
[54] Azizi, N.; Alipour, M. *J. Mol. Liq.* **2015**, *206*, 268-271.

tartaric acid.[55] The same solvent was used for the synthesis of other DMU containing compounds.[56]

Organocatalyzed reactions in DESs

As aforementioned, the broad tunability properties of DESs enables their use in acid- or base-catalyzed processes as a solvent and/or catalysts. With regard to organocatalysis, the first application in this field was the enantioselective cross-aldol reaction by interfacing enzyme catalysis with organocatalysis in ChCl:glycerol (1:2) eutectic mixture (Scheme 2).[57]



Scheme 2. Cross-aldol reaction *via* tandem enzyme catalysis and organocatalysis in DESs.

Afterwards, several studies have emerged for the asymmetric Michael[58] reaction using DESs as reaction media. Interestingly, novel chiral DESs have recently been emerged as both reaction media and chiral organocatalysts.[59]

DESs in the synthesis of heterocycles

DESs have been successfully used in cyclocondesation reactions for the preparation of a wide range of heterocycles. Different synthetic approaches were employed for the

[55] Gore, S.; Baskaran, S.; König, B. *Green Chem.* **2011**, *13*, 1009-1013.

[56] a) Gore, S.; Baskaran, S.; König, B. *Adv. Synth. Catal.* **2012**, *354*, 2368-2372; b) Kotha, S.; Gupta, N. K.; Aswar, V. R. *Chem. Asian. J.* **2019**, *14*, 3188-3197.

[57] Müller, C. R.; Meiners, I.; Domínguez de María, P. *RSC Adv.* **2014**, *4*, 46097-46101.

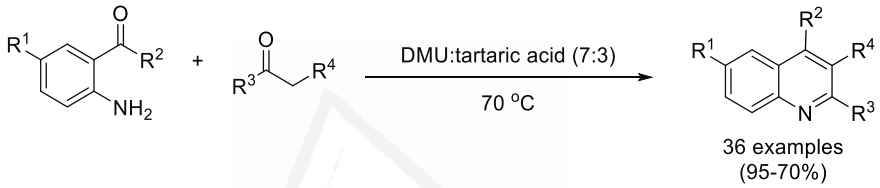
[58] a) Massolo, E.; Palmieri, S.; Benaglia, M.; Capriati, V.; Perna, F. M. *Green Chem.* **2016**, *18*, 792-797; b) Ñíguez, D. R.; Guillena, G.; Alonso, D. A. *ACS Sustainable Chem. Eng.* **2017**, *5*, 10649-10656; c) Torregrosa-Chinillach, A.; Sánchez-Laó, A.; Santagostino, E.; Chinchilla, R. *Molecules* **2019**, *24*, 4058.

[59] Palomba, T.; Ciancaleoni, G.; Del Giacco, T.; Germani, R.; Ianni, F.; Tiecco, M. *J. Mol. Liq.* **2018**, *262*, 285-294.

synthesis of diverse five-membered heterocycles in DESs, as for example, different nitrogen- and/or oxygen-containing rings[60] and even, thiophenes.[61]

A very interesting reaction such as the regiospecific Fischer indole synthesis using ChCl:$ZnCl_2$ (1:2) mixture, as dual catalyst-solvent promoter, has been reported.[62] DESs were also employed to perform indole based reactions to obtain different compounds.[63]

Another classic reaction that has been reported in DESs, is the Friedländer synthesis of quinolines using different acidic eutectic mixtures (Scheme 3).[64]



Scheme 3. Synthesis of quinoline derivatives.

Urea based eutectic mixtures have also been employed as effective reaction media to prepare *N*-arylphtalimide[65] and aurone[66] derivatives with a considerable improvement in the results compared with those obtained when using VOCs as reaction media.

[60] a) Handy, S.; Lavender, K. *Tetrahedron Lett.* **2013**, *54*, 4377-4379; b) More, P. A.; Gadilohar, B. L.; Shankarling, G. S. *Catal. Lett.* **2014**, *144*, 1393-1398; c) Wang, P.; Ma, F.-P.; Zhang, Z.-H. *J. Mol. Liq.* **2014**, *198*, 259-262; d) Sebest, F.; Haselgrove, S.; White, A. J. P.; Díez-González, S. *Synlett* **2020**, *31*, 605-609.

[61] Mancuso, R.; Maner, A.; Cicco, L.; Perna, F. M.; Capriati, V.; Gabriele, B. *Tetrahedron* **2016**, *72*, 4239-4244.

[62] Calderon Morales, R.; Tambyrajah, V.; Jenkins, P. R.; Davies, D. L.; Abbott, A. P. *Chem. Commun.* **2004**, 158-159.

[63] a) Jella, R. R.; Nagarajan, R. *Tetrahedron* **2013**, *69*, 10249-10253; b) Handy, S.; Wright, M. *Tetrahedron Lett.* **2014**, *55*, 3440-3442; c) Sanap, A. K.; Shankarling, G. S. *RSC Adv.* **2014**, *4*, 34938-34943; d) Chandam, D.; Mulik, A.; Patil, P.; Jagdale, S.; Patil, D.; Sankpal, S.; Deshmukh, M. *J. Mol. Liq.* **2015**, *207*, 14-20.

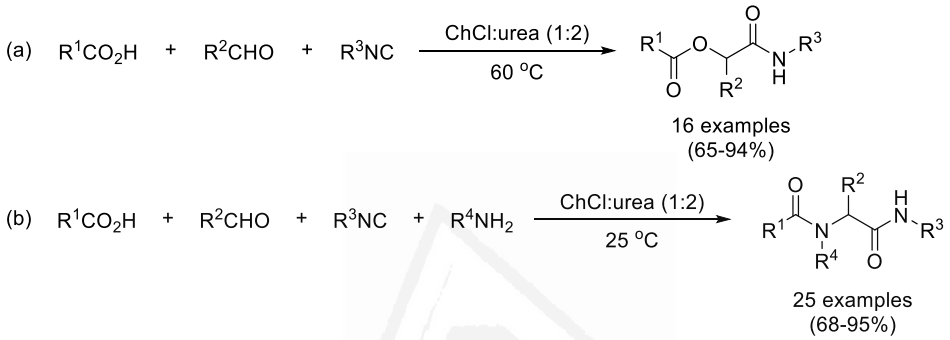
[64] a) Ma, F.-P.; Cheng, G.-T.; He, Z.-G.; Zhang, Z.-H. *Aust. J. Chem.* **2012**, *65*, 409-416; b) Bafti, B.; Khabazzadeh, H. *J. Chem. Sci.* **2014**, *126*, 881-887.

[65] Lobo, H. R.; Singh, B. S.; Shankarling, G. S. *Green Chem. Lett. Rev.* **2012**, *5*, 487-533.

[66] Taylor, K. M.; Taylor, Z. E.; Handy, S. T. *Tetrahedron Lett.* **2017**, *58*, 240-241.

Multicomponent reactions in DESs

Multicomponent reactions (MCRs) are particularly attractive transformations in terms of sustainability owing this to the multi-bond formation in a one-pot process, resulting in high atom economy and efficient synthetic routes. Many important MCRs have been performed in DESs such as the isocyanide-based Passerini[67] and Ugi[68] reactions (Scheme 4).



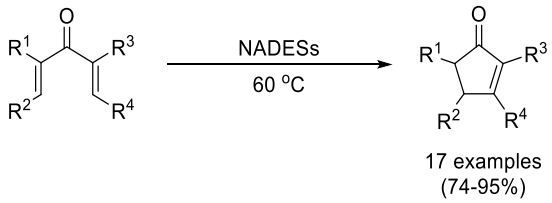
Scheme 4. (a) Passerini and (b) Ugi reactions catalyzed in DESs.

Other MCRs have been successfully applied in DESs as Biginelli reaction,[69] Mannich-type transformations[70] or the A^3-coupling reaction. [71]

Miscellaneous transformations in DESs

DESs have been investigated on several other transformations such as carbon-carbon bond formation processes, including the Diels-Alder reaction, Knoevenagel condensation, ring opening of epoxides or Nazarov cyclization, among others (Scheme 5).[72]

[67] Shaabani, A.; Afshari, R.; Hooshmand, S. E. *Res. Chem. Intermed.* **2016**, *42*, 5607-5616.
[68] Azizi, N.; Dezfooli, S.; Hashemi, M. M. *C. R. Chim.* **2013**, *16*, 1098-1102.
[69] Navarro, C. A.; Sierra, C. A.; Ochoa-Puentes, C. *RSC Adv.* **2016**, *6*, 65355-65365.
[70] a) Disale, S. T.; Kale, S. R.; Kahandal, S. S.; Srinivasan, T. G.; Jayaram, R. V. *Tetrahedron Lett.* **2012**, *53*, 2277-2279; b) Keshavarzipour, F.; Tavakol, H. *Catal. Lett.* **2015**, *145*, 1062-1066.
[71] Obst, M.; Srivastava, A.; Baskaran, S.; König, B. *Synlett* **2018**, *29*, 185-188.
[72] a) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Green Chem.* **2002**, *4*, 24-26; b) Azizi, N.; Batebi, E. *Catal. Sci. Technol.* **2012**, *2*, 2445-2448; c) Nejrotti, S.; Iannicelli, M.; Jamil, S. S.; Arnodo, D.; Blangetti, M.; Prandi, C. *Green Chem.* **2020**, *22*, 110-117; d) Srivastava, S. *ChemistrySelect* **2020**, *5*, 799-803.



Scheme 5. NADES-catalyzed Nazarov cyclization.

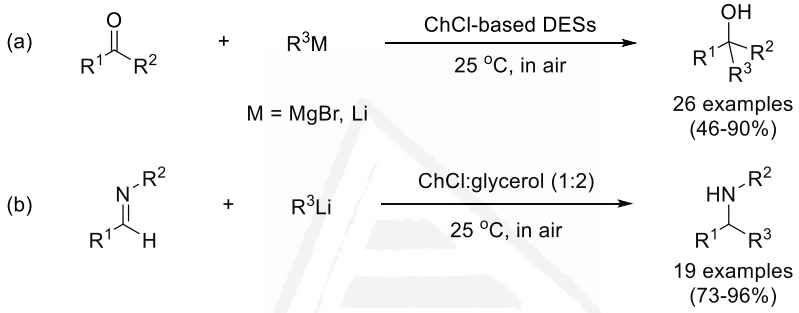
Aromatic amines have been mono-*N*-alkylated with alkyl bromides in ChCl:urea (1:2),[73] and the same DES was used in the *O*-benzylation of phenols.[74] Additionally, different redox reactions can occur in a DES medium, such as oxidation of alcohols or sulfides, reduction of carbonyl compounds or alkynes and halogenation reactions.[75] Even DESs, have been applied for the synthesis of supramolecular macrocycles, in particular pillar[*n*]arenes.[76]

Metal-promoted organic transformations in DESs

Metal-catalyzed organic reactions comprise one of the most frequently used protocols in organic synthesis. Although several metal catalysts were very efficient to promote organic reactions, the recovery and reuse of these catalysts were difficult. Consequently, intensive research efforts have been focused on proceeding metal-catalyzed reactions in DESs, which in most cases, enabled facile recovery and reuse of metal catalysts without any decrease of activity.[77]

[73] Singh, A. S.; Shendage, S. S.; Nagarkar, J. M. *Tetrahedron Lett.* **2014**, *55*, 7243-7246.
[74] Singh, B.; Lobo, H.; Shankarling, G. *Catal. Lett.* **2011**, *141*, 178-182.
[75] a) Chen, Z.; Zhu, W.; Zheng, Z.; Zou, X. *J. Fluorine Chem.* **2010**, *131*, 340-344; b) Azizi, N.; Batebi, E.; Bagherpour, S.; Ghafuri, H. *RSC Adv.* **2012**, *2*, 2289-2293; c) Azizi, N.; Khajeh, M.; Alipour, M. *Ind. Eng. Chem. Res.* **2014**, *53*, 15561-15565; d) Dai, D.-y.; Wang, L.; Chen, Q.; He, M.-Y. *J. Chem. Res.* **2014**, *38*, 183-185; e) Wu, C.; Xiao, H.-J.; Wang, S.-W.; Tang, M.-S.; Tang, Z.-L.; Xia, W.; Li, W.-F.; Cao, Z.; He, W.-M. *ACS Sustainable Chem. Eng.* **2019**, *7*, 2169-2175.
[76] Cao, J.; Shang, Y.; Qi, B.; Sun, X.; Zhang, L.; Liu, H.; Zhang, H.; Zhou, X. *RSC Adv.* **2015**, *5*, 9993-9996.
[77] Peng, L.; Hu, Z.; Lu, Q.; Tang, Z.; Jiao, Y.; Xu, X. *Chin. Chem. Lett.* **2019**, *30*, 2151-2156.

Interestingly, the addition of Grignard and organolithium reagents to ketones or imines has been reported in ChCl-based eutectic mixtures (Scheme 6).[78] The unusual results were attributed to the kinetic activation of these polar organometallic reagents, through the *in situ* formation of highly nucleophilic and reactive anionic magnesiates or lithiates. At the same time but in independent studies, the direct ortho-lithiation/functionalization of diaryltetrahydrofurans was published, and the same group described a lithium-mediated ring opening reaction of *o*-tolyltetrahydrofuran derivatives accompanied with a C-C bond formation.[79]



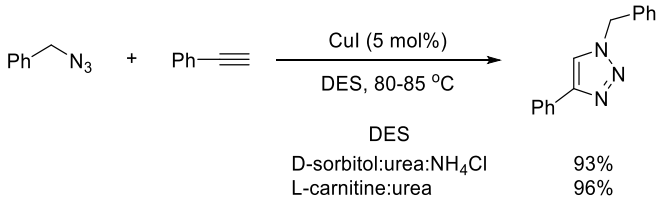
Scheme 6. Addition of polar organometallic reagents to (a) ketones and (b) imines in DESs.

Taking into account the observed positive effect of DESs in main-group chemistry, it is not surprising the fact that DESs have already been employed as sustainable solvents in transition metal-catalyzed reactions. The use of DESs, together with some metal salts have been tested in the Diels-Alder reaction promoted by scandium triflate in L-carnitine:urea melt. Also, the [3+2] dipolar cycloaddition of benzyl azide and phenylacetylene, has been described in the same work (Scheme 7).[80]

[78] a) Vidal, C.; García-Álvarez, J.; Hernán-Gómez, A.; Kennedy, A. R.; Hevia, E. *Angew. Chem. Int. Ed.* **2014**, *53*, 5969-5973; b) Vidal, C.; García-Álvarez, J.; Hernán-Gómez, A.; Kennedy, A. R.; Hevia, E. *Angew. Chem. Int. Ed.* **2016**, *55*, 16145-16148.

[79] a) Mallardo, V.; Rizzi, R.; Sassone, F. C.; Mansueto, R.; Perna, F. M.; Salomone, A.; Capriati, V. *Chem. Commun.* **2014**, *50*, 8655-8658; b) Sassone, F. C.; Perna, F. M.; Salomone, A.; Florio, S.; Capriati, V. *Chem. Commun.* **2015**, *51*, 9459-9462.

[80] Ilgen, F.; König, B. *Green Chem.* **2009**, *11*, 848-854.



Scheme 7. [3+2] Dipolar cycloaddition in different DESs.

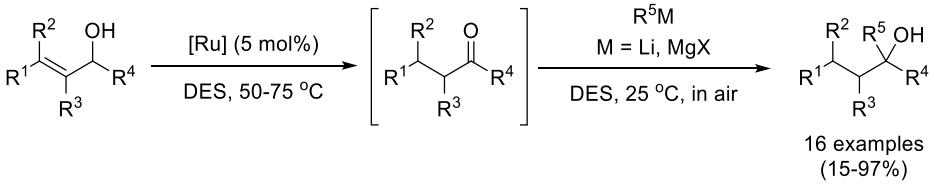
Metallic nanoparticles, mainly based on copper and palladium, have been used as recyclable catalysts for the multicomponent synthesis of imidazo[1,2-*a*]pyridines,[81] the cross-dehydrogenative coupling between tetrahydroisoquinolines and terminal alkynes,[82] the hydrogenation of 1-dodecine[83] and the synthesis of primary carbonates and *N,N*-disubstituted ureas.[84]

Regarding palladium-catalyzed reactions, several transformations have been reported such as cross-coupling reactions,[85] the synthesis of substituted thiophenes,[86] the aminocarbonylation of diverse aryliodides,[87] or the α-alkylation of ketones with benzyl alcohols.[88]

Alternatively, copper salts have been efficiently employed in the Ullman amine synthesis[89] and the multicomponent synthesis of sulfonamides.[90]

[81] Lu, J.; Li, X. T.; Ma, E. Q.; Mo, L. P.; Zhang, Z. H. *ChemCatChem* **2014**, *6*, 2854-2859.
[82] Marset, X.; Pérez, J. M.; Ramón, D. J. *Green Chem.* **2016**, *18*, 826-833.
[83] Iwanow, M.; Finkelmeyer, J.; Söldner, A.; Kaiser, M.; Gärtner, T.; Sieber, V.; König, B. *Chem. Eur. J.* **2017**, *23*, 12467-12470.
[84] Inaloo, I. D.; Majnooni, S.; Esmaeilpour, M. *Eur. J. Org. Chem.* **2018**, 3481-3488.
[85] Hooshmand, S. E.; Afshari, R.; Ramón, D. J.; Varma, R. S. *Green Chem.* **2020**, *22*, 3668-3692.
[86] Mancuso, R.; Maner, A.; Cicco, L.; Perna, F. M.; Capriati, V.; Gabriele, B. *Tetrahedron* **2016**, *72*, 4239-4244.
[87] Messa, F.; Perrone, S.; Capua, M.; Tolomeo, F.; Troisi, L.; Capriati, V.; Salomone, A. *Chem. Commun.* **2018**, *54*, 8100-8103.
[88] Teja, C.; Nawaz Khan, F. R. *ACS Omega* **2019**, *4*, 8046-8055.
[89] Quivelli, A. F.; Vitale, P.; Perna, F. M.; Capriati, V. *Front. Chem.* **2019**, *7*, 723.
[90] Marset, X.; Torregrosa-Crespo, J.; Martínez-Espinosa, R. M.; Guillena, G.; Ramón, D. J. *Green Chem.* **2019**, *21*, 4127-4132.

The ruthenium-catalyzed redox isomerization of allylic alcohols into carbonylic compounds was reported using ChCl:glycerol (1:2) as solvent. Subsequently, the authors decided to assemble the isomerization of allylic compounds in DESs with the addition of Grignard and organolithium reagents to the *in situ* generated ketones (Scheme 8).[91]



Scheme 8. Ru-catalyzed isomerization of allylic alcohols followed by organometallic addition.

Other transition metal-catalyzed reactions proceeding in DESs such as rhodium-catalyzed hydrogenation and hydroformilation reactions[80,92] and gold-catalyzed cycloisomerizations,[93] were reported.

[91] a) Vidal, C.; Suárez, F. J.; García-Álvarez, J. *Catal. Commun.* **2014**, *44*, 76-79; b) Cicco, L.; Rodríguez-Álvarez, M. J.; Perna, F. M.; García-Álvarez, J.; Capriati, V. *Green Chem.* **2017**, *19*, 3069-3077.

[92] a) Jérôme, F.; Ferreira, M.; Bricout, H.; Menuel, S.; Monflier, E.; Tilloy, S. *Green Chem.* **2014**, *16*, 3876-3880; b) Ferreira, M.; Jérôme, F.; Bricout, H.; Menuel, S.; Landy, D.; Fourmentin, S.; Tilloy, S.; Monflier, E. *Catal. Commun.* **2015**, *63*, 62-65.

[93] Vidal, C.; Merz, L.; García-Álvarez, J. *Green Chem.* **2015**, *17*, 3870-3878.

RESULTS

CHAPTER I

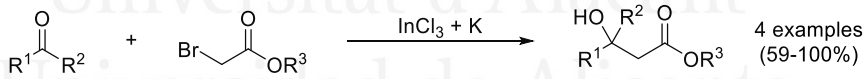
C-C bond formation reactions

1.1 INDIUM MEDIATED ALLYLATION OF CARBONYL COMPOUNDS

1.1.1 Precedents

Organometallic reagents prepared from main group metals, such as organolithium, organomagnesium or organozinc compounds, have demonstrated their importance in synthetic organic chemistry over the last century.[94] However, these reactive organometallic species are highly sensitive to air and moisture, which make their preparation and handling quite difficult. In these regards, organoindium reagents offer an attractive alternative to other organometallic reagents because of their appealing properties, including high stability against air and moisture, mild reactivity and robust functional group tolerance.[95]

The first preparation of organoindium reagents can be traced back to 1934 when trimethylindium (Me_3In) was synthesized *via* transmetalation of dimethylmercury with indium.[96] Other methodologies for the preparation of organoindium reagents (R_3In, R_2InX, $RInX_2$) appeared,[97] but most of these earlier works were focused on their synthesis and not on the application of these organometallic reagents in organic transformations. It was not until 1975 that the first application of indium in organic synthesis was reported in the Reformatsky reaction. In this case, a pre-activated indium prepared from the reduction of indium(III) chloride by potassium was used as reaction mediator (Scheme 9).[98]



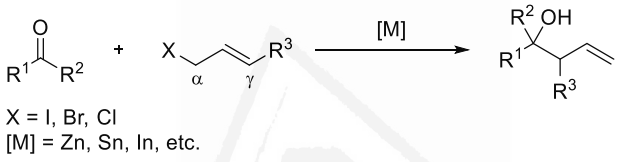
Scheme 9. Indium mediated Reformatsky reaction.

Later, it was reported that commercially available indium powder readily inserts into allyl halides to generate allylindium reagents, which can react with carbonyl compounds to afford

[94] Knochel, P. *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim (Germany), 2005.
[95] Singh, A. K. *Synlett* **2013**, *24*, 1457-1458.
[96] Dennis, L. M.; Work, R. W.; Rochow, E. G.; Study, M.; Chamot, E. M. *J. Am. Chem. Soc.* **1934**, *56*, 1047-1049.
[97] a) Schmidbaur, H.; Schindler, F. *Chemische Berichte* **1966**, *99*, 2178-2186; b) Clark, H. C.; Pickard, A. L. *J. Organomet. Chem.* **1968**, *13*, 61-71; c) Maeda, T.; Okawara, R. *J. Organomet. Chem.* **1972**, *39*, 87-91.
[98] Chao, L.-C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253-2255.

homoallylic alcohols in high efficiency.[99] Since then, the use of indium and organoindium reagents in organic transformations had notably increased.[100] In addition, the excellent compatibility of most organoindium compounds with protic solvents led to the development of indium mediate reactions in an alcohol and/or water reaction media.[101]

Specifically, allylation of carbonyl compounds with organometallic reagents, Barbier allylation, represents one of the most valuable transformations in organic synthesis since a new C-C bond and a stereocenter is formed (Scheme 10).[102] Conventionally, these metal-mediated Barbier reactions are highly γ-selective to give γ-adducts, but the regioselectivity is highly dependent on the nature of the metals and solvents employed.[103]



Scheme 10. Conventional Barbier allylation of carbonyl compounds.

This Barbier type allylation has been carried out with various metals in different reaction media, including conventional organic solvents,[104] water,[105] ionic liquids[106] and under neat conditions.[107] However, as aforementioned in the General Introduction, all these reaction

[99] Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831-1833.

[100] a) Shen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Rev.* **2013**, *113*, 271-401; b) Zhao, K.; Shen, L.; Shen, Z.-L.; Loh, T.-P. *Chem. Soc. Rev.* **2017**, *46*, 586-602.

[101] a) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997-1999; b) Chen, Y. H.; Sun, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 2236-2239.

[102] a) Holmes, M.; Schwartz, L. A.; Krische, M. J. *Chem. Rev.* **2018**, *118*, 6026-6052; b) Spielmann, K.; Niel, G.; de Figueiredo, R. M.; Campagne, J.-M. *Chem. Soc. Rev.* **2018**, *47*, 1159-1173.

[103] a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763-2794; b) Pratihar, S.; Roy, S. *Organometallics* **2011**, *30*, 3257-3269.

[104] a) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774-7854; b) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595-5698.

[105] Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. *Chem. Rev.* **2018**, *118*, 679-746.

[106] a) Gordon, C. M.; Ritchie, C. *Green Chem.* **2002**, *4*, 124-128; b) Dey, P.; Koli, M.; Goswami, D.; Sharma, A.; Chattopadhyay, S. *Eur. J. Org. Chem.* **2018**, 1333-1341.

[107] a) Zhang, Y.; Jia, X.; Wang, J.-X. *Eur. J. Org. Chem.* **2009**, 2983-2986; b) Li, S.; Wang, J.-X.; Wen, X.; Ma, X. *Tetrahedron* **2011**, *67*, 849-855.

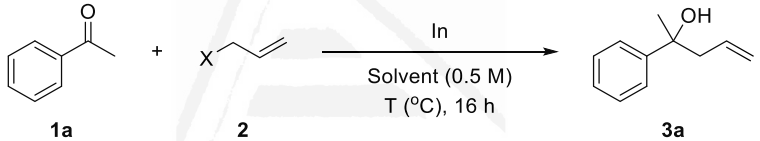
conditions present some limitations in the context of sustainable chemistry. Thus, the use of environmentally-friendly solvents for allylation reactions remains in demand.

Inspired by the previously reported compatibility of organometallic reagents in DESs, as it was introduced in the General Introduction chapter,[108] our aim was to develop a sustainable methodology for the Barbier reaction by pioneering the *in situ* generation of organoindium reagents in DESs as a green and recyclable reaction medium.

1.1.2 Results

The study started by optimizing the reaction conditions employing acetophenone (**1a**), allyl halides **2** and indium powder as the model reaction (Table 1).

Table 1. Optimization of the reaction conditions.[a]



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

Entry	Solvent	T (ºC)	X	Yield (%)[b]
1	ChCl:glycerol (1:2)[c]	90	Br	80
2	ChCl:ethylene glycol (1:2)	90	Br	99
3	ChCl:urea (1:2)	90	Br	79
4	AcChCl:acetamide (1:2)[d]	90	Br	45
5	ChCl:glycerol (1:2)	25	Br	58
6	ChCl:ethylene glycol (1:2)	25	Br	99
7	ChCl:urea (1:2)	25	Br	36
8	AcChCl:acetamide (1:2)	25	Br	62
9	Decanoic acid:TBAB (2:1)	25	Br	23
10	Decanoic acid:menthol (1:2)	25	Br	33
11	ChCl:ethylene glycol (1:2)	25	Cl	75
12	AcChCl:acetamide (1:2)	25	Cl	35
13	ChCl:ethylene glycol (1:2)	25	Cl	74[e]
14	AcChCl:acetamide (1:2)	25	Cl	67[e]

[a] Reaction conditions: acetophenone **1a** (0.25 mmol), allyl halide **2** (0.5 mmol) and In (0.5 mmol) in 0.5 mL of solvent at different temperatures for 16 h; [b] Yield determined by CG using DTBB as internal standard; [c] ChCl: choline chloride; [d] AcChCl: acetylcholine chloride; [e] 20 µL of acetic acid were added.

[108] a) García-Álvarez, J. *Eur. J. Inorg. Chem.* **2015**, 5147-5157; b) Hevia, E. *Chimia* **2020**, *74*, 681-688.

Promising results were obtained in the first attempt to use DESs as reaction media at 90 ^{o}C (entries 1-4). A decrease in the reaction temperature led to an important drop of yield in some DESs (entries 5 and 7) but fortunately, using ChCl:ethylene glycol (1:2) and AcChCl:acetamide (1:2) the excellent yield was maintained and even, increased, respectively (entries 6 and 8). Hydrophobic DESs were also employed with unsuccessful results (entries 9-10). More challenging allyl chlorides were reacted with acetophenone (**1a**) in the best yielding DESs so far, obtaining 75% yield in ChCl:ethylene glycol (1:2) and 35% yield in AcChCl:acetamide (1:2; entries 11-12). Trying to improve the yield through the activation of the ketone, acetic acid was added to the reaction mixture, it should be noted that indium species can be stabilized in a protic system.[109] Only an increase of the results in AcChCl:acetamide (1:2) was observed (entries 13-14).

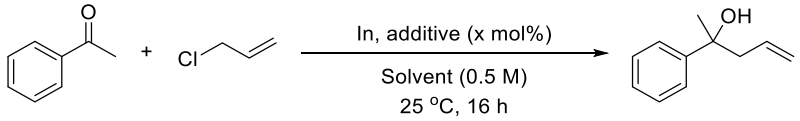
Previous works reported the favorable use of ammonium salts on this allylation reaction under water conditions.[110] Therefore, we decided to study their influence under DES conditions (Table 2). Several DESs were tested employing NH_4Cl (28 mol%; entries 1-6), observing a positive effect in both solvents AcChCl:acetamide (1:2) and ChCl:ethylene glycol (1:2; entries 1-2). Although excellent results were obtained in those eutectic mixtures, further studies were performed in AcChCl:acetamide (1:2) due to its more benign nature in comparison with ChCl:ethylene glycol (1:2).[111] The reaction performed with NH_4OAc (28 mol%) also gave excellent results (entry 6). Different amounts of the ammonium salts were tested, being 28 mol% the optimal quantity (compare entries 1 and 6 with 7 and 8). Note that at lower amounts of the ammonium salts (14 mol%), NH_4Cl was superior in activity to NH_4OAc (entries 7-8).

[109] a) Tussa, L.; Lebreton, C.; Mosset, P. *Chem. Eur. J.* **1997**, *3*, 1064-1070; b) Lee, J.-H.; Park, Y.-S.; Nam, M.-H.; Lee, S.-H.; Cho, M.-Y.; Yoon, C.-M. *Bull. Korean Chem. Soc.* **2005**, *26*, 496-498.

[110] a) Jõgi, A.; Mäeorg, U. *Molecules* **2001**, *6*, 964-968; b) Hui, A.; Xu, X.; Zha, Z.; Zhou, C.; Wang, Z. *Arkivoc* **2004**, *9*, 52-59.

[111] a) Wen, Q.; Chen, J.-X.; Tang, Y.-L.; Wang, J.; Yang, Z. *Chemosphere* **2015**, *132*, 63-69; b) Torregrosa-Crespo, J.; Marset, X.; Guillena, G.; Ramón, D. J.; Martínez-Espinosa, R. M. *Sci. Total Environ.* **2020**, *704*, 135382.

Table 2. Study of the additive effect.[a]



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

Entry	Solvent	Additive (mol%)	Yield (%)[b]
1	AcChCl:acetamide (1:2)	NH_4Cl (28)	99
2	ChCl:ethylene glycol (1:2)	NH_4Cl (28)	99
3	ChCl:glycerol (1:2)	NH_4Cl (28)	68
4	ChCl:urea (1:2)	NH_4Cl (28)	50
5	Ph_3PMeBr:glycerol (1:2)	NH_4Cl (28)	20
6	AcChCl:acetamide (1:2)	NH_4OAc (28)	99
7	AcChCl:acetamide (1:2)	NH_4Cl (14)	56
8	AcChCl:acetamide (1:2)	NH_4OAc (14)	35
9	AcChCl:acetamide (1:2)	KOAc (14)	14
10	AcChCl:acetamide (1:2)	NaOAc (14)	0

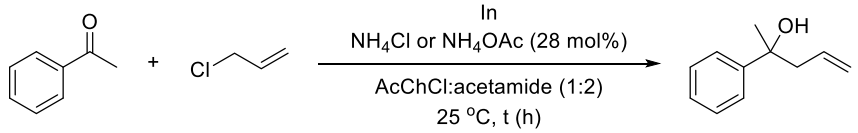
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), In (0.5 mmol) and different additives in 0.5 mL of solvent were stirred at 25 °C for 16 hours; [b] Yield determined by CG using DTBB as internal standard.

In order to clarify the possible roles of ammonium acetate, other acetate salts were tested. A poor yield and no reaction was noticed when KOAc and NaOAc were employed, respectively (Table 2, entries 9-10). It was reported that the ammonium salt acted as a source of protons within the media in a zinc-mediated reaction,[112] but in our case it seems to play a different role since the addition of acetic acid did not give better results.

Next, the reaction time was optimized using both ammonium salts (Table 3), since they showed an analogous effect in the previous study (see Table 2, entries 1 and 6). Similar results were obtained regardless of the ammonium salt employed, with the reaction being complete after 12 h (Table 3, entries 1-4). At this point, it was decided to employ NH_4Cl instead of NH_4OAc since it is cheaper and easier to handle. Later, a study of the amount of indium and allyl chloride was performed. All the attempts to decrease the molar equivalents of indium or allyl chloride were unsuccessful since lower yields were obtained (entries 5-7). As it was expected, the reaction did not proceed without the presence of indium powder (entry 8).

[112] Gao, Y.; Wang, X.; Sun, L.; Xie, L.; Xu, X. *Org. Biomol. Chem.* **2012**, *10*, 3991-3998.

Table 3. Optimization of the reaction time and equivalents of reagents.[a]



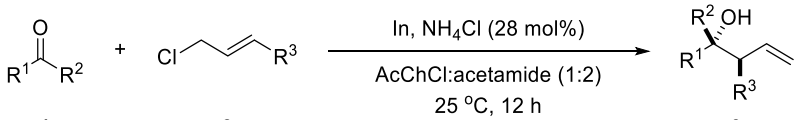
1a **2a** **3a**

Entry	Ammonium salt	Time (h)	Yield (%)[b]
1	NH_4Cl/NH_4OAc	1	0/0
2	NH_4Cl/NH_4OAc	3	64/65
3	NH_4Cl/NH_4OAc	8	88/86
4	NH_4Cl/NH_4OAc	12	95/98
5	NH_4Cl	12	65[c]
6	NH_4Cl	12	60[d]
7	NH_4Cl	12	55[e]
8	NH_4Cl	12	0[f]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), NH_4Cl or NH_4OAC (28 mol%) and In (0.5 mmol) in 0.5 mL of AcChCl:acetamide (1:2) were stirred at 25 °C; [b] Yield determined by CG using DTBB as internal standard; [c] 1.5 equiv. of **2** and indium powder; [d] 1.5 equiv. of **2** and 1 equiv. of indium powder; [e] 1 equiv. of **2** and indium powder; [f] no indium powder was used.

Subsequently, in order to study the scope of the reaction, different ketones **1** and allylic chlorides **2** were used under the optimal reaction conditions (Table 4). Electron-poor substituted aromatic ketones gave excellent yields (entries 2-3). Whereas, on the contrary, a lower yield was observed when electron-donating substituents were placed on the aromatic ketone (entry 4). The reaction was also compatible with a longer aliphatic chain (R^2 = Et), obtaining good results (entry 5). α-Tetralone (**1f**) gave a satisfactory 85% yield (entry 6), which seems to indicate the low basicity of nucleophilic species involved. A more sterically hindered ketone **1g** was also compatible (entry 7), as well as, cyclic aliphatic ketones (entry 8). Additionally, a range of aldehydes were tested observing excellent yields in all of the cases (entries 9-11). γ-Substituted allyl chlorides were reacted with acetophenone (**1a**) obtaining moderate to good yields (entries 12-13). A mixture of diastereoisomers was observed when (*E*)-1-chlorobut-2-ene (**2b**) was used as substrate, obtaining (2*R**,3*R**)-3-methyl-2-phenylpent-4-en-2-ol (**3l**) as the major product (entry 12). Surprisingly, a single diastereoisomer was formed in a moderate yield when a more hindered cinnamyl chloride (**2c**) was employed (entry 13) as a nucleophilic source.

Table 4. Scope of the reaction using different carbonyl and allylic compounds.

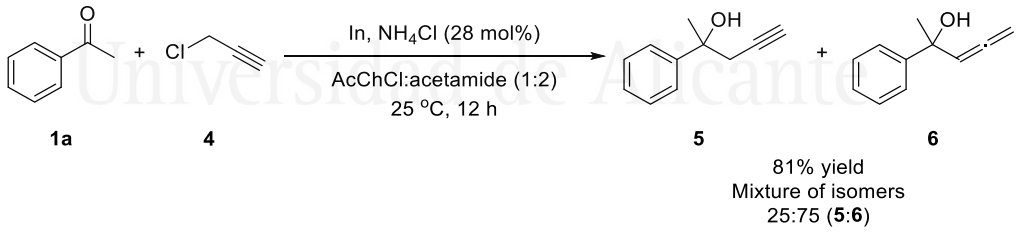


1 **2** **3**

Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	Ph	Me	H	**3a**	95
2	*p*-FC_6H_5	Me	H	**3b**	99
3	*p*-$CF_3C_6H_5$	Me	H	**3c**	90
4	*p*-$MeOC_6H_5$	Me	H	**3d**	56
5	Ph	Et	H	**3e**	88
6	-[1,2-$C_6H_4(CH_2)_3$]-		H	**3f**	85
7	Ph	Ph	H	**3g**	71
8	-$(CH_2)_5$-		H	**3h**	90
9	Ph	H	H	**3i**	99
10	furyl	H	H	**3j**	90
11	-$(CH_2)_5$CH-	H	H	**3k**	90
12	Ph	Me	Me	**3l**	75 (95:5)
13	Ph	Me	Ph	**3m**	52

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), NH_4Cl (28 mol%) and In (0.5 mmol) in 0.5 mL of AcChCl:acetamide (1:2) were stirred at 25 °C for 12 hours; [b] Isolated yield after flash column chromatography.

Finally, propargyl chloride (**4**) efficiently reacted with acetophenone (**1a**) with 81% overall yield, but a mixture of isomers (**5** and **6**) was isolated in 25:75 proportion (Scheme 11).



1a **4** **5** **6**

81% yield
Mixture of isomers
25:75 (**5**:**6**)

Scheme 11. Propargyl chloride (**4**) as substrate for the Barbier allylation.

One of the main advantages of the use of DESs as reaction media lies in the possible recyclability of the solvent. Thus, the recycling of the DES together with NH_4Cl was attempted using the model reaction. Once the reaction was finished, the organic compounds were extracted with a renewable biomass derived solvent (2-MeTHF). Following that, the

mixture of DES containing the ammonium salt was reused, after being dried under vacuum. The system could be efficiently recycled up to 4 consecutive cycles without a significant loss of catalytical activity (Figure 10). Since the reaction yield dropped in the fifth cycle, the addition of fresh ammonium salt was considered, observing a slightly improvement in the reaction yield (cycle 6 in Figure 10). The accumulative presence of different salts in the reaction medium could explain this final decrease of the catalytical activity in comparison with the first cycle.

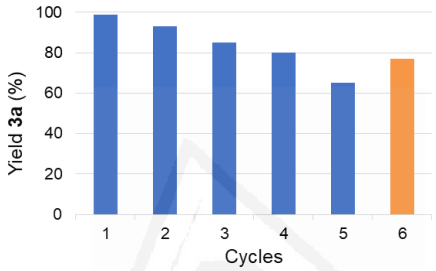
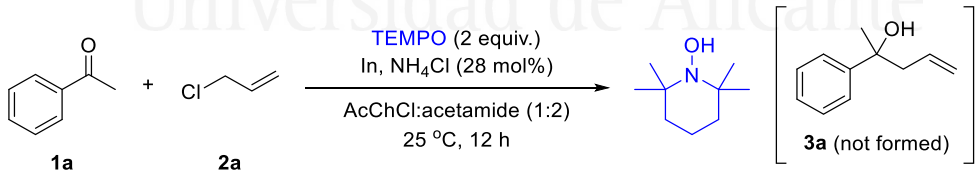


Figure 10. Recyclability of the system.

In spite of the many applications, the mechanism of Barbier reaction in neoteric solvents, such as water, is not well-understood. It has been speculated that either the mechanism involves a radical pathway or the generation of allylmetal species.[113] However, for the different metals and reaction media, there are still a number of unanswered questions with regarding of the reaction mechanism. For this reason, a control experiment was carried out using a radical quencher (TEMPO) under the optimal reaction conditions (Scheme 12).



Scheme 12. Study of the reaction mechanism using TEMPO as radical quencher.

[113] Dam, J. H.; Fristrup, P.; Madsen, R. *J. Org. Chem.* **2008**, *73*, 3228-3235.

The reaction was completely inhibited with TEMPO and the corresponding product **3a** was not detected. Only the formation of 2,2,6,6-tetramethylpiperidin-1-ol was observed by GC-MS analysis, which seems to indicate the formation of radical species during the reaction.[114]

It has been reported that radical diffusion is highly influenced by the solvent properties such as density or viscosity, among others.[115] In light of this, a linear relationship between the solvent density and the reaction yield was found, indicating that lower densities favor the reaction (Figure 11, left). Additionally, a similar tendency between the viscosity of the different DESs and the reaction yield was also observed (Figure 11, right). Previous studies postulated that a solvent "cage radical pair" could be generated when radical species are involved in the reaction, and this "cage" is treated as a "hole" in the solvent network. Moreover, the escape from this "cage" is highly dependent on the solvent properties such as density or viscosity. Based on the results, it seems that lower densities and viscosities favor this radical escape and therefore, higher yields were observed.

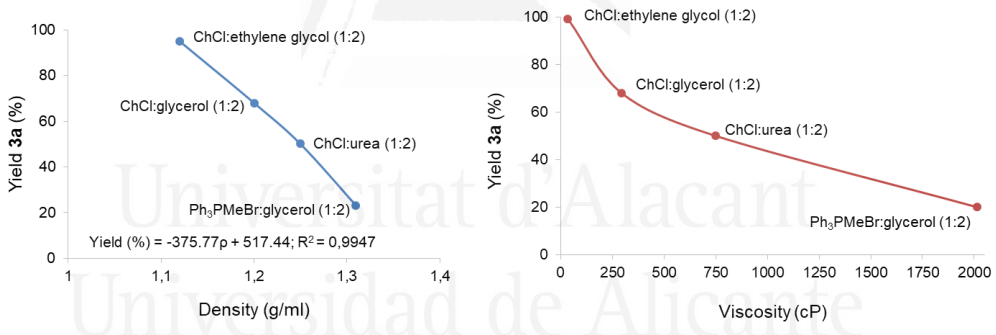


Figure 11. Density and viscosity relation between reaction yield.

In addition, the study of the presence of reagents/products *versus* reaction time was performed (Figure 12). At the beginning of the reaction the amount of the starting allyl chloride **2c** decreased, whilst the ketone **1a** remains unchanged and the corresponding product **3m** was not detected. Only after approximately 90 min of the reaction, product **3m**

[114] Shen, Z.-L.; Yeo, Y.-L.; Loh, T.-P. *J. Org. Chem.* **2008**, *73*, 3922-3924.

[115] a) Kimura, Y.; Kanda, D.; Terazima, M.; Hirota, N. *J. Phys. Chem. B* **1997**, *101*, 4442-4447; b) Shevick, S. L.; Wilson, C. V.; Kotesova, S.; Kim, D.; Holland, P. L.; Shenvi, R. A. *Chem. Sci.* **2020**, *11*, 12401-12422.

appeared (detected by GC of the crude mixture). This induction period seems to demonstrate the generation of radical species prior to the formation of product **3m**.

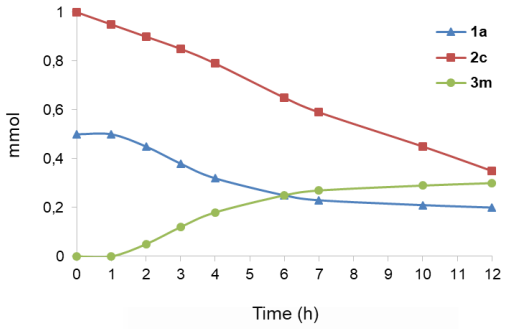


Figure 12. Kinetics of the reaction between **1a** and **2c**.

According to these observations, a plausible mechanism has been prosed supported by similar previous reports in literature (Figure 13).[116]

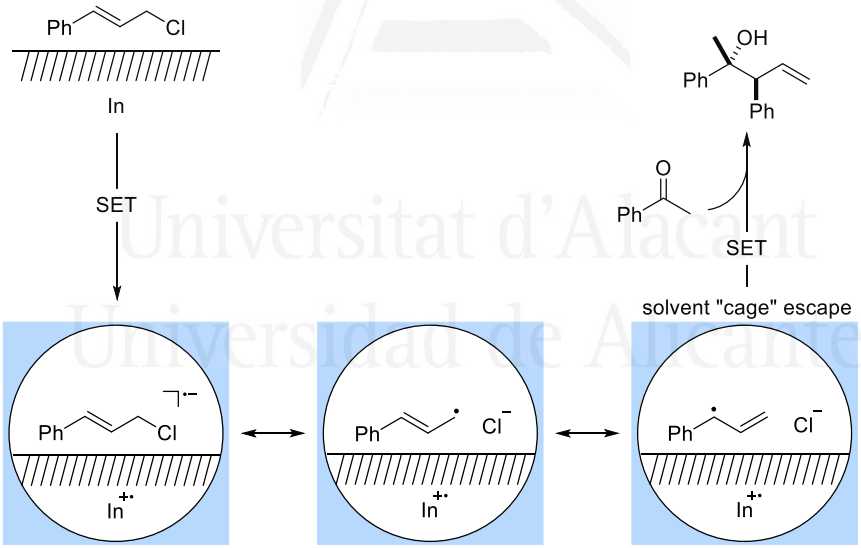


Figure 13. Proposed reaction mechanism.

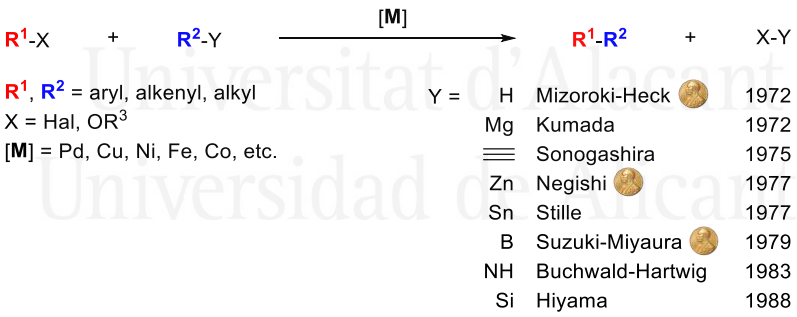
[116] Zhao, L.-M.; Gao, H.-S.; Li, D.-F.; Dong, J.; Sang, L.-L.; Ji, J. *Org. Biomol. Chem.* **2017**, *15*, 4359-4366.

As illustrated in Figure 13, the reaction was initiated by a SET (single-electron transfer) from indium to cinnamyl chloride (**2c**) to afford an allyl radical anion (in accordance with the kinetic studies). Then, the radical evolves toward a more stable benzyl radical (in this specific case using **2c** as starting material). This radical escapes from the solvent "cage" favoured by the beneficial solvent properties (low density and viscosity). The aforementioned radical, after a further SET process, reacts with the acetophenone (**1a**) to give the corresponding alkoxide anion. Finally, a subsequent hydrolysis would furnish the desired product **3m**.

1.2 CROSS-COUPLING REACTIONS

1.2.1 Precedents

Since their discovery in the 1970s, transition metal-catalyzed cross-coupling reactions have become a powerful tool for the formation of C-C and C-heteroatom bonds.[117] Specifically, these transformations are one of the most employed methodologies for the synthesis of substituted (hetero)arenes. Their development and extensive application can be attributed to the abundant availability and low cost of (hetero)aryl halides or phenol derivatives. In addition, cross-coupling reactions permit the synthesis of relatively complex molecules through an easy, selective and robust process that can even be scalable. Considering all these advantages, it is not surprising that metal catalyzed cross-coupling reactions have been implemented into the industrial manufacture of pharmaceutical, fine chemicals and agrochemicals.[118] Eventually, the success and popularity of these reactions led to the attribution of the Nobel Prize in Chemistry in 2010 (Scheme 13).[119] Several metal catalysts are capable of catalyzing these reactions, but undoubtedly palladium catalysts dominate the scene, owing to their high selectivity, reactivity and tolerance to a broad scope of functional groups.[120]

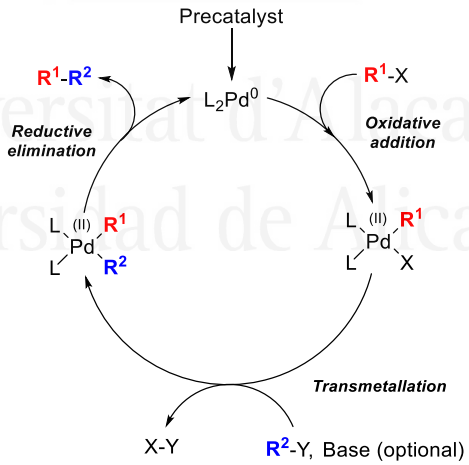


Scheme 13. Cross-coupling reaction catalyzed by transition metals.

[117] Campeau, L.-C.; Hazari, N. *Organometallics* **2018**, *38*, 3-35.
[118] Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027-3043.
[119] Johansson Seechurn, C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.
[120] Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. *Chem. Rev.* **2018**, *118*, 2249-2295.

The activity and stability of palladium complexes is highly dependent on the nature of palladium ligand complexation. Hence, the design of proper ligands is essential for successful catalytic applications. The ligand plays a very important role in transition metal catalysis in the following ways: i) the ligand coordination changes the structure and reactivity of the metal catalyst; ii) the ligand inherently changes the activation energy of the elementary steps involved in the catalytic process; iii) ligands can influence the selectivity of metal catalysts; iv) the ligand increases the solubility of metal in solvents and v) many ligands stabilize and avoid aggregation of the *in situ* formed metal NPs.

In particular, the use of strong σ-donating ligands accelerates the oxidative addition step and the reductive elimination step is favoured by the use of bulky ligands in cross-coupling reactions (Scheme 14). Initially, bulky phosphine ligands were employed in several cross-coupling reactions, but due to their inherent disadvantages such as their high cost and air sensitivity, they have been recently replaced by other ligands such as N-heterocyclic carbenes (NHCs) or bipyridyl (bipy) ligands. These ligands offer similar electronic properties to phosphines, the strong σ-donation by carbene or nitrogen favours the oxidative addition, and their steric bulk can be easily tuned.[121]

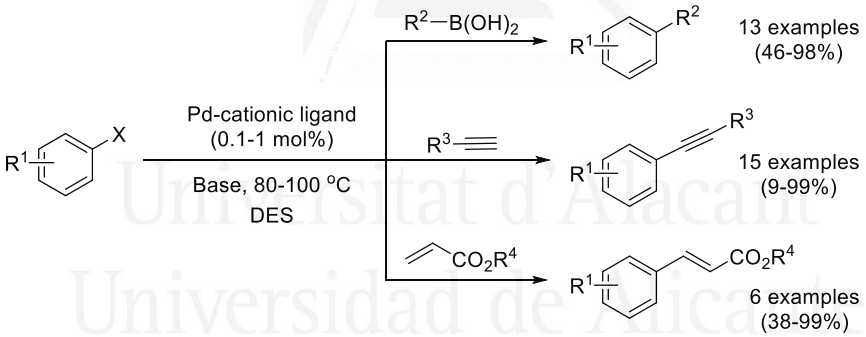


Scheme 14. General catalytic cycle for cross-coupling reactions.

[121] a) Gildner, P. G.; Colacot, T. J. *Organometallics* **2015**, *34*, 5497-5508; b) Kumbhar, A. *J. Organomet. Chem.* **2017**, *848*, 22-88; c) Kumbhar, A. *J. Organomet. Chem.* **2019**, *881*, 79-129.

Over the years, numerous protocols for cross-coupling reactions have been reported. However, most of these transformations are performed using hazardous and toxic VOCs as solvents. Hence, much of the effort to decrease the environmental impact of cross-coupling reactions has focused on using more benign solvents.[122] In respect of palladium-catalyzed cross-coupling reactions in DESs, König *et al.* reported the use of mannitol-DMU-NH_4Cl eutectic mixture in the Suzuki-Miyaura reaction for the first time.[123] A few months later, the same group published the use of urea based melts as solvent for the Stille cross-coupling reaction,[124] and also the Sonogashira and Heck reactions were performed in a sugar or L-carnitine based melts, respectively.[80]

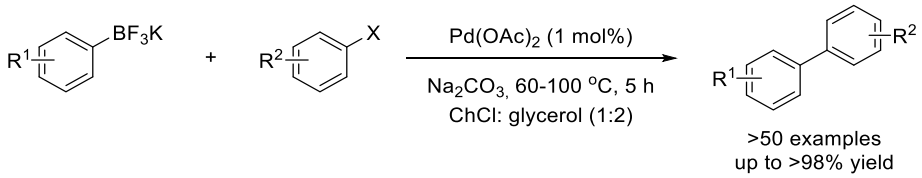
Our research group also contributed to this research field. A cationic phosphine palladium-catalyst was successfully employed in several cross-coupling reactions using DESs as reaction media, but this catalytic system was not suitable for the Hiyama reaction (Scheme 15).[125] Therefore, a pincer-type palladium catalyst was developed as an effective catalyst for the aforementioned transformation.[126]



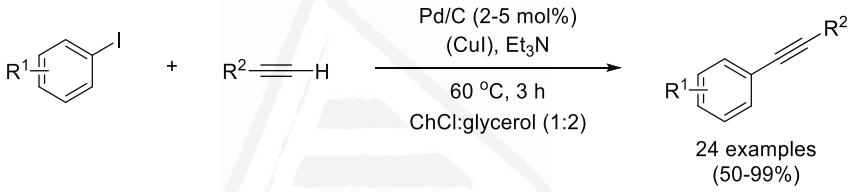
Scheme 15. Palladium-catalyzed cross-coupling reactions in DESs reported by our group.

[122] Hooshmand, S. E.; Heidari, B.; Sedghi, R.; Varma, R. S. *Green Chem.* **2019**, *21*, 381-405.
[123] Imperato, G.; Höger, S.; Lenoir, D.; König, B. *Green Chem.* **2006**, *8*, 1051-1055.
[124] Imperato, G.; Vasold, R.; König, B. *Adv. Synth. Catal.* **2006**, *348*, 2243-2247.
[125] Marset, X.; Khoshnood, A.; Sotorrios, L.; Gómez-Bengoa, E.; Alonso, D. A.; Ramón, D. J. *ChemCatChem* **2017**, *9*, 1269-1275.
[126] Marset, X.; De Gea, S.; Guillena, G.; Ramón, D. J. *ACS Sustainable Chem. Eng.* **2018**, *6*, 5743-5748.

Moreover, Capriati *et al.* published the Suzuki-Miyaura cross-coupling reaction using aryltrifluoroborates as nucleophilic partners in ChCl:glycerol (1:2) as an environmentally friendly reaction medium (Scheme 16).[127] Additionally, the same group developed a sustainable ligand-free Sonogashira reaction in ChCl:glycerol (1:2) eutectic mixture (Scheme 17).[128]



Scheme 16. Suzuki-Miyaura reaction using aryltrifluoroborates as substrates in DES.



Scheme 17. A ligand-free palladium-catalyzed Sonogashira reaction in DES.

More recently, DESs were utilized as solvent in a sequential one-pot cyclization and palladium-catalyzed Suzuki-Miyaura or Sonogashira cross-coupling reactions through a base-free methodology for the synthesis of nitrogen- and oxygen-containing heterocycles.[129] Also, a cellulose-modified magnetite-graphene oxide nanocomposite was employed for the immobilization of palladium nanoparticles, and this system was used as catalyst in various cross-coupling reaction in DESs.[130]

Regarding the combination of metal catalysis and biocatalysis, a chemoenzymatic cascade of palladium-catalyzed Suzuki-Miyaura cross-coupling reaction followed by an

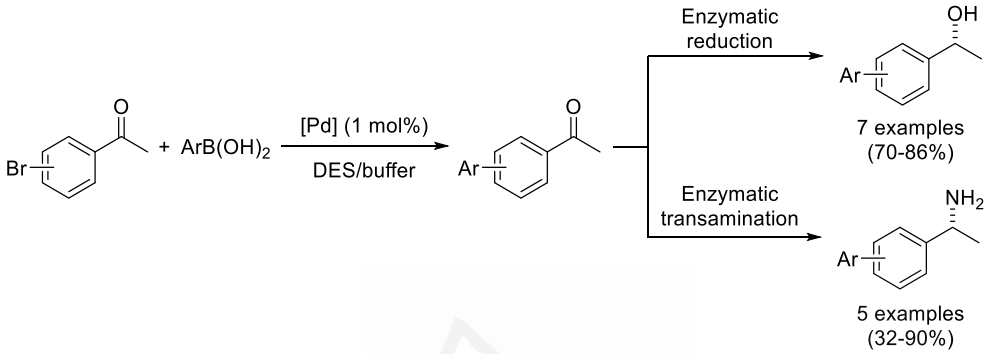
[127] Dilauro, G.; Garcia, S. M.; Tagarelli, D.; Vitale, P.; Perna, F. M.; Capriati, V. *ChemSusChem* **2018**, *11*, 3495-3501.

[128] Messa, F.; Dilauro, G.; Perna, F. M.; Vitale, P.; Capriati, V.; Salomone, A. *ChemCatChem* **2020**, *12*, 1979-1984.

[129] Thiyagamurthy, P.; Khan, F. R. N. *ChemistrySelect* **2020**, *5*, 2610-2617.

[130] Niakan, M.; Masteri-Farahani, M.; Shekaari, H.; Karimi, S. *Carbohydr. Polym.* **2021**, *251*, 117109.

enzymatic reduction or transamination was implemented in mixtures of DES/buffer (Scheme 18).[131] Likewise, a recyclable Pd-DNA-Fe_3O_4 catalyst was employed in the Suzuki-Miyaura reaction using DESs as reaction medium.[132]



Scheme 18. One-pot Suzuki-Miyaura reaction and enzymatic reduction or transamination.

Clearly, cross-coupling reactions in DESs have gained importance over the last few years as it is proven by the growing number of related publications in this field. However, more efficient systems with broader applicability are still to be developed.

1.2.2 Results

1.2.2.1 Palladium mesoionic carbene catalyst for cross-coupling reactions in DESs

As aforementioned, the catalytic activity of metal complexes in cross-coupling reactions is often improved by the use of ligands with strong electron-donating properties. In this regard, N-heterocyclic carbene (NHC) ligands, are strong σ-donors and weak π-acceptors. However, it has been reported that abnormal N-heterocyclic carbene (aNHC) are stronger σ-donor ligands.[133] This stronger σ-donor ability increases the electron density of the metal

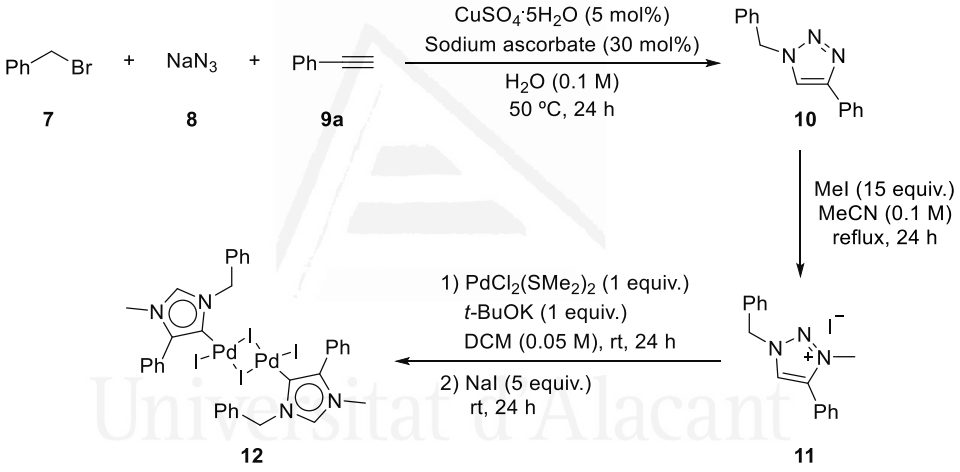
[131] a) Paris, J.; Ríos-Lombardía, N.; Morís, F.; Gröger, H.; González-Sabín, J. *ChemCatChem* **2018**, *10*, 4417-4423; b) Paris, J.; Telzerow, A.; Ríos-Lombardía, N.; Steiner, K.; Schwab, H.; Morís, F.; Gröger, H.; González-Sabín, J. *ACS Sustainable Chem. Eng.* **2019**, *7*, 5486−5493.

[132] Chakraborty, S.; Mruthunjayappa, M. H.; Aruchamy, K.; Singh, N.; Prasad, K.; Kalpana, D.; Ghosh, D.; Sanna Kotrappanavar, N.; Mondal, D. *ACS Sustainable Chem. Eng.* **2019**, *7*, 14225-14235.

[133] Crabtree, R. H. *Coord. Chem. Rev.* **2013**, *257*, 755-766.

center, enhancing the propensity of the metal to undergo oxidative addition.[134] For this reason, we aimed to synthetize an abnormal NHC-Pd complex for testing its catalytic activity in different cross-coupling reactions in DESs.

To explore the assumption, our initial investigations started with the synthesis of the palladium complex **12** according to literature procedures (Scheme 19). First, a multicomponent click-type reaction was performed to obtain triazole **10**, which was subjected to an alkylation reaction, yielding the salt **11**. Then, ligand **11** was deprotonated and treated with a palladium salt precursor. Finally, an excess of NaI was added to afford the palladium carbene dimer **12**.



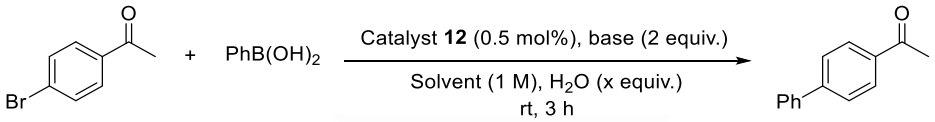
Scheme 19. Synthesis of palladium complex **12**.

Once the palladium catalyst was prepared, it was tested in the Suzuki-Miyaura cross-coupling reaction, using 4'-bromoacetophenone (**13a**) and phenylboronic acid (**14a**) as model reaction for the optimization studies (Table 5). A 40% yield of product **15a** was obtained using water as solvent, while only 12% yield was observed using ChCl:ethylene glycol (1:2) mixture (entries 1-2). Although water is a non-toxic and inexpensive solvent, dealing with aqueous residues is not an easy task. For this reason, it was decided to employ

[134] a) Krüger, A.; Albrecht, M. *Aust. J. Chem.* **2011**, *64*, 1113-1117; b) Donnelly, K. F.; Petronilho, A.; Albrecht, M. *Chem. Commun.* **2013**, *49*, 1145-1159; c) Albrecht, M. *Adv. Organomet. Chem.* **2014**, *62*, 111-158.

DESs as reaction media. The positive effect of water was tested, observing an increase in the reaction rate when 1 to 10 equivalents of water were added, while adding more equivalents resulted in a decrease of the reaction yield (entries 3-7). Other solvents were tested (entries 8-16) including typical VOCs, highlighting the beneficial effect of DESs in comparison of its individual components (compare entries 6 and 8 with entries 12 and 13).

Table 5. Suzuki-Miyaura optimization.[a]



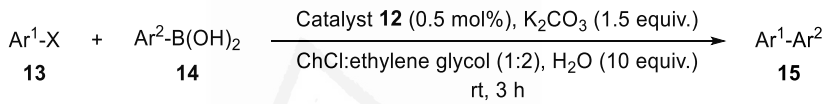
13a **14a** **15a**

Entry	Solvent	Base	Equiv. H_2O	Yield (%)[b]
1	H_2O	K_2CO_3	0	40
2	ChCl:ethylene glycol (1:2)	K_2CO_3	0	12
3	ChCl:ethylene glycol (1:2)	K_2CO_3	1	41
4	ChCl:ethylene glycol (1:2)	K_2CO_3	3	56
5	ChCl:ethylene glycol (1:2)	K_2CO_3	5	60
6	ChCl:ethylene glycol (1:2)	K_2CO_3	10	90
7	ChCl:ethylene glycol (1:2)	K_2CO_3	20	10
8	ChCl:glycerol (1:2)	K_2CO_3	10	62
9	ChCl:urea (1:2)	K_2CO_3	10	10
10	ChCl:DMU (1:2)	K_2CO_3	10	10
11	ChCl:resorcinol (1:2)	K_2CO_3	10	44
12	Ethylene glycol	K_2CO_3	10	36
13	Glycerol	K_2CO_3	10	12
14	Ethanol	K_2CO_3	10	60
15	DMF	K_2CO_3	10	67
16	Toluene	K_2CO_3	10	27
17	ChCl:ethylene glycol (1:2)	-	10	0
18	ChCl:ethylene glycol (1:2)	KF	10	50
19	ChCl:ethylene glycol (1:2)	NaOH	10	60
20	ChCl:ethylene glycol (1:2)	Cs_2CO_3	10	95
21	ChCl:ethylene glycol (1:2)	iPr_2NH	10	0
22	ChCl:ethylene glycol (1:2)	K_2CO_3	10	90[c]
23	ChCl:ethylene glycol (1:2)	K_2CO_3	10	99[d]

[a] Reaction conditions: aryl bromide (0.2 mmol), K_2CO_3 (0.4 mmol), phenylboronic acid (0.25 mmol) and complex **12** (0.5 mol%) in 0.2 mL of solvent; [b] Yield determined by GC using tridecane as internal standard; [c] 0.3 mmol of K_2CO_3 were used; [d] 0.3 mmol of K_2CO_3 and 0.21 mmol of $PhB(OH)_2$ were used.

After that, different bases were used (entries 17-23) with the best results being obtained with ChCl:ethylene glycol (1:2), 10 equivalents of water and 1.5 equivalents of K_2CO_3 as base (99% yield; entry 23). With the optimal conditions in hand, the scope of the Suzuki-Miyaura cross-coupling reaction was evaluated (Table 6). Moderate to excellent yields were obtained for electron-poor and electron-rich aryl bromides. More challenging aryl chlorides were also coupled with phenylboronic acid (**14a**) with moderate to good yields at room temperature in 10 h. Different arylboronic acids were successfully employed as coupling partners with good to excellent yields (entries 18-21).

Table 6. Scope of Suzuki-Miyaura reaction.[a]

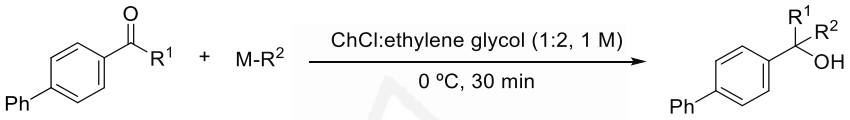


Entry	Ar^1	Ar^2	X	Product	Yield (%)[b]
1	4-(MeCO)C_6H_4	Ph	Br	**15a**	99
2	4-(MeCO)C_6H_4	Ph	Cl	**15a**	50[c]
3	4-(HO_2C)C_6H_4	Ph	Br	**15b**	90
4	4-(HO_2C)C_6H_4	Ph	Cl	**15b**	60[c]
5	4-(CHO)C_6H_4	Ph	Br	**15c**	95
6	4-(CHO)C_6H_4	Ph	Cl	**15c**	60[c]
7	4-(O_2N)C_6H_4	Ph	Br	**15d**	95
8	4-(O_2N)C_6H_4	Ph	Cl	**15d**	90[c]
9	4-(NC)C_6H_4	Ph	Br	**15e**	98
10	4-(NC)C_6H_4	Ph	Cl	**15e**	95[c]
11	Ph	Ph	Br	**15f**	60
12	4-FC_6H_4	Ph	Br	**15g**	79
13	4-MeC_6H_4	Ph	Br	**15h**	49
14	1-naphthyl	Ph	Br	**15i**	80
15	1-naphthyl	Ph	Cl	**15i**	43[c]
16	4-(HO)C_6H_4	Ph	Br	**15j**	50
17	4-(HO)C_6H_4	Ph	Cl	**15j**	20[c]
18	4-(MeCO)C_6H_4	3-MeC_6H_4	Br	**15k**	87
19	4-(MeCO)C_6H_4	4-(HO)C_6H_4	Br	**15l**	75
20	4-(MeCO)C_6H_4	4-ClC_6H_4	Br	**15m**	95
21	4-(MeCO)C_6H_4	4-FC_6H_4	Br	**15n**	84

[a] Reaction conditions: Aryl halide (0.2 mmol), phenylboronic acid (0.21 mmol), K_2CO_3 (0.3 mmol), complex **12** (0.5 mol%) and water (36 μL) in 0.2 mL of ChCl:ethylene glycol (1:2) were stirred at rt for 3 h; [b] Isolated yield after flash column chromatography; [c] Reaction time 10 h.

Inspired by the previously published compatibility of DESs with organolithium or organomagnesium reagents, we decided to test the compatibility of our system with the addition of different organometallic species in ChCl:ethylene glycol (1:2) DES (Table 7). Ketone **15a** could be reduced to the corresponding alcohol with $NaBH_4$ (entry 1) or reacted with Grignard reagents (entry 2) or *n*-BuLi (entry 3), finding higher yields when more reactive nucleophiles were used. However, similar results were obtained for the reduction of aldehyde **15c** with $NaBH_4$ (entry 4) or its reaction with *n*-BuLi (entry 5).

Table 7. Organometallic addition to carbonyl compounds in DESs.[a]



15 **16** **17**

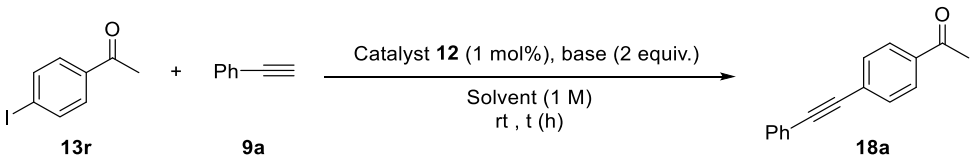
Entry	M-R^2	R^1	R^2	Product	Conv. (%)[b]
1	$NaBH_4$	Me	H	**17a**	10
2	H_2C=$CHCH_2MgBr$	Me	H_2C=$CHCH_2$	**17b**	15
3	*n*-BuLi	Me	*n*-Bu	**17c**	70
4	$NaBH_4$	H	H	**17d**	10
5	*n*-BuLi	H	*n*-Bu	**17e**	25

[a] Reaction conditions: to a vigorously stirred solution of product **15a** or **15c** (0.2 mmol) in 0.3 mL of ChCl:ethylene glycol at 0 ºC, 0.5 mmol of the corresponding reagent **16** was added. The solution was stirred at rt for 30 min; [b] Conversion determined by GC.

To further extend the applicability of the catalyst, other cross-coupling reactions were evaluated. The Sonogashira reaction was optimized testing different DESs as reaction medium, various bases and reaction times (Table 8), obtaining the best results with AcChCl:urea (1:2) as solvent and $iPrNH_2$ as base in 2 h at room temperature (entry 11).

Then, the scope of the reaction was evaluated (Table 9). Different aryl iodides were cross-coupled with phenyl acetylene, excellent yields were obtained for electron-poor substituted aryl iodides but the yield was lower for neutral or electron-rich substituted aryl halides. An improvement in the results was observed with higher temperatures or reaction times, which proved the stability of the catalyst at higher temperatures. Additionally, 4'-bromoacetophenone and 4'-chloroacetophenone were submitted to the reaction with phenylacetylene but the reaction failed.

Table 8. Optimization of Sonogashira coupling.[a]

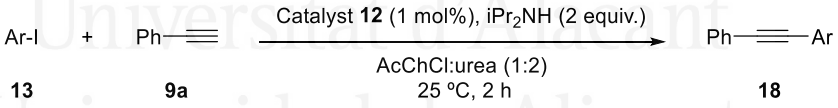


13r **9a** **18a**

Entry	Base	t (h)	Solvent	Yield (%)[b]
1	$iPrNH_2$	3	ChCl:ethylene glycol (1:2)	91
2	$iPrNH_2$	3	ChCl:glycerol (1:2)	86
3	$iPrNH_2$	3	AcChCl:urea (1:2)	93
4	$iPrNH_2$	3	Decanoic acid:menthol (1:2)	0
5	$iPrNH_2$	3	Decanoic acid:TBAB (2:1)	50
6	Na_2CO_3	3	AcChCl:urea (1:2)	5
7	$NaHCO_3$	3	AcChCl:urea (1:2)	1
8	K_2CO_3	3	AcChCl:urea (1:2)	75
9	NaOAc	3	AcChCl:urea (1:2)	39
10	K_3PO_4	3	AcChCl:urea (1:2)	56
11	$iPrNH_2$	2	AcChCl:urea (1:2)	95
12	$iPrNH_2$	1	AcChCl:urea (1:2)	34

[a] Reaction conditions: Aryl iodide (0.2 mmol), phenylacetylene (0.4 mmol), base (0.4 mmol), complex **12** (1 mol%) in 0.2 mL solvent were stirred at rt; [b] Yield determined by GC using tridecane as internal standard.

Table 9. Scope of Sonogashira coupling.[a]



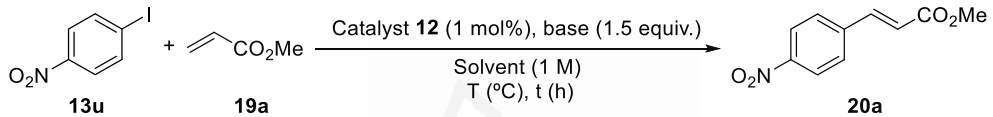
13 **9a** **18**

Entry	Ar	Product	Yield (%)[b]
1	4-(MeCO)C_6H_4	**18a**	93
2	Ph	**18b**	56, (68),[c] (81)[d]
3	4-MeC_6H_4	**18c**	36, (46),[c] (22),[d] (76)[e]
4	4-(O_2N)C_6H_4	**18d**	82
5	2-MeC_6H_4	**18e**	26, (38),[c] (31),[d] (53)[e]
6	2-thienyl	**18f**	36, (38)[c]
7	4-FC_6H_4	**18g**	51, (62),[c] (99)[d]
8	4-(MeO)C_6H_4	**18h**	28, (46),[c] (30),[d] (60)[e]

[a] Reaction conditions: Aryl iodide (0.2 mmol), phenylacetylene (0.4 mmol), iPr_2NH (0.4 mmol), complex **12** (1 mol%) in 0.2 mL of AcChCl:urea (1:2) were stirred at rt for 2 h; [b] Isolated yield after flash column chromatography; [c] Reaction performed in 6 h; [d] Reaction performed for 6 h at 80 ºC; [e] Reaction performed for 24 h.

Next, the Heck cross-coupling reaction was also evaluated (Table 10). Temperature was proved to be a crucial factor since the reaction gave a 53% yield at 80 ºC (compare entries 1-2). Then, different hydrophilic and hydrophobic eutectic mixtures were tested (entries 2-6 and entries 7-8, respectively), observing that AcChCl:urea (1:2) was the best solvent as in the previous reaction (entry 3). Other inorganic bases were used, obtaining low yields (entries 9-12). It was also corroborated that the reaction was not completed at lower reaction times, only after 6 h were quantitative yields observed (entries 3 and 13-14).

Table 10. Optimization Heck coupling.[a]



13u **19a** **20a**

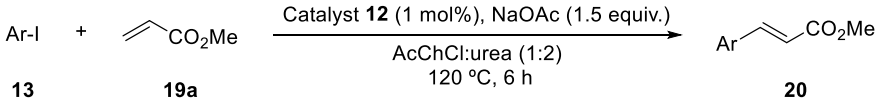
Entry	Base	T (ºC)	t (h)	Solvent	Yield (%)[b]
1	NaOAc	80	6	ChCl:ethylene glycol (1:2)	53
2	NaOAc	120	6	ChCl:ethylene glycol (1:2)	90
3	NaOAc	120	6	AcChCl:urea (1:2)	>99
4	NaOAc	120	6	ChCl:glycerol (1:2)	52
5	NaOAc	120	6	ChCl:urea (1:2)	0
6	NaOAc	120	6	AcChCl:acetamide (1:2)	59
7	NaOAc	120	6	Decanoic acid:menthol (1:2)	0
8	NaOAc	120	6	Decanoic acid:TBAB (2:1)	45
9	Na_2CO_3	120	6	AcChCl:urea (1:2)	0
10	K_2CO_3	120	6	AcChCl:urea (1:2)	19
11	K_3PO_4	120	6	AcChCl:urea (1:2)	0
12	$NaHCO_3$	120	6	AcChCl:urea (1:2)	0
13	NaOAc	120	3	AcChCl:urea (1:2)	40
14	NaOAc	120	5	AcChCl:urea (1:2)	58

[a] Reaction conditions: Aryl iodide (0.2 mmol), methyl acrylate (0.25 mmol), base (0.3 mmol), complex **12** (1 mol%) in 0.2 mL of solvent; [b] Yield determined by GC using tridecane as internal standard.

Regarding the scope of the Heck cross-coupling reaction, good to excellent yields were obtained for the coupling of aryl iodides bearing electron-withdrawing groups with methyl acrylate (**19a**) under optimized reaction conditions (Table 11, entries 1-3). Electron-neutral aryl iodides were also efficiently coupled, observing a slight decrease on the yield when a more prominent substrate was employed (entries 4-5). However, in the case of using electron-rich substituted starting materials the reaction time should be increased to 16 h in order to obtain the corresponding cross-coupling products with good to excellent yields

(entries 6-8). Also, as in the previous cross-coupling reaction, aryl bromides (4'-bromoacetophenone) and aryl chlorides (4'-chloroacetophenone) were not successfully yielded.

Table 11. Scope of Heck coupling.[a]



13 **19a** **20**

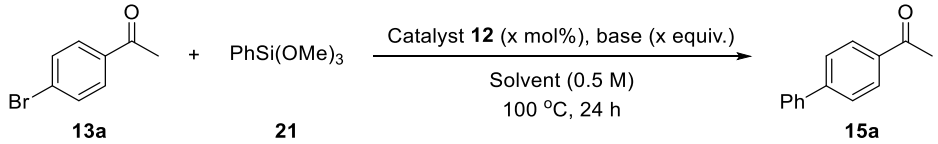
Entry	Ar	Product	Yield (%)[b]
1	4-(O_2N)C_6H_4	**20a**	99
2	4-(MeCO)C_6H_4	**20b**	95
3	4-(F_3C)C_6H_4	**20c**	80
4	Ph	**20d**	72
5	1-naphthyl	**20e**	48
6	2-MeC_6H_4	**20f**	57[c]
7	4-MeC_6H_4	**20g**	91[c]
8	4-(MeO)C_6H_4	**20h**	78[c]

[a] Reaction conditions: Aryl iodide (0.2 mmol), methyl acrylate (0.25 mmol), NaOAc (0.3 mmol), complex **12** (1 mol%) in 0.2 mL of AcChCl:urea (1:2) were stirred at 120 ºC for 6 h; [b] Isolated yield after flash column chromatography; [c] Reaction performed for 16 h.

Biaryl compounds have been typically synthesized under Suzuki-Miyaura conditions. Nevertheless, Hiyama cross-coupling reaction unlike Suzuki-Miyaura coupling, employs organosilanes as coupling partners which offer certain advantages from a sustainable and economic point of view.[135] For this reason, the catalytical activity of catalyst **12** was studied for the Hiyama coupling (Table 12). Different DESs were employed as reaction medium (entries 1-6), observing the best result by far with ChCl:glycerol (1:2) eutectic mixture (entry 1). Various bases and their amount were tested without any improvement in respect to the previous results (compare entry 1 and entries 7-14). Additionally, the decrease of the catalytic amount of catalyst **12** gave lower yields (entries 14-16). In an attempt to reduce the reaction time, the reaction was carried out for 6 and 16 h but moderate yields were obtained in all cases (entries 17-18). The temperature was also decreased to 50 ºC obtaining 55% yield (entry 19). Thus, the best result was obtained using ChCl:glycerol (1:2) as solvent, 1.5 equiv. of K_2CO_3 as base at 100 ºC for 24 h (entry 12).

[135] Nakao, Y.; Hiyama, T. *Chem. Soc. Rev.* **2011**, *40*, 4893-4901.

Table 12. Optimization of Hiyama coupling.[a]



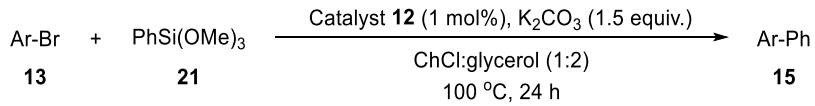
13a **21** **15a**

Entry	Catalyst (mol%)	Base (equiv.)	Solvent	Yield (%)[b]
1	1	K_2CO_3 (2)	ChCl:glycerol (1:2)	73
2	1	K_2CO_3 (2)	ChCl:ethylene glycol (1:2)	12
3	1	K_2CO_3 (2)	ChCl:urea (1:2)	0
4	1	K_2CO_3 (2)	Decanoic acid:TBAB (2:1)	0
5	1	K_2CO_3 (2)	AcChCl:urea (1:2)	0
6	1	K_2CO_3 (2)	AcChCl:acetamide (1:2)	0
7	1	Na_2CO_3 (2)	ChCl:glycerol (1:2)	55
8	1	$NaHCO_3$ (2)	ChCl:glycerol (1:2)	30
9	1	K_3PO_4 (2)	ChCl:glycerol (1:2)	24
10	1	-	ChCl:glycerol (1:2)	0
11	1	K_2CO_3 (1)	ChCl:glycerol (1:2)	53
12	1	K_2CO_3 (1.5)	ChCl:glycerol (1:2)	70
13	1	K_2CO_3 (2.5)	ChCl:glycerol (1:2)	38
14	-	K_2CO_3 (2)	ChCl:glycerol (1:2)	0
15	0.70	K_2CO_3 (2)	ChCl:glycerol (1:2)	35
16	1.5	K_2CO_3 (2)	ChCl:glycerol (1:2)	71
17	1	K_2CO_3 (2)	ChCl:glycerol (1:2)	54[c]
18	1	K_2CO_3 (2)	ChCl:glycerol (1:2)	60[d]
19	1	K_2CO_3 (2)	ChCl:glycerol (1:2)	55[e]

[a] Reaction conditions: Aryl bromide (0.5 mmol), $PhSi(OMe)_3$ (0.75 mmol), base (x equiv.), complex **12** (x mol%) in 1 mL of solvent; [b] Yield determined by GC using tridecane as internal standard; [c] Reaction time 6 h; [d] Reaction time 16 h; [e] Reaction temperature 50 °C.

To evaluate the scope of the reaction, different aryl bromides were coupled with phenyltrimethoxysilane (**21**; Table 13) under the optimized reaction conditions. The electronic nature of the substituents of aryl bromides seems to have no influence in the results since good to excellent yields were obtained for both, electron-poor (entries 1-4) and electron-rich (entries 5-6) coupling partners. The reaction was also compatible with heteroaryl bromides, affording the corresponding heterobiaryls in excellent yields (entries 7-9).

Table 13. Scope of the Hiyama coupling.[a]



Entry	Ar	Product	Yield (%)[b]
1	4-(MeCO)C_6H_4	**15a**	70
2	4-(O_2N)C_6H_4	**15d**	88
3	Ph	**15f**	95
4	4-FC_6H_4	**15g**	95
5	4-(HO)C_6H_4	**15j**	85
6	4-(MeO)C_6H_4	**15o**	67
7	3-pyridyl	**15p**	95
8	3-furyl	**15q**	88
9	2-thienyl	**15r**	88

[a] Reaction conditions: Aryl bromide (0.5 mmol), $PhSi(OMe)_3$ (0.75 mmol), K_2CO_3 (0.75 mmol), complex **12** (1 mol%) in 1 mL of ChCl:glycerol (1:2) were stirred at 100 ºC for 24 h; [b] Isolated yield after flash column chromatography.

The recyclability of the catalyst and solvent was studied for the Suzuki-Miyaura and Hiyama reactions under the previously described optimal conditions, respectively. Once the reaction was finished, the organic compounds were extracted with 2-MeTHF (a renewable VOC solvent).[136] However, an important drop in the reaction yield was observed in the second cycle (from 92 and 95% to 36 and 40%, respectively). This could probably be explained by the formation of inactive palladium black, as well as, the iodine poisoning of palladium nanoparticles.[137]

In order to gain better insight into the catalytic process, a mercury poisoning test was performed. The four cross-coupling reactions were set up under optimal conditions but in the presence of 250 mol% of Hg(0). Thus, if the palladium nanoparticles were the catalytically active species in the reaction, an important drop in the reaction yield should be noticed.[138] A complete inhibition of the reaction was observed in the Suzuki-Miyaura, Sonogashira and

[136] Pace, V.; Hoyos, P.; Castoldi, L.; Domínguez de María, P.; Alcántara, A. R. *ChemSusChem* **2012**, *5*, 1369-1379.

[137] Cano, R.; Pérez, J. M.; Ramón, D. J.; McGlacken, G. P. *Tetrahedron* **2016**, *72*, 1043-1050.

[138] Sigeev, A. S.; Peregudov, A. S.; Cheprakov, A. V.; Beletskaya, I. P. *Adv. Synth. Catal.* **2015**, *357*, 417-429.

Heck cross-coupling reactions. Surprisingly, no inhibition was noticed in the case of the Hiyama coupling, which is in concordance with previous results employing a Pd-NCN pincer catalyst in DES, which was correlated with a different mechanism involving Pd(IV) species.[126]

Since the formation of palladium nanoparticles seemed to be vital for the outcome of the aforementioned cross-coupling reactions, the crude mixture was analyzed after the completion of the corresponding reactions by Transmission Electron Microscopy (TEM) to characterize those PdNPs (Figure 14).

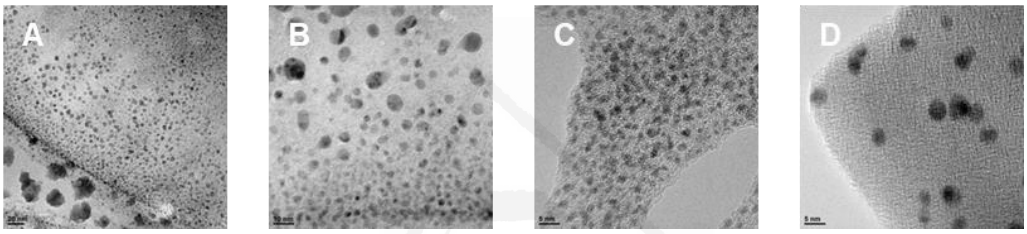


Figure 14. TEM images of the crude media after a) Suzuki, b) Sonogashira, c) Heck and d) Hiyama cross-coupling reactions.

The size distributions of the observed PdNPs are summarized in Table 14. Although the reaction conditions were different for the Suzuki-Miyaura and Sonogashira reactions, a similar size of nanoparticles was observed in both cases. The average size of PdNPs for the Heck reaction was smaller, probably due to the higher temperature of the reaction and the different composition of the employed eutectic mixture. Bigger nanoparticles were found in the Hiyama reaction mixture. However, the longer reaction time required for this transformation (24 h) could favor the nanoparticles aggregation, which could explain the recyclability issues.

Table 14. Size distribution of PdNPs in the different cross-coupling reactions.

Reaction	Average length (nm)[a]
Suzuki-Miyaura	6.1 ± 3.0
Sonogashira	6.7 ± 2.9
Heck	2.1 ± 0.4
Hiyama	8.7 ± 3.2

[a] Average calculated from at least 200 NPs observed in TEM images.

Kinetics studies were performed in order to better understand the nature of the catalytic process (Figure 15). In the Suzuki-Miyaura kinetic plot, an induction period was observed for the first 60 min, which seems to indicate that until palladium nanoparticles were not formed, the reaction did not occur. So, in concordance with the mercury test, palladium(0) nanoparticles seems to be the real catalyst of the cross-coupling reaction. On the contrary, in the Hiyama reaction no induction period was noticed at the beginning of the reaction, even decreasing the catalytic amount.

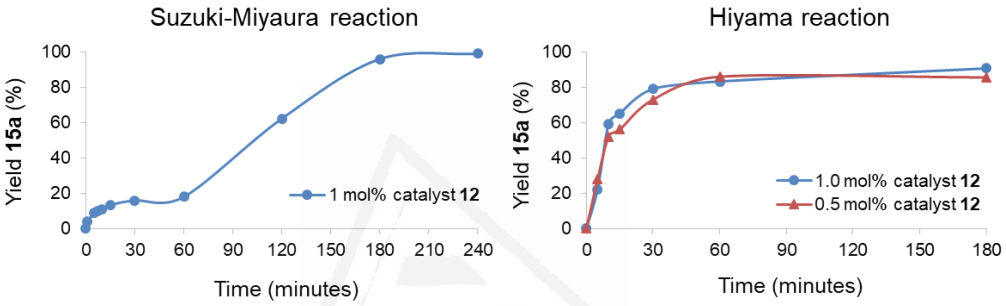


Figure 15. Kinetic plot of the Suzuki-Miyaura (left) and Hiyama (right) reactions.

Pre-formed PdNPs were employed to carry out the Hiyama reaction under optimized reaction conditions but no catalysis was observed. This result might indicate that soluble palladium species coordinated with aNHC ligands are the active species for the reaction through a Pd(II)-Pd(IV) catalytic process.[139]

Additionally, XPS (X-ray Photoelectron Spectroscopy) analysis shows that after the Suzuki-Miyaura reaction, the oxidation state of the initial carbene palladium catalyst **12** (monomer or dimer) changes completely to palladium(0) and palladium(II) oxide species (Figure 16).

[139] a) Szulmanowicz, M. S.; Gniewek, A.; Gil, W.; Trzeciak, A. M. *ChemCatChem* **2013**, *5*, 1152-1160; b) Modak, S.; Gangwar, M. K.; Nageswar Rao, M.; Madasu, M.; Kalita, A. C.; Dorcet, V.; Shejale, M. A.; Butcher, R. J.; Ghosh, P. *Dalton Trans.* **2015**, *44*, 17617-17628; c) Mondal, T.; De, S.; Dutta, S.; Koley, D. *Chem. Eur. J.* **2018**, *24*, 6155-6168.

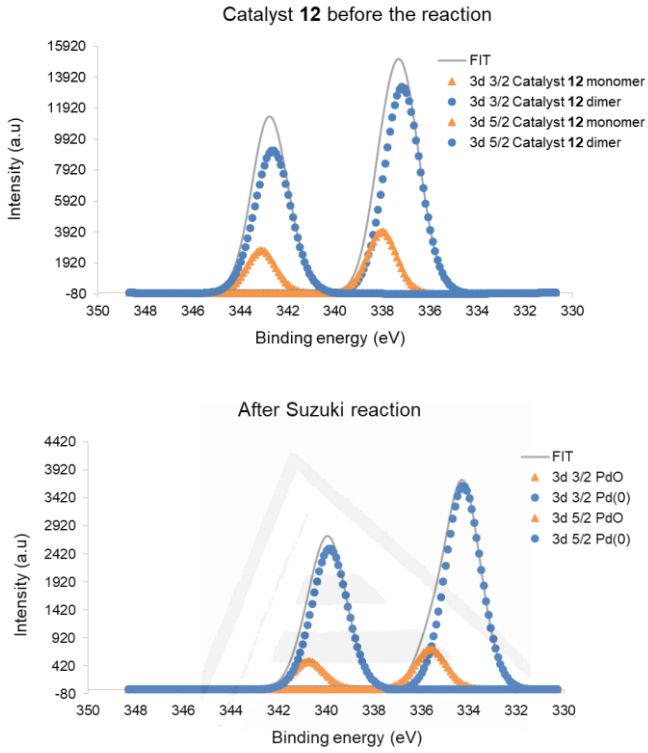


Figure 16. XPS analysis of the catalyst before and after the Suzuki-Miyaura reaction.

1.2.2.2 Bipyridine palladium catalyst for cross-coupling reactions in DESs

So far, all the palladium catalysts that our group or other groups have synthesized and designed to be compatible with DESs, could be classified as hydrogen bond acceptor component, taking into account the two possible role of DES components, such as acceptor or donor character in the hydrogen bond. Therefore, our main idea was the design of a new amino-bipyridine palladium complex with full compatibility with DESs due to its intrinsic capacity of hydrogen bond formation as donor ligand, in order to study if this new role might improve the applicability and recyclability of previous catalysts.

Our investigations started with the design and synthesis of the novel bipyridine-palladium catalysts **25**. First, ligands **24** were synthesized through a simple and previously described synthetic procedure and then, these ligands were treated with $PdCl_2$ to afford the desired complexes **25** (Figure 17). Once the palladium complexes were prepared, the main objective was to test their applicability in different cross-coupling reactions.

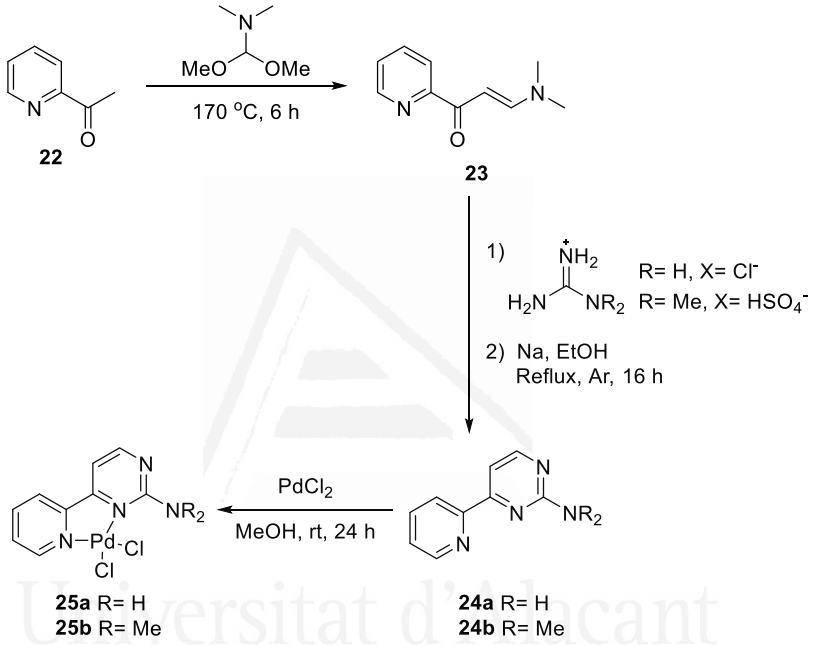
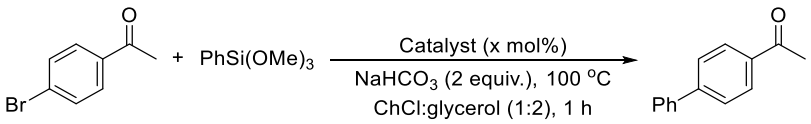


Figure 17. Bipyridine-palladium catalyst synthesis.

Different palladium catalysts were evaluated as pre-catalysts for the Hiyama reaction (Table 15). Initially, it was proved that the reaction failed without any catalyst (entry 1). After this control experiment, different amounts of catalyst **25a** were used obtaining a better result with 1 mol% of catalyst (entries 2-3). The importance of ligand **24a**, was demonstrated when $PdCl_2$ was employed as solely pre-catalyst (entry 4) or in the presence of uncoordinated bipyridine ligand (entry 5), obtaining 58% and 30% yield, respectively. Surprisingly, an excess of ligand **24a** together with pre-catalyst **25a** inhibited the reaction (entry 6). The amino group of bipyridine moiety proved to be relevant as the yield dropped to 5% with its absence (entry 7) or to 54% when dimethylaminobipyridine palladium complex **25b** was used as pre-catalyst (entry 8).

Table 15. Optimization of palladium catalysts for the Hiyama cross-coupling reaction.[a]



13a **21** **15a**

Entry	Catalyst (x mol%)	Yield (%)[b]
1	-	0
2	**25a** (1 mol%)	88
3	**25a** (0.5 mol%)	75
4	$PdCl_2$ (1 mol%)	58
5	$PdCl_2$ (1 mol%) + **24a** (1:1)	30
6	**25a** (1 mol%) + **24a** (1:1)	0
7	(2,2'-bipyridine)dichloropalladium(II) (1 mol%)	5
8	**25b** (1 mol%)	54

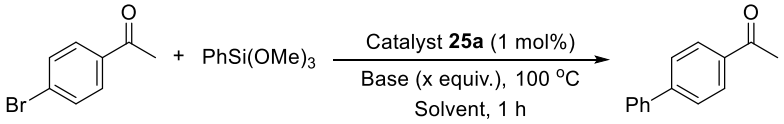
[a] Reaction conditions: Aryl bromide (0.5 mmol), $PhSi(OMe)_3$ (0.75 mmol), $NaHCO_3$ (2 equiv.), catalyst (x mol%) at 100 °C in 1 mL of ChCl:glycerol (1:2) for 1 h; [b] Yield determined by GC using tridecane as internal standard.

This fact could be attributable to the hydrogen bond interactions between the free amino group present in the catalyst **25a** and the DES network, which probably enhances the catalytical activity of the palladium pre-catalyst. This cooperative effect has been previously described in the isomerization of allylic alcohols in DESs.[140]

Then, the study continued with the optimization of the reaction conditions (Table 16). Temperature proved to be a crucial factor since the reaction at 50 °C did not take place, but 83% yield was obtained at 100 °C (entries 1-2). Different bases were employed (entries 3-9), finding out that $NaHCO_3$ (2 equiv.) provided the best yield (entry 7). All sorts of DESs, hydrophilic (entries 7, 10-14) and even, hydrophobic eutectic mixtures (entries 15-16) were tested. The benefit of using DESs as reaction medium was demonstrated when a lower catalytical activity was obtained using only one of the DES components as pure glycerol or water as reaction medium (entries 17-18).

[140] a) Vidal, C.; Suárez, F. J.; García-Álvarez, J. *Catal. Commun.* **2014**, *44*, 76-79; b) Wang, H.; Liu, S.; Zhao, Y.; Wang, J.; Yu, Z. *ACS Sustainable Chem. Eng.* **2019**, *7*, 7760-7767.

Table 16. Optimization of the Hiyama reaction conditions.[a]



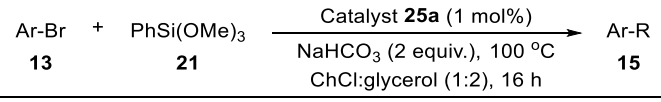
13a **21** **15a**

Entry	Base (x equiv.)	Solvent	Yield (%)[b]
1	K_2CO_3 (2 equiv.)	ChCl:glycerol (1:2)	0[c]
2	K_2CO_3 (2 equiv.)	ChCl:glycerol (1:2)	83
3	K_3PO_4 (2 equiv.)	ChCl:glycerol (1:2)	70
4	Na_2CO_3 (2 equiv.)	ChCl:glycerol (1:2)	23
5	NaOAc (2 equiv.)	ChCl:glycerol (1:2)	68
6	NaF (2 equiv.)	ChCl:glycerol (1:2)	30
7	$NaHCO_3$ (2 equiv.)	ChCl:glycerol (1:2)	88
8	$NaHCO_3$ (1 equiv.)	ChCl:glycerol (1:2)	74
9	-	ChCl:glycerol (1:2)	0
10	$NaHCO_3$ (2 equiv.)	ChCl:urea (1:2)	7
11	$NaHCO_3$ (2 equiv.)	ChCl:ethylene glycol (1:2)	20
12	$NaHCO_3$ (2 equiv.)	Ph_3PMeBr:glycerol (1:2)	7
13	$NaHCO_3$ (2 equiv.)	AcChCl:urea (1:2)	0
14	$NaHCO_3$ (2 equiv.)	Guanidine:glycerol (1:1)	0
15	$NaHCO_3$ (2 equiv.)	Decanoic acid:menthol (1:2)	0
16	$NaHCO_3$ (2 equiv.)	Decanoic acid:TBAB (2:1)	0
17	$NaHCO_3$ (2 equiv.)	Glycerol	55
18	$NaHCO_3$ (2 equiv.)	H_2O	5

[a] Reaction conditions: Aryl bromide (0.5 mmol), $PhSi(OMe)_3$ (0.75 mmol), base (x equiv.), complex **25a** (1 mol%) at 100 °C in 1 mL of solvent for 1 h; [b] Yield determined by GC using tridecane as internal standard; [c] Reaction performed at 50 °C.

After establishing the optimum reaction conditions, the substrate scope was evaluated (Table 17). In general, very good isolated yields were obtained between the couplings of different activated and deactivated aryl bromides with trimethoxyphenylsilane (**21**), regardless of the electronic nature of their aryl moieties (entries 1-7). Heteroaromatic bromides were also successfully coupled with **21** (entries 8-9) and even, benzyl bromide gave a satisfactory 89% yield (entry 10). However, various alkyl bromides (1-bromopentane and 1-bromodecane) and allylic bromide were tested with no success.

Table 17. Scope of the Hiyama reaction.[a]



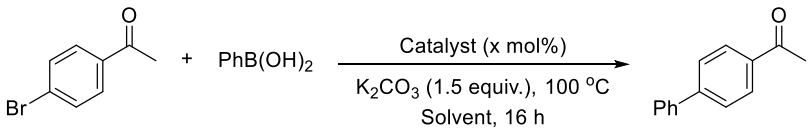
Entry	Ar	Product	Yield (%)[b]
1	4-(MeCO)C_6H_4	**15a**	88[c]
2	4-(O_2N)C_6H_4	**15d**	90[d]
3	4-FC_6H_4	**15g**	88
4	Ph	**15f**	95
5	4-MeC_6H_4	**15h**	73
6	4-(HO)C_6H_4	**15j**	70
7	4-(MeO)C_6H_4	**15o**	33
8	3-pyridyl	**15p**	67
9	3-furyl	**15q**	80
10	CH_2Ph	**15s**	89

[a] Reaction conditions: Aryl bromide (0.5 mmol), $PhSi(OMe)_3$ (0.75 mmol), base (2 equiv.), complex **25a** (1 mol%) at 100 °C in 1 mL of ChCl:glycerol (1:2) for 16 h; [b] Isolated yield after flash column chromatography; [c] Reaction performed for 1 h; [d] Reaction performed for 2 h.

The applicability of the bipyridine palladium pre-catalyst **25a** was also tested for the Suzuki-Miyaura cross-coupling reaction (Table 18). Preliminary optimization studies pointed out K_2CO_3 as the best base and 100 °C the optimal temperature. Generally, better results were obtained with alcoholic based eutectic mixtures as reaction media (entries 1-11). Although decanoic acid:menthol (1:2) presented the best yield (entry 2 and 12), the purification step was more tedious due to the hydrophobic nature of this eutectic mixture since a large amount of menthol was extracted in the organic phase after the usual work-up process. Pure ethylene glycol and water were utilized as solvents but higher yields were obtained with ChCl:ethylene glycol (1:2) mixture (entries 13-15). The use of $PdCl_2$ as pre-catalyst (entries 16-17) or the use of lower catalytical amounts of catalyst (entries 3, 7, and 17) led to worse results (compare entries 7 and 17). Note that the difference in catalytical activity between $PdCl_2$ and catalyst **25a** was not so significant (compare entries 13 and 16), as for other cross-coupling reactions.

Other aryl bromides and boronic acids were evaluated employing the optimal reaction conditions (Table 19). Regarding aryl bromides, the presence of electron-withdrawing groups favoured the cross-coupling reaction (entries 1-3). Electron neutral or electron-donating substituted aryl derivatives gave low to moderate yields (entries 4-7).

Table 18. Optimization of the Suzuki-Miyaura reaction conditions.[a]



13a **14a** **15a**

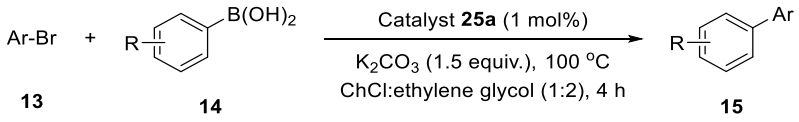
Entry	Catalyst (x mol%)	Solvent	Yield (%)[b]
1	**25a** (1 mol%)	ChCl:glycerol (1:2)	87
2	**25a** (1 mol%)	Decanoic acid:menthol (1:2)	98
3	**25a** (0.5 mol%)	Decanoic acid:menthol (1:2)	62
4	**25a** (1 mol%)	ChCl:urea (1:2)	33
5	**25a** (1 mol%)	Decanoic acid:TBAB (2:1)	16
6	**25a** (1 mol%)	ChCl:ethylene glycol (1:2)	93
7	**25a** (0.5 mol%)	ChCl:ethylene glycol (1:2)	64
8	**25a** (1 mol%)	Ph_3PMeBr:glycerol (1:2)	0
9	**25a** (1 mol%)	ChCl:oxalic acid (1:1)	0
10	**25a** (1 mol%)	ChCl:L-tartaric acid (1:1)	0
11	**25a** (1 mol%)	ChCl:L-malic acid (1:1)	4
12	**25a** (1 mol%)	Decanoic acid:menthol (1:2)	99[c]
13	**25a** (1 mol%)	ChCl:ethylene glycol (1:2)	91[c]
14	**25a** (1 mol%)	Ethylene glycol	88[c]
15	**25a** (1 mol%)	H_2O	89[c]
16	$PdCl_2$ (1 mol%)	ChCl:ethylene glycol (1:2)	85[c]
17	$PdCl_2$ (0.5 mol%)	ChCl:ethylene glycol (1:2)	48

[a] Reaction conditions: Aryl bromide (0.5 mmol), $PhB(OH)_2$ (0.55 mmol), K_2CO_3 (1.5 equiv.), catalyst (x mol%) at 100 °C in 2 mL of solvent for 16 h; [b] Yield determined by GC using tridecane as internal standard; [c] Reaction performed in 1 h.

Various heteroaromatic bromides were efficiently coupled with phenylboronic acid (**14a**; entries 8-10). Additionally, different boronic acids were reacted with 4'-bromoacetophenone (**13a**) giving moderate to good yields (entries 11-14), with a favourable trend in the case of substrates bearing electron-donating groups.

The Heck cross-coupling reaction was also tested (Table 20). An array of different DESs were used as solvent at 100 °C (entries 1-7), obtaining the best yield in ChCl:ethylene glycol (1:2) mixture (entry 1). The reaction time could be significantly reduced just by increasing the temperature to 120 °C (compare entries 1 and 8).

Table 19. Scope of the Suzuki-Miyaura reaction.[a]

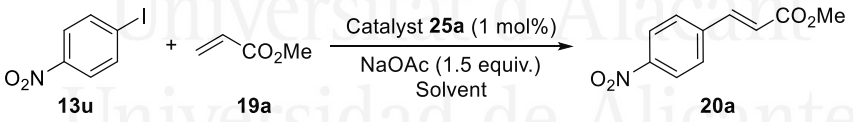


13 14 15

Entry	Ar	R	Product	Yield (%)[b]
1	4-(MeCO)C_6H_4	H	**15a**	91[c]
2	4-(O_2N)C_6H_4	H	**15d**	65
3	4-FC_6H_4	H	**15g**	54
4	Ph	H	**15f**	20
5	4-*t*-BuC_6H_4	H	**15t**	20
6	4-(HO)C_6H_4	H	**15j**	42
7	4-(MeO)C_6H_4	H	**15o**	46
8	3-pyridyl	H	**15p**	55
9	2-thienyl	H	**15r**	50
10	3-quinolinyl	H	**15u**	53
11	4-(MeCO)C_6H_4	3-Me	**15k**	53
12	4-(MeCO)C_6H_4	4-F	**15n**	57
13	4-(MeCO)C_6H_4	4-HO	**15l**	70
14	4-(MeCO)C_6H_4	2-MeO	**15v**	72

[a] Reaction conditions: Aryl bromide (0.5 mmol), $ArB(OH)_2$ (0.55 mmol), K_2CO_3 (1.5 equiv.), catalyst **25a** (1 mol%) at 100 °C in 2 mL of ChCl:ethylene glycol (1:2) for 4 h; [b] Isolated yield after flash column chromatography; [c] Reaction performed in 1 h.

Table 20. Optimization of the Heck coupling reaction.[a]



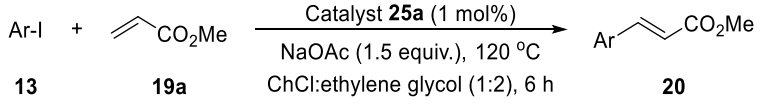
13u 19a 20a

Entry	T (°C)	t (h)	Solvent	Yield (%)[b]
1	100	24	ChCl:ethylene glycol (1:2)	94
2	100	24	ChCl:glycerol (1:2)	83
3	100	24	ChCl:urea (1:2)	0
4	100	24	AcChCl:ethylene glycol (1:2)	51
5	100	24	Ph_3PMeBr:glycerol (1:2)	82
6	100	24	Decanoic acid:menthol (1:2)	0
7	100	24	Decanoic acid:TBAB (2:1)	0
8	120	6	ChCl:ethylene glycol (1:2)	93

[a] Reaction conditions: Aryl iodide (0.5 mmol), methyl acrylate (0.60 mmol), NaOAc (1.5 equiv.), catalyst **25a** (1 mol%) in 1 mL of solvent; [b] Yield determined by GC using tridecane as internal standard.

Based on these results, we attempted the cross-coupling reaction of various aryl iodides **13** with methyl acrylate **19a** to study the scope of the Heck reaction (Table 21). Electron poor aryl iodides gave good to excellent yields (entries 1-3), as well as, electron neutral or electron rich substituted aryl iodides (entries 4 and 7-9). Exceptionally, 2-methyl and 4-methyl derivatives led to slightly lower yields (entries 5 and 6).

Table 21. Scope of the Heck coupling reaction.[a]



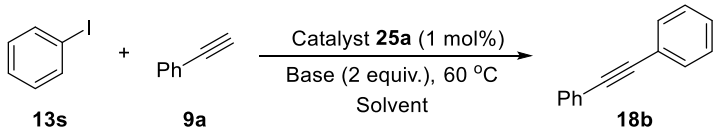
13 **19a** **20**

Entry	Ar	Product	Yield (%)[b]
1	4-(O_2N)C_6H_4	**20a**	93
2	4-(MeCO)C_6H_4	**20b**	67
3	4-(F_3C)C_6H_4	**20c**	95
4	Ph	**20d**	90
5	2-MeC_6H_4	**20f**	66
6	4-MeC_6H_4	**20g**	79
7	2-HOC_6H_4	**20i**	84
8	4-(MeO)C_6H_4	**20h**	86
9	1-naphthyl	**20e**	94

[a] Reaction conditions: Aryl iodide (0.5 mmol), methyl acrylate (0.60 mmol), NaOAc (1.5 equiv.), catalyst **25a** (1 mol%) at 120 °C in 1 mL of ChCl:ethylene glycol (1:2) for 6 h; [b] Isolated yield after flash column chromatography.

Finally, the catalytic activity of pre-catalyst **25a** was evaluated in the copper-free Sonogashira cross-coupling reaction (Table 22). A range of DESs were tested (entries 1-5) but Ph_3PMeBr:glycerol (1:2) emerged as the best reaction medium (entry 5). Different organic and inorganic bases were examined (entries 6-9 and 11), observing similar yields with iPr_2NH (entry 9) and K_2CO_3 (entry 11). To evaluate which base gave better results, a higher catalytical amount and reaction time were used, showing that the organic base (iPr_2NH) was the best one (compare entries 10 and 12). Trying to increase the yield of the reaction, 3 mol% of pre-catalyst **25a** was used obtaining the best yield (84%; entry 13).

Table 22. Optimization of the Sonogashira coupling reaction.[a]



13s **9a** **18b**

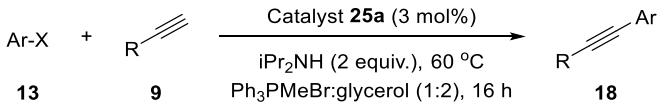
Entry	Base	t (h)	Solvent	Yield (%)[b]
1	iPr_2NH	2	ChCl:ethylene glycol (1:2)	30[c]
2	iPr_2NH	2	ChCl:urea (1:2)	33[c]
3	iPr_2NH	2	AcChCl:ethylene glycol (1:2)	20[c]
4	iPr_2NH	2	ChCl:glycerol (1:2)	32[c]
5	iPr_2NH	2	Ph_3PMeBr:glycerol (1:2)	55[c]
6	NaOAc	2	Ph_3PMeBr:glycerol (1:2)	6[c]
7	Na_2CO_3	2	Ph_3PMeBr:glycerol (1:2)	33[c]
8	K_3PO_4	2	Ph_3PMeBr:glycerol (1:2)	54[c]
9	iPr_2NH	2	Ph_3PMeBr:glycerol (1:2)	61
10	iPr_2NH	16	Ph_3PMeBr:glycerol (1:2)	80[d]
11	K_2CO_3	5	Ph_3PMeBr:glycerol (1:2)	68[d]
12	K_2CO_3	16	Ph_3PMeBr:glycerol (1:2)	71[d]
13	iPr_2NH	16	Ph_3PMeBr:glycerol (1:2)	84[e]

[a] Reaction conditions: Aryl iodide (0.5 mmol), phenylacetylene (0.60 mmol), base (2 equiv.), catalyst **25a** (1 mol%) at 60 °C in 2 mL of solvent; [b] Yield determined by GC using tridecane as internal standard; [c] Reaction performed at 80 °C; [d] Reaction performed with **25a** (2 mol%); [e] Reaction performed with **25a** (3 mol%).

To survey the scope and versatility of catalyst **25a** in the Sonogashira reaction, both aryl iodides and bromides were coupled with various terminal alkynes **9** under the optimized reaction conditions (Table 23). In general, aryl halides bearing electron-neutral or electron-withdrawing groups gave good results (entries 1-8), only a decrease of yield was detected for bromobenzene (**13k**; entry 2). In this case, the electronic nature of the aromatic ring had a notable impact on the reaction yield, obtaining lower yields when electron-rich substituted aryl iodides were used (entries 9-12). Aliphatic terminal alkynes and heteroaryl iodides were also examined (entries 13-14).

A crucial point for the sustainability of a process is the recyclability. For this purpose, after completion of each cross-coupling reaction the organic compounds were extracted with 2-MeTHF and then, the mixture of DES and catalyst was reused under the same reaction conditions (Figure 18).

Table 23. Scope of the Sonogashira reaction.[a]



13 **9** **18**

Entry	Ar/X	R	Product	Yield (%)[b]
1	Ph/I	Ph	**18b**	84
2	Ph/Br	Ph	**18b**	11
3	4-(O_2N)C_6H_4/I	Ph	**18d**	90
4	4-(O_2N)C_6H_4/Br	Ph	**18d**	85
5	4-(MeCO)C_6H_4/I	Ph	**18a**	91
6	4-(MeCO)C_6H_4/Br	Ph	**18a**	71
7	4-(F_3C)C_6H_4/I	Ph	**18i**	83
8	4-FC_6H_4/I	Ph	**18g**	56
9	2-MeC_6H_4/I	Ph	**18e**	29
10	4-MeC_6H_4/I	Ph	**18c**	54
11	4-(MeO)C_6H_4/I	Ph	**18h**	15
12	2-(H_2N)C_6H_4/I	Ph	**18j**	64
13	4-(O_2N)C_6H_4/I	C_6H_{11}	**18k**	48
14	2-thienyl/I	Ph	**18f**	74

[a] Reaction conditions: Aryl iodide (0.5 mmol), methyl acrylate (0.60 mmol), iPr_2NH (2 equiv.), catalyst **25a** (3 mol%) at 60 °C in 2 mL of Ph_3PMeBr:glycerol (1:2) for 16 h; [b] Isolated yield after flash column chromatography.

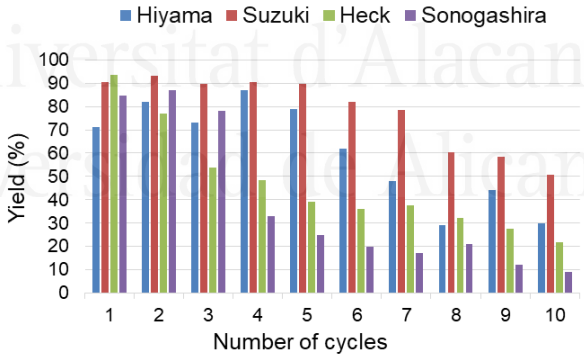


Figure 18. Recyclability of the system.

For the Hiyama and Suzuki coupling reactions, the catalyst could be recycled up to 5 consecutive cycles. In the case of Heck and Sonogashira reactions, the system could be efficiently recycled 3 consecutive cycles. It should be pointed out that the progressive decrease of catalytic activity detected in the recycling experiments could be explained by the

observed formation of palladium back during the sequence of the reactions. However, the good catalytical activity detected after 3 or 5 consecutive cycles could be attributed to a stabilizing effect of DES components on the formed PdNPs.[141] To confirm this fact, after the completion of the reaction (first cycle), the crude mixture was analyzed by TEM (Figure 19).

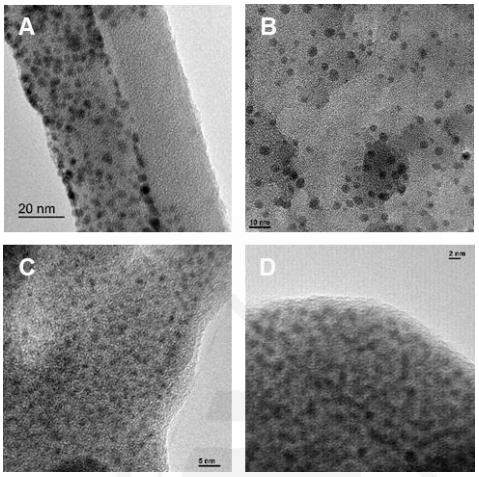


Figure 19. TEM images of PdNPs after the first cycle of the Hiyama (A), Suzuki-Miyaura (B), Heck (C) and Sonogashira (D) reactions.

As expected, palladium nanoparticles were observed in all cross-coupling reactions with an average of 4.16±1.10 nm diameter (Hiyama), 3.17±0.69 nm diameter (Suzuki-Miyaura), 1.81±0.40 nm diameter (Heck) and 1.66±0.33 nm diameter (Sonogashira). XPS analysis also confirmed that part of the initial palladium(II) species were reduced to palladium(0) during the course of the Hiyama reaction (Figure 20). The mercury test confirmed that the *in situ* generated PdNPs were the catalytic active species since only 2% of conversion of **15a** was observed for the Hiyama reaction.

Additionally, kinetic studies showed an induction period with low catalytic loading in all the coupling reactions (Figure 21).

[141] Reetz, M. T.; Westermann, E. *Angew. Chem. Int. Ed.* **2000**, *39*, 165-168.

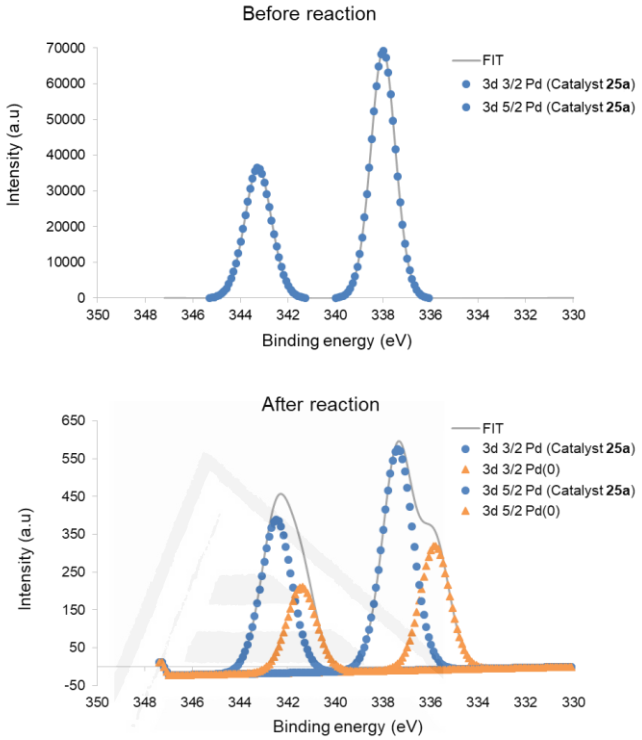


Figure 20. XPS analysis of the catalyst before and after the Hiyama reaction.

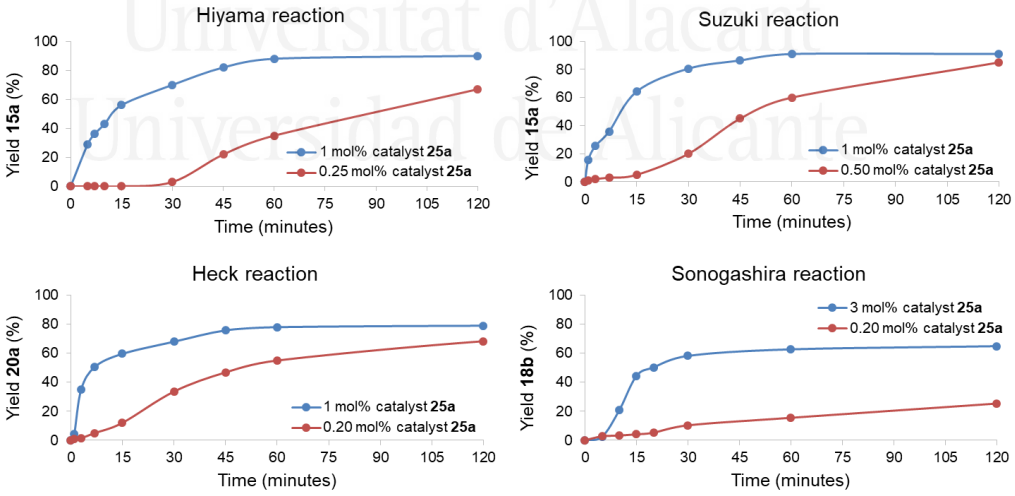


Figure 21. Kinetic studies of all cross-coupling reactions.

During this initial period, it was confirmed by TEM images that any PdNPs were present in the crude mixture. Moreover, the PdNPs isolated from the first Hiyama reaction cycle (after aqueous work-up and centrifugation) were utilized in a second cycle with fresh solvent and reagents obtaining 56% yield of **15a**. These results seem to indicate that catalyst **25a** plays a pre-catalyst role and the *in situ* generated palladium(0) nanoparticles might be the real catalyst of cross-coupling reactions.

Experimental UV/Vis titration studies exhibit the formation of a 1:2 metal/ligand complex. Thus, the spectrophotometric titration of 2 mL of ligand **24a** in acetonitrile ($5 \cdot 10^{-5}$ M) with successive additions of 15 µL of $Pd(MeCN)_2Cl_2$ in acetonitrile ($2.5 \cdot 10^{-4}$ M; 35 additions) confirmed that palladium was initially coordinated by two bipyridine ligands **24a**. Representative spectra for the UV/Vis studies are shown in Figure 22 (λ = 244 and 223 nm).

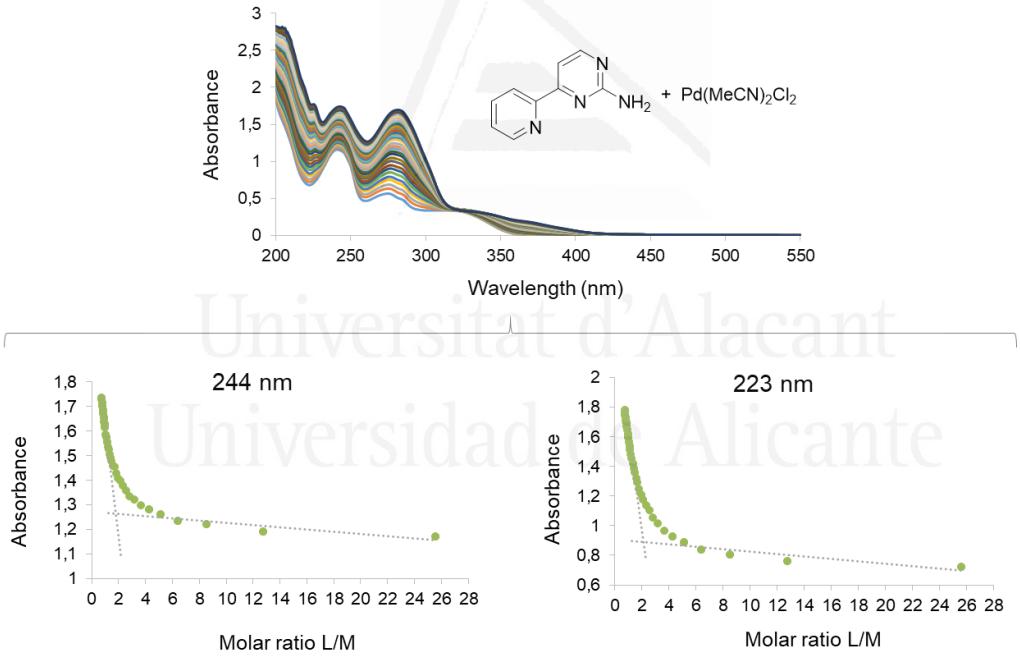


Figure 22. Molar ratio = 1:2 (metal:ligand) obtained by UV/Vis titration studies.

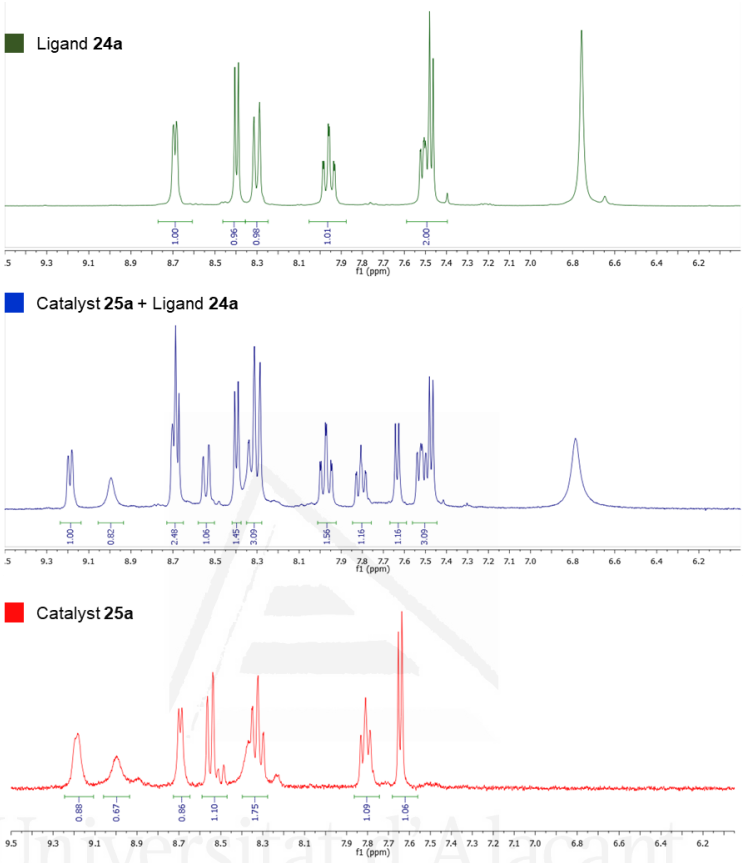


Figure 23. ^{1}H NMR spectra of ligand **24a**, catalyst **25a** + ligand **24a** and catalyst **25a**.

However, the ^{1}H NMR analysis of ligand **24a**, complex **25a** and the crude mixture of complex **25a** synthesized with an excess of ligand **24a**, showed only the presence of one ligand per one palladium atom (Figure 23). Therefore, we began to suspect that the UV/Vis titration showed the formation of an initial complex with a palladium atom coordinated with two bipyridine ligands by the more donating nitrogen atoms (NH_2 moiety; complex A in Figure 24). Then, this initial complex evolves toward the thermodynamic complex formed by coordination with the two nitrogen atoms of the bipyridine unit (C), probably through an intermediate complex involving the coordination with the amino pyridine subunit of the ligand (complex B in Figure 24).

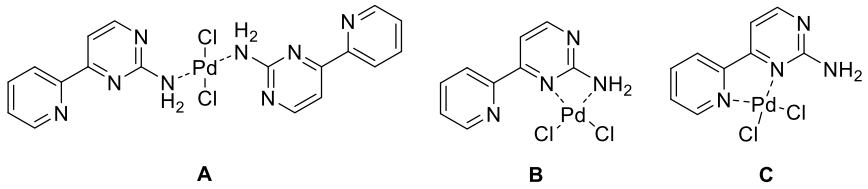


Figure 24. Different coordination of palladium with ligand **24a**.

To gain more insight into the formation of complex **25a**, a UV/Vis study of the evolution of the coordination of ligand **24a** ($5 \cdot 10^{-5}$ M in acetonitrile) to palladium salt [$Pd(MeCN)_2Cl_2$ $2.5 \cdot 10^{-4}$ M in acetonitrile] was performed (Figure 25). The experiments showed that the initial complex (t = 0 min, grey) was changing until the final orange shape (t = 6 h, orange), which is in consonance with the spectrum of the previously synthesized and isolated complex **25a** ($2.5 \cdot 10^{-4}$ M in acetonitrile).

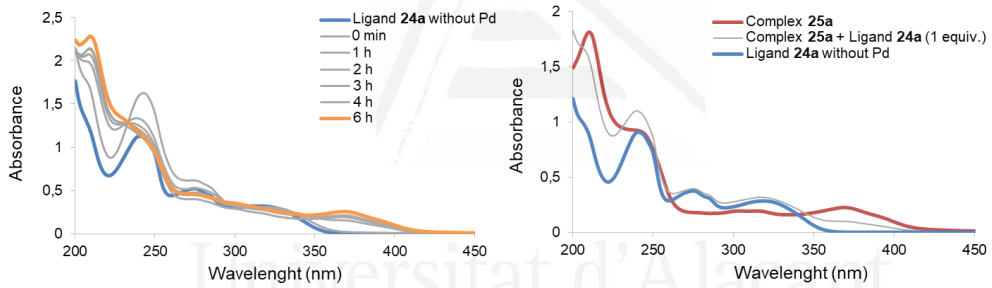
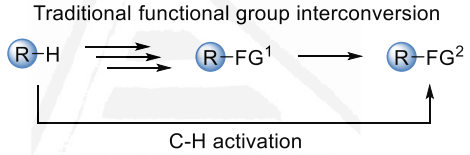


Figure 25. Evolution of palladium coordination with ligand **24a**.

1.3 RUTHENIUM CATALYZED C-H ACTIVATION

1.3.1 Precedents

Over the centuries, generations of chemists have learned how to prepare new molecular structures, typically by the interconversion of pre-existing functional groups. However, the interconversion of these functional groups requires multistep preparative sequences, throughout which undesired by-products are generated. In sharp contrast, transition-metal catalyzed C-H activation has surfaced as an increasingly viable, environmentally benign alternative, in terms of high-atom economy, low *E* factor (generates less waste), and high resource economy. Thus, the direct transformation of C-H bonds allows for the use of unfunctionalized starting materials, thereby providing a more straightforward and sustainable synthetic route (Scheme 20).[142]



Scheme 20. Traditional functional group interconversion *versus* C-H activation.

As a consequence, this strategy has led to the development of an impressive number of transformations for the preparation of pharmaceuticals, natural compounds, agrochemicals, and other practically useful products,[143] even through more challenging enantioselective C-H functionalizations.[144] Various transition metal catalysts are now contributing to this field, including ruthenium(II) species as one of the most important catalysts to promote C-H bond catalytic transformations.[145]

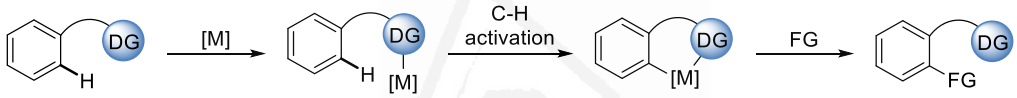
[142] Crabtree, R. H.; Lei, A. *Chem. Rev.* **2017**, *117*, 8481-8482.

[143] a) Chen, D. Y.-K.; Youn, S. W. *Chem. Eur. J.* **2012**, *18*, 9452-9474; b) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369; c) Karimov, R. R.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2018**, *57*, 4234-4241.

[144] a) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908-8976; b) Woźniak, Ł.; Tan, J.-F.; Nguyen, Q.-H.; Madron du Vigné, A.; Smal, V.; Cao, Y.-X.; Cramer, N. *Chem. Rev.* **2020**, *120*, 10516-10543.

[145] a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879-5918; b) Manikandan, R.; Jeganmohan, M. *Chem. Commun.* **2017**, *53*, 8931-8947; c) Duarah, G.; Kaishap, P.; Begum, T.; Gogoi, S. *Adv. Synth. Catal.* **2019**, *361*, 654-672.

Owed to the omnipresence of C-H bonds in all kind of organic molecules, a major challenge of this approach lies in achieving selective C-H activation at a single and strategic site in the presence of multiple C-H bonds with similar bond strengths and electronic properties.[146] In this context, the use of directing groups (DG) has become the strategic choice to allow site-selective functionalization. Because of its coordination ability, the DG directs the transition metal into close proximity of the C-H bond to be activated, promoting the C-H activation and controlling the selectivity of the reaction (Scheme 21). A large number of functional groups such as amides, pyridines, carboxylic acids and ketones have been used as directing groups.[147] Among them, *N*-alkoxy amides play an important role since the directing group could also serve as an internal oxidant for regeneration of the metal catalyst during the catalytic cycle.[148]



[M] = Pd, Rh, Ir, Ru, etc.

Scheme 21. Chelate-assisted C-H activation.

Recent trends towards improving the sustainability of C-H activation include the use of earth-abundant metal catalysts[149] or electrochemical methods,[150] amongst others.[151] Despite these notable advances, the main environmental drawback associated with C-H activation is actually represented by the nature of the reaction media. In general, volatile, toxic and flammable organic solvents such as acetic acid, methanol, tetrahydrofuran (THF),

[146] Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. *Chem. Rev.* **2017**, *117*, 8622-8648.

[147] a) Gandeepan, P.; Ackermann, L. *Chem* **2018**, *4*, 199-222; b) Rasheed, O. K.; Sun, B. *ChemistrySelect* **2018**, *3*, 5689-5708; c) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788-1887.

[148] a) Zhu, R. Y.; Farmer, M. E.; Chen, Y. Q.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578-10599; b) Wang, Z.; Xie, P.; Xia, Y. *Chin. Chem. Lett.* **2018**, *29*, 47-53; c) Subhedar, D. D.; Mishra, A. A.; Bhanage, B. M. *Adv. Synth. Catal.* **2019**, *361*, 4149-4195.

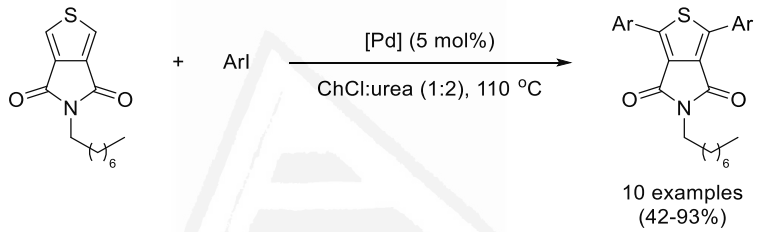
[149] Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2018**, *119*, 2192-2452.

[150] a) Sauermann, N.; Meyer, T. H.; Qiu, Y.; Ackermann, L. *ACS Catal.* **2018**, *8*, 7086-7103; b) Ackermann, L. *Acc. Chem. Res.* **2019**, *53*, 84-104.

[151] a) Gensch, T.; Hopkinson, M.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900-2936; b) Santoro, S.; Kozhushkov, S. I.; Ackermann, L.; Vaccaro, L. *Green Chem.* **2016**, *18*, 3471-3493.

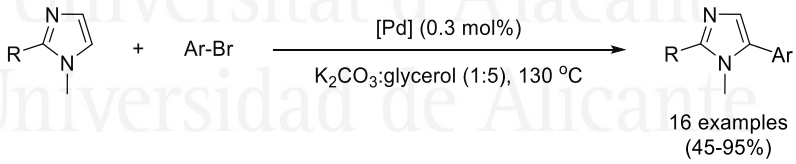
dichloromethane (DCM) or dimethylformamide (DMF), are the most commonly used solvents in this transformation. Hence, the quest to find benign and environmentally friendly solvents in C-H activation is of great importance to develop this transformation in an eco-friendly manner.

A few reports describe C-H activation in green reaction media such as water or different biomass-derived solvents.[152] Regarding the use of DESs, only two examples have been recently reported for C-H activation reactions using palladium species. In 2017, the direct arylation of thiophenes *via* C-H activation in ChCl:urea (1:2) eutectic mixture was described (Scheme 22).[153]



Scheme 22. Palladium-catalyzed direct arylation of thiophenes *via* C-H activation in DESs.

Later, a palladium supported catalyst was used in the direct C-H arylation of different imidazoles with aryl bromides in an alkaline DES (Scheme 23).[154]



Scheme 23. Direct C-H arylation of imidazoles in an alkaline DES.

[152] a) Fischmeister, C.; Doucet, H. *Green Chem.* **2011**, *13*, 741-753; b) Santoro, S.; Ferlin, F.; Luciani, L.; Ackermann, L.; Vaccaro, L. *Green Chem.* **2017**, *19*, 1601-1612; c) Gandeepan, P.; Kaplaneris, N.; Santoro, S.; Vaccaro, L.; Ackermann, L. *ACS Sustainable Chem. Eng.* **2019**, *7*, 8023-8040.

[153] Punzi, A.; Coppi, D. I.; Matera, S.; Capozzi, M. A.; Operamolla, A.; Ragni, R.; Babudri, F.; Farinola, G. M. *Org. Lett.* **2017**, *19*, 4754-4757.

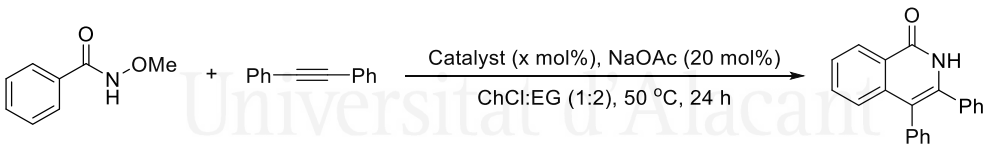
[154] Shariatipour, M.; Salamatmanesh, A.; Nejad, M. J.; Heydari, A. *Catal. Commun.* **2020**, *135*, 105890.

However, these methodologies present some disadvantages included in the first C-H activation reaction, such as the use of an expensive and complex catalytical system, several additives, high temperatures and reaction times, as well as, quite specific and structurally complex starting materials. On the other hand, moderate catalytical activity was observed in the direct C-H arylation of imidazoles and high temperatures were needed. Thus, there is still room for the development of more versatile, accessible and environmentally friendly C-H activation reactions under mild conditions.

1.3.2 Results

In pursuit of an efficient and sustainable alternative, our investigation started with the optimization of the catalytic system for the reaction between *N*-methoxybenzamide (**26a**) and diphenylacetylene (**27a**) as model reaction (Table 24). Initial attempts pointed out $[RuCl_2(p\text{-cymene})]_2$ as a highly efficient catalyst for this C-H activation reaction in DESs, with an optimal catalytical amount of 3 mol% (entries 1-4). Other ruthenium catalyst were tested with no success (entries 5-6).

Table 24. Optimization of the ruthenium catalyst.[a]



26a **27a** **28a**

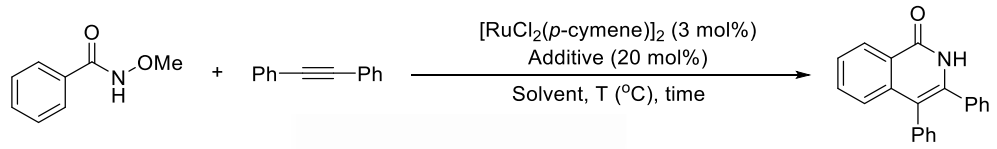
Entry	Catalyst (x mol%)	Yield (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$ (1 mol%)	64
2	$[RuCl_2(p\text{-cymene})]_2$ (2 mol%)	69
3	$[RuCl_2(p\text{-cymene})]_2$ (3 mol%)	88
4	$[RuCl_2(p\text{-cymene})]_2$ (5 mol%)	57
5	$RuCl_3 \cdot xH_2O$ (3 mol%)	0
6	$Ru(acac)_3$ (3 mol%)	0

[a] Reaction conditions: **26a** (0.1 mmol), **27a** (0.12 mmol), NaOAc (20 mol%), catalyst (1-5 mol%) at 50 °C in 0.5 mL of solvent; [b] Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

Once the catalytical system was established, other reaction parameters were evaluated (Table 25). Low to moderate yields were obtained with almost all the tested eutectic mixtures (entries 1-6), but fortunately ChCl:ethylene glycol gave a satisfactory 88% yield (entry 6).

Then, both temperature and reaction time were optimized, obtaining the best results at 70 ^{o}C after 16 h (compare entry 6 with entries 7-9 and entries 10-11). The absence of the basic additive (NaOAc) or a change to other sodium bases resulted in a significant drop in the reaction yield (entries 12-16), which seems to indicate the important role of the acetate in a possible carboxylate-assisted C-H metalation pathway.

Table 25. Optimization of the reaction conditions.[a]



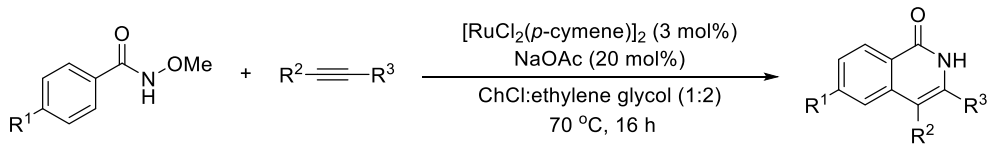
26a **27a** **28a**

Entry	Solvent	Additive	T (^{o}C)	time (h)	Yield (%)[b]
1	ChCl:urea (1:2)	NaOAc	50	24	5
2	AcChCl:urea (1:2)	NaOAc	50	24	45
3	AcChCl:acetamide (1:2)	NaOAc	50	24	19
4	ChCl:glycerol (1:2)	NaOAc	50	24	41
5	Ph_3PMeBr:glycerol (1:2)	NaOAc	50	24	44
6	ChCl:ethylene glycol (1:2)	NaOAc	50	24	88
7	ChCl:ethylene glycol (1:2)	NaOAc	30	24	43
8	ChCl:ethylene glycol (1:2)	NaOAc	70	24	>99
9	ChCl:ethylene glycol (1:2)	NaOAc	90	24	>99
10	ChCl:ethylene glycol (1:2)	NaOAc	70	8	55
11	ChCl:ethylene glycol (1:2)	NaOAc	70	16	>99
12	ChCl:ethylene glycol (1:2)	-	70	16	0
13	ChCl:ethylene glycol (1:2)	Na_2CO_3	70	16	9
14	ChCl:ethylene glycol (1:2)	$NaHCO_3$	70	16	8
15	ChCl:ethylene glycol (1:2)	NaOH	70	16	14
16	ChCl:ethylene glycol (1:2)	Na_3PO_4	70	16	10

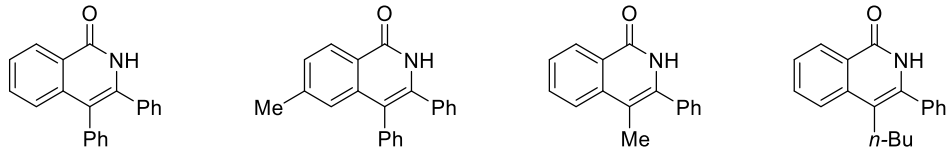
[a] Reaction conditions: **26a** (0.1 mmol), **27a** (0.12 mmol), additive (20 mol%), $[RuCl_2(p\text{-cymene})]_2$ (3 mol%) in 0.5 mL of solvent; [b] Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

In order to prove the versatility of the process, the scope of the reaction was evaluated (Table 26). Good to excellent yields were obtained when internal alkynes with aromatic substituents were used, but when aryl alkyl substituted alkynes were employed the yield dropped.

Table 26. Scope of the C-H activation reaction.[a]



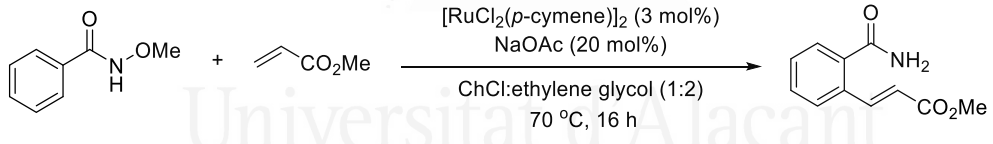
26 **27** **28**



28a (93% yield) **28b** (80% yield) **28c** (85% yield) **28d** (39% yield)

[a] Reaction conditions: **26** (0.2 mmol), **27** (0.24 mmol), NaOAc (20 mol%), $[RuCl_2(p\text{-cymene})]_2$ (3 mol%) in 1.0 mL of ChCl:ethylene glycol (1:2) at 70 °C for 16 h; [b] Isolated yield after flash column chromatography or precipitation with Et_2O.

Additionally, electron poor olefins were successfully employed as substrates in the C-H activation reaction. *N*-methoxybenzamide (**26a**) reacted with methyl acrylate (**19a**) in a quantitative yield under the optimal reaction conditions (Scheme 24).



26a **19a** **29a** (99% yield)

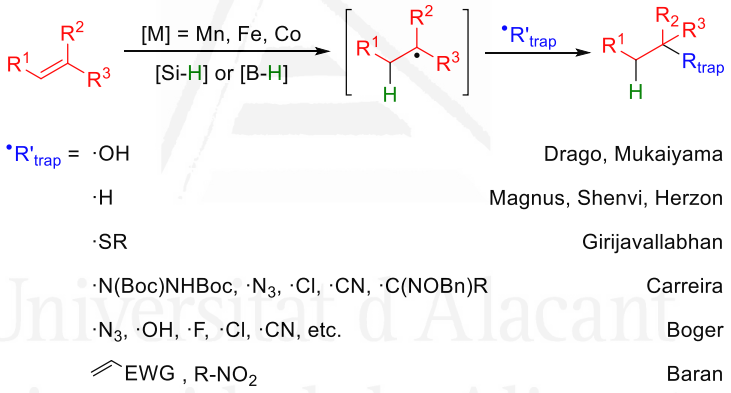
Scheme 24. Electron poor olefins as substrates in C-H activation.

1.4 IRON CATALYZED RADICAL CONJUGATED ADDITION OF OLEFINS

1.4.1 Precedents

Radical reactions have gained widespread application in the construction of C-C bonds, mainly through the conjugate addition of carbon-centered radicals into unsaturated electrophiles.[155] Among the plethora of carboradical precursors, olefins represent ideal starting materials since they are ubiquitous functional groups in a variety of feedstock chemicals and they are typically bench-stable, in comparison with other radical precursors.

Due to the aforementioned advantages, the application of hydrogen-atom transfer (HAT) to generate carbon-centered radicals from olefins has recently been established as a robust strategy to develop new bond-forming reactions in organic synthesis (Scheme 25).[156]



Scheme 25. Pioneering olefin radical hydrofunctionalizations reactions.

The research groups of Drago[157] and Mukaiyama[158] were pioneers in the use of HAT with alkenes, as radical precursors, by employing non-toxic first-row metals to synthesize the corresponding hydration products. After that, many researchers have expanded the scope of this process to include other electrophiles. For example, various authors reported the

[155] Hoffmann, R. W. *Chem. Soc. Rev.* **2016**, *45*, 577-583.
[156] Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 12692-12714.
[157] Zombeck, A.; Hamilton, D. E.; Drago, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 6782-6784.
[158] a) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. *Chem. Lett.* **1989**, *18*, 449-452; b) Mukaiyama, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 17-35.

hydrogenation of non-activated olefins.[159] The synthesis of sulfides was also described by Girijavallabhan's group using this radical pathway.[160] Carreira's lab reacted carbon-centered radicals with diazo and azido compounds, nitriles and electrophilic chlorine sources, among others.[161] Additionally, the research group of Boger reported the functionalization of unactivated alkenes with a range of free radical traps.[162] However, the potential of these reactions to form C-C bonds was not demonstrated until relatively recently, when the Baran's group reported an unique method for the direct coupling of unactivated olefins to electron-deficient olefins in both intra- and intermolecular variants, in the presence of an iron catalyst and phenylsilane as reducing agent.[163] In light of this, other related methodologies have been subsequently reported over the last years.[164] However, to date most of the published protocols are not environmentally benign in terms of sustainability since these procedures employ toxic and volatile organic solvents, air and moisture sensitive reducing agents and, complex and expensive metal catalysts. Thus, the development of efficient HAT-reactions, operating under environmentally benign conditions, is still sought.

[159] a) Magnus, P.; Payne, A. H.; Waring, M. J.; Scott, D. A.; Lynch, V. *Tetrahedron Lett.* **2000**, *41*, 9725-9730; b) Crossley, S. W.; Barabé, F.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 16788-16791; c) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 1300-1303; d) King, S. M.; Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 6884-6887; e) Ma, X.; Herzon, S. B. *Chem. Sci.* **2015**, *6*, 6250-6255; f) Obradors, C.; Martinez, R. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 4962-4971; g) Green, S. A.; Huffman, T. R.; McCourt, R. O.; van der Puyl, V.; Shenvi, R. A. *J. Am. Chem. Soc.* **2019**, *141*, 7709-7714.

[160] Girijavallabhan, V.; Alvarez, C.; Njoroge, F. G. *J. Org. Chem.* **2011**, *76*, 6442-6446.

[161] a) Waser, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 5676-5677; b) Waser, J.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 8294-8295; c) Gaspar, B.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4519-4522; d) Gaspar, B.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 5758-5760; e) Gaspar, B.; Carreira, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 13214-13215.

[162] a) Gotoh, H.; Sears, J. E.; Eschenmoser, A.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13240-13243; b) Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428-1431.

[163] a) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343-348; b) Lo, J. C.; Yabe, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304-1307; c) Dao, H. T.; Li, C.; Michaudel, Q.; Maxwell, B. D.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 8046-8049; d) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E. *Science* **2015**, *348*, 886-891; e) Lo, J. C.; Kim, D.; Pan, C.-M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutiérrez, S.; Giacoboni, J.; Smith, M. W. *J. Am. Chem. Soc.* **2017**, *139*, 2484-2503.

[164] Crossley, S. W.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912-9000.

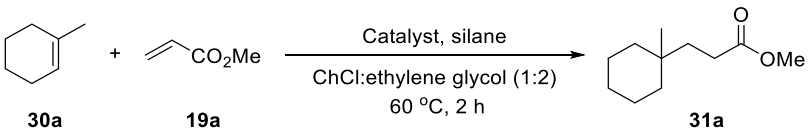
Although DESs have been applied in several organic transformations, the field of radical-mediated organic reactions remains unexplored, with there only being a few examples related to polymer material synthesis. In view of these precedents, we decided to develop an unprecedented, practical and sustainable methodology for the reductive coupling of a broad range of olefins *via* radicals, using a readily available and inexpensive iron catalyst, a cheap, non-toxic and stable silane [polymethylhydrosiloxane (PMHS)] as reducing agent and DESs as sustainable reaction medium.

1.4.2 Results

Our initial investigation started by optimizing the reaction conditions, using 1-methylcyclohexene (**30a**) and methyl acrylate (**19a**) as a model reaction (Table 27). Different silanes were used as reducing agents, achieving higher yields when using alkoxysilanes instead of phenyl derivatives (entries 1-6). Among them, PMHS was selected because this silane is a non-toxic, cheap and air and moisture stable reductant. After that, the optimal amount of silane was set at 5.5 molar equivalents (entries 7-10). The reaction was performed at different reaction times, obtaining the maximum yield after 2 h (entries 9, 11 and 12). As it was expected, the reaction failed without catalyst (entry 13). The amount of iron catalyst was next evaluated, the best result was obtained with 10% mol of catalyst (see entries 14-15) and an increase of this amount did not produce any significant change (compare entries 6, 9, 14 and 15). The reaction temperature seemed to be crucial since a drop in the reaction yield was noticed when the reaction was performed at 30 ^{o}C (entry 16). Previous literature results suggest that a catalytically active iron complex could be formed in the presence of an alcoholic solvent and therefore, this favors the formation of polar and easily separable alkoxysilanes. In view of this, the amount of solvent was reduced to study its possible effect on the reaction, resulting in a negative impact (entry 17). Thus, the solvent seems to have an important role in the reaction. Other metal salts were employed as catalysts, but no catalytical activity was observed (entries 18-24).

Then, different DESs were evaluated as reaction medium. As shown in Figure 26, the presence of an alcohol in the DES might favor the reaction as previously discussed. The best results was obtained with ChCl:ethylene glycol as solvent (91% yield).

Table 27. Optimization of the reaction conditions.[a]



30a **19a** **31a**

Entry	Catalyst	Silane	Yield (%)[b]
1	$Fe(acac)_3$ (20 mol%)	$PhSiH_3$ (5.5 equiv.)	51
2	$Fe(acac)_3$ (20 mol%)	Ph_2SiH_2 (5.5 equiv.)	55
3	$Fe(acac)_3$ (20 mol%)	Ph_3SiH (5.5 equiv.)	0
4	$Fe(acac)_3$ (20 mol%)	$PhMe_2SiH$ (5.5 equiv.)	0
5	$Fe(acac)_3$ (20 mol%)	$(EtO)_3SiH$ (5.5 equiv.)	76
6	$Fe(acac)_3$ (20 mol%)	PMHS (5.5 equiv.)	89
7	$Fe(acac)_3$ (30 mol%)	PMHS(1.5 equiv.)	37
8	$Fe(acac)_3$ (30 mol%)	PMHS(3 equiv.)	45
9	$Fe(acac)_3$ (30 mol%)	PMHS(5.5 equiv.)	90
10	$Fe(acac)_3$ (30 mol%)	PMHS(10 equiv.)	49
11	$Fe(acac)_3$ (30 mol%)	PMHS(5.5 equiv.)	59[c]
12	$Fe(acac)_3$ (30 mol%)	PMHS(5.5 equiv.)	57[d]
13	no catalyst	PMHS(5.5 equiv.)	0
14	$Fe(acac)_3$ (5 mol%)	PMHS(5.5 equiv.)	78
15	$Fe(acac)_3$ (10 mol%)	PMHS(5.5 equiv.)	91
16	$Fe(acac)_3$ (10 mol%)	PMHS(5.5 equiv.)	24[e]
17	$Fe(acac)_3$ (10 mol%)	PMHS(5.5 equiv.)	72[f]
18	$Co(acac)_2$ (10 mol%)	PMHS(5.5 equiv.)	0
19	$Ni(acac)_2$ (10 mol%)	PMHS(5.5 equiv.)	0
20	$Pd(acac)_2$ (10 mol%)	PMHS(5.5 equiv.)	0
21	$FeCl_3$ (10 mol%)	PMHS(5.5 equiv.)	0
22	$CoCl_2$ (10 mol%)	PMHS(5.5 equiv.)	0
23	$NiCl_2 \cdot 6H_2O$ (10 mol%)	PMHS(5.5 equiv.)	0
24	$PdCl_2$ (10 mol%)	PMHS(5.5 equiv.)	0

[a] Reaction conditions: compound **30a** (0.3 mmol), methyl acrylate (0.9 mmol), silane and catalyst in 1.5 mL of solvent at 60 °C for 2 h; [b] Yield determined by GC using 4,4′-di-*tert*-butylbiphenyl (DTBB) as internal standard; [c] Reaction performed for 1 h; [d] Reaction performed for 3 h; [e] Reaction performed at 30 °C; [f] Reaction with 1.0 ml of solvent.

With the optimal conditions in hand (Table 27, entry 15), the scope of the reaction was evaluated. Different acceptor olefins were tested using 1-methylcyclohexene (**30a**) as the donor olefin. Good tolerance and results were obtained using olefins conjugated with esters, ketones, amides, nitriles and sulfones (Table 28, entries 1-5). Acyclic and cyclic disubstituted acceptor olefins gave moderate to good yields (entries 6-8).

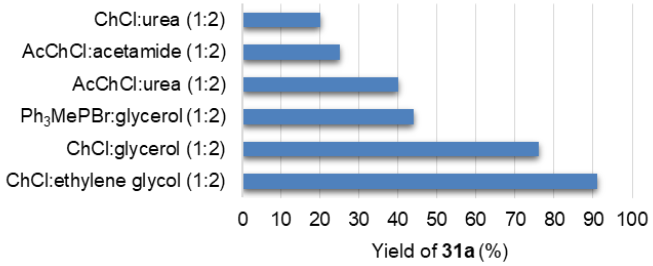
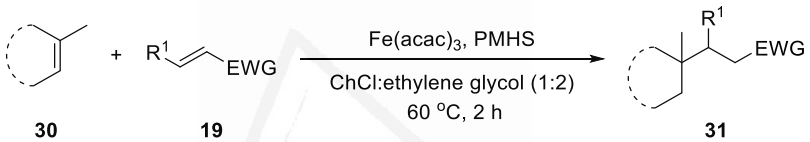


Figure 26. Solvent optimization.

Table 28. Scope of the reaction using trisubstituted donor olefins.[a]



30 **19** **31**

Entry	**Compound** 30	R^1	EWG	Product	Yield (%)[b]
1	1-methylcyclohexene	H	CO_2Me	**31a**	91
2	1-methylcyclohexene	H	COMe	**31b**	75
3	1-methylcyclohexene	H	$CON(Me)_2$	**31c**	89
4	1-methylcyclohexene	H	CN	**31d**	84
5	1-methylcyclohexene	H	SO_2Ph	**31e**	54[c]
6	1-methylcyclohexene	CO_2Me	CO_2Me	**31f**	60
7	1-methylcyclohexene	-$(CH_2)_2$CO-		**31g**	70[c]
8	1-methylcyclohexene	-$(CH_2)_3$CO-		**31h**	48[c]
9	α-ionone	-		**31i**	95

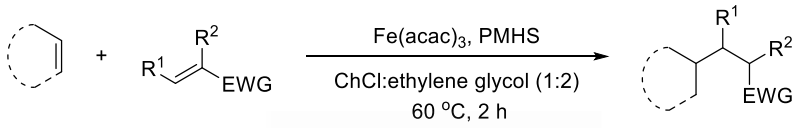
[a] Reaction conditions: compound **30** (0.3 mmol), compound **19** (0.9 mmol), PMHS (5.5 equiv.) and $Fe(acac)_3$ (10 mol%) in 1.5 mL of ChCl:ethylene glycol (1:2) at 60 °C for 2 h; [b] Isolated yield after flash column chromatography; [c] Reaction performed for 5 h.

Additionally, an intermolecular cyclization was carried out using a terpenoid scaffold, α-ionone (**30b**), which gave the corresponding cyclopropane in an excellent yield (entry 9).

On the other hand, more challenging donor disubstituted olefins were employed using this methodology, obtaining similar results to those using the trisubstituted ones (Table 29).[163] Cyclohexene (**30c**) was used as donor olefin, generating a secondary radical that efficiently reacted with electron-poor olefins bearing different electron withdrawing groups, for example esters, ketones, or nitriles (entries 1-3). Cyclo enol ethers, as 3,4-dihydro-2*H*-pyran (**30d**), could be used with a high regioselectivity due to the stabilizing presence of the

oxygen atom adjacent to the formed radical (entry 5). This radical stabilization was not achieved using 1-dodecene (**30e**), obtaining a mixture of isomers with a major presence of the product generated from the secondary radical intermediate. Finally, a monosubstituted donor olefin attached to a sulfur atom was successfully coupled with acrylonitrile (**30d**; entry 7).

Table 29. Scope of the reaction using mono- or disubstituted donor olefins.[a]

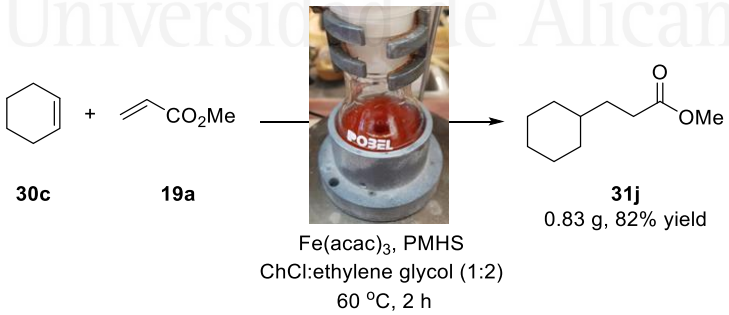


30 **19** **31**

Entry	**Compound** 30	R^1	R^2	EWG	Product	Yield (%)[b]
1	cyclohexene	H	H	CO_2Me	**31j**	98
2	cyclohexene	H	H	COMe	**31k**	95
3	cyclohexene	H	H	CN	**31l**	80
4	cyclohexene	Me	CO_2Et	CO_2Et	**31m**	40
5	3,4-dihydro-2*H*-pyran	H	H	CO_2Me	**31n**	83
6	1-dodecene	H	H	CO_2Me	**31o**	80[c]
7	phenyl vinyl sulfide	H	H	CN	**31p**	80[d]

[a] Reaction conditions: compound **30** (0.3 mmol), compound **19** (0.9 mmol), PMHS (5.5 equiv.) and $Fe(acac)_3$ (10 mol%) in 1.5 mL of ChCl:ethylene glycol (1:2) at 60 °C for 2 h; [b] Isolated yield after flash column chromatography; [c] A mixture of isomers was observed; [d] Reaction performed for 5 h.

Moreover, the reaction was performed on a gram-scale in order to prove and extend the applicability of the process (Scheme 26).



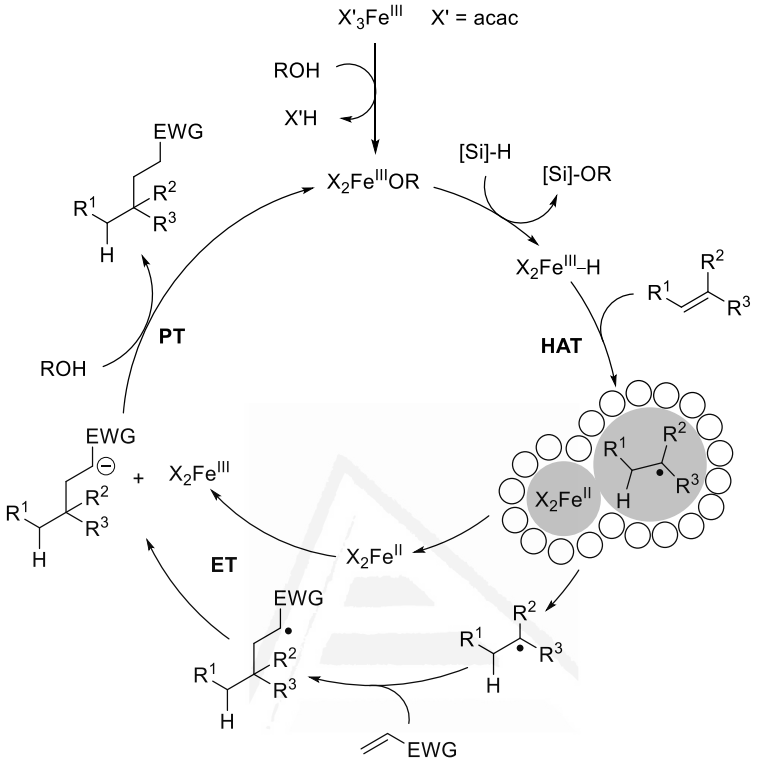
30c **19a** **31j**
0.83 g, 82% yield

Scheme 26. Gram-scale reaction.

A slight decrease in the yield was noticed, probably due to the silane aggregates observed during the reaction course.

Regarding the reaction mechanism, it was determined that a radical pathway occurs since the model reaction was inhibited by the use of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). A TEMPO adduct (olefin **19a** trapped with TEMPO) was detected by ^{1}H NMR and GC-MS analysis. According to the literature,[165,115b] it was presumed that initially the solvolysis of FeX_3 precatalyst with the alcoholic solvent generates a catalytically active iron species ($X_2Fe^{III}OR$). Then, this catalyst reacts with the silane, leading to an iron hydride complex and an alkoxysilane compound. Note that the formation of such weak bond (Fe-H) must be compensated by the strong bond formation in another product (Si-O bond). One of the important roles of ethylene glycol present in the DES, might be to generate the catalytically active iron catalyst ($X_2Fe^{III}OR$) and consequently, to provide the alkoxide that supplies the aforementioned driving force for Si-O bond formation. This fact could explain the higher yields observed when alcohol based DESs were used as reaction medium (Figure 26). The next step involves the hydrogen atom transfer (HAT) to the alkene from the transient iron hydride complex, to generate a carbo-radical metallo-radical pair surrounded by a "cage" of solvent molecules (Scheme 27). To escape from this pocket, the solvent properties are crucial, so the "strength" of the solvent cage could be tuned through the careful selection of the reaction media.[165c] Thus, DESs have demonstrated to be a proper medium that favors the "cage" escape. It should be noted that homocoupling products were not observed in any case. The released radical is then trapped by an electron-poor acceptor olefin, and the formation of the new C-C bond generates a product with a radical adjacent to the electron-withdrawing group. Finally, this radical accepts an electron (ET) and a proton from the protic solvent (PT) to afford the desired product.

[165] a) Jiang, H.; Lai, W.; Chen, H. *ACS Catal.* **2019**, *9*, 6080-6086; b) Kim, D.; Rahaman, S. M. W.; Mercado, B. Q.; Poli, R.; Holland, P. L. *J. Am. Chem. Soc.* **2019**, *141*, 7473-7485.



Scheme 27. Proposed reaction mechanism.

1.5 ENANTIOSELECTIVE ORGANOCATALYZED REACTIONS IN EUTECTOGELS

1.5.1 Precedents

Supramolecular gels are emerging materials originated by the self-assembly of small molecules (Low Molecular Weight Gelators, LMWGs) in dilute solution.[166] The structure of the gel is formed by non-covalent interactions (hydrogen bonding, van der Waals, π-interactions) established between the low molecular weight gelator and the solvent.[167] Since these networks involve weak interactions, they can be readily transformed to a fluid by heating and are generally thermally reversible. Gels can be classified in different ways depending on the type of cross-linking agent and the medium they encompass. Based on which solvent is hardened, gels are distinguished in hydrogels[168] and organogels,[169] originated from solutions of water and organic solvents, respectively. A recent development in the field is represented by gels formed using Ionic Liquids (ionogels)[170] and even, Deep Eutectic Solvents (eutectogels).[171]

Although numerous types of molecules have been used to induce the gelation, amino acids are the simplest biological building blocks capable of forming discreet nanostructures by supramolecular self-assembly[172] and, in turn, amino acids are well-known catalysts for

[166] a) Okesola, B. O.; Smith, D. K. *Chem. Soc. Rev.* **2016**, *45*, 4226-4251; b) Draper, E. R.; Adams, D. J. *Chem.* **2017**, *3*, 390-410.

[167] Amabilino, D. B.; Smith, D. K.; Steed, J. W. *Chem. Soc. Rev.* **2017**, *46*, 2404-2420.

[168] Roy, S.; Banerjee, A. *Soft Matter* **2011**, *7*, 5300-5308.

[169] Bairi, P.; Roy, B.; Routh, P.; Sen, K.; Nandi, A. K. *Soft Matter* **2012**, *8*, 7436-7445.

[170] a) Marr, P. C.; Marr, A. C. *Green Chem.* **2016**, *18*, 105-128; b) Marullo, S.; Rizzo, C.; Dintcheva, N. T.; Giannici, F.; D'Anna, F. *J. Colloid Interface Sci.* **2018**, *517*, 182-193.

[171] a) Joos, B.; Vranken, T.; Marchal, W.; Safari, M.; Van Bael, M. K.; Hardy, A. T. *Chem. Mater.* **2018**, *30*, 655-662; b) Marullo, S.; Meli, A.; Giannici, F.; D'Anna, F. *ACS Sustainable Chem. Eng.* **2018**, *6*, 12598-12602; c) Delbecq, F.; Delfosse, P.; Laboureix, G.; Paré, C.; Kawai, T. *Colloids Surf., A* **2019**, *567*, 55-62; d) Ruiz-Olles, J.; Slavik, P.; Whitelaw, N. K.; Smith, D. K. *Angew. Chem. Int. Ed.* **2019**, *131*, 4217-4222; e) Joos, B.; Volders, J.; da Cruz, R. R.; Baeten, E.; Safari, M.; Van Bael, M. K.; Hardy, A. T. *Chem. Mater.* **2020**, *32*, 3783-3793; f) Smith, C. J.; Wagle, D. V.; Bhawawet, N.; Gehrke, S.; Hollóczki, O.; Pingali, S. V.; O'Neill, H.; Baker, G. A. *J. Phys. Chem. B* **2020**, *124*, 7647-7658; g) Zeng, C.; Zhao, H.; Wan, Z.; Xiao, Q.; Xia, H.; Guo, S. *RSC Adv.* **2020**, *10*, 28376-28382.

[172] a) Chakraborty, P.; Gazit, E. *ChemNanoMat* **2018**, *4*, 730-740; b) Marullo, S.; Meli, A.; Dintcheva, N. T.; Infurna, G.; Rizzo, C.; D'Anna, F. *ChemPlusChem* **2020**, *85*, 301-311.

the aldol reaction.[173] This reaction is one of the most renowned transformation in organic synthesis with several possibilities to control the stereochemical outcome of the process, using natural amino acids as organocatalysts, the most sustainable protocol. However, as a drawback, most of these protocols imply the use of organic solvents[174] and only, a few examples have reported the aldol transformation using DESs.[175] As a consequence, the development of new environmentally friendly methodologies for the aldol reaction remains in demand.

In supramolecular gels, catalytic behavior derived from non-covalent interactions, could be used for the construction of a multicomponent catalyst.[176] The careful choice of the gelators (e.g. natural amino acids) along with its precise organization, could be effectively used for asymmetric catalysis. Previously, a supramolecular gel formed by L-proline and a non-sustainable acetonitrile solvent was used to perform the enantioselective aldol reaction, observing a different behavior between solution and gel phase.[177] In this vein, a novel supramolecular gel of L-proline has been developed in ChCl:urea (1:2), demonstrating its catalytic application in asymmetric aldol reactions (Figure 27).[178]

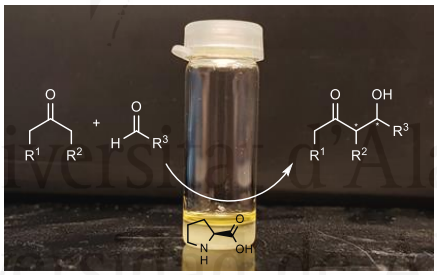
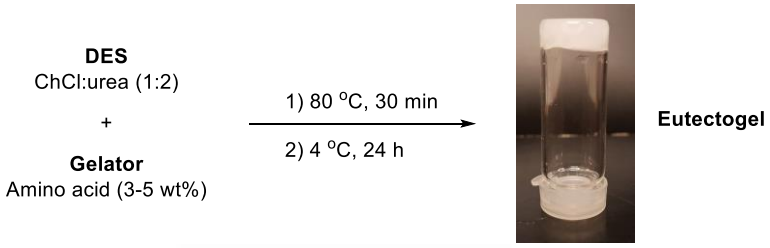


Figure 27. Eutectogel for catalytic application in the enantioselective aldol reaction.

[173] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.
[174] Liu, J.; Wang, L. *Synthesis* **2017**, *49*, 960-972.
[175] a) Müller, C. R.; Meiners, I.; de María, P. D. *RSC Adv.* **2014**, *4*, 46097-46101; b) Müller, C. R.; Rosen, A.; Domínguez de María, P. *Sustainable Chem. Processes* **2015,** *3*, art. 12, DOI: 10.1186/s40508-015-0030-0; c) Brenna, D.; Massolo, E.; Puglisi, A.; Rossi, S.; Celentano, G.; Benaglia, M.; Capriati, V. *Beilstein J. Org. Chem.* **2016**, *12*, 2620-2626; d) Fanjul-Mosteirín, N.; Concellón, C.; del Amo, V. *Org. Lett.* **2016**, *18*, 4266-4269; e) Martínez, R.; Berbegal, L.; Guillena, G.; Ramón, D. J. *Green Chem.* **2016**, *18*, 1724-1730.
[176] Escuder, B.; Rodríguez-Llansola, F.; Miravet, J. F. *New J. Chem.* **2010**, *34*, 1044-1054.
[177] Rodríguez-Llansola, F.; Miravet, J. F.; Escuder, B. *Chem. Commun.* **2009**, 7303-7305.
[178] This work has been carried out in collaboration with research group of Prof. Dr. D'Anna in Palermo (Italy).

1.5.2 Results

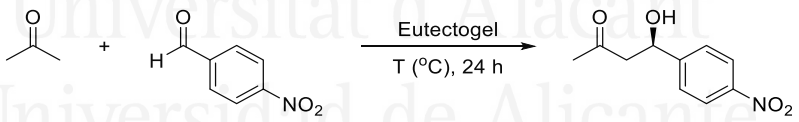
Firstly, eutectogels based on ChCl:urea (1:2) and different amino acids were prepared as shown in Scheme 28.



Scheme 28. Schematic representation of amino acids-based eutectogels preparation.

Then, the aldol reaction between acetone (**32a**) and *p*-nitrobenzaldehyde (**33a**) with different ChCl:urea (1:2) based eutectogels was tested in absence of any solvent (Table 30). Different amino acids were employed to form the eutectogels with ChCl:urea (1:2) DES, but when L-proline gel was used as gelator a higher yield was obtained (entries 1-4). Then, lower temperatures were tested in order to improve the enantiomeric excess, but a decrease in the reactivity was noticed without any improvement of the enantioselectivity (entries 5-6).

Table 30. Optimization of the aldol reaction.[a]



32a **33a** **34a**

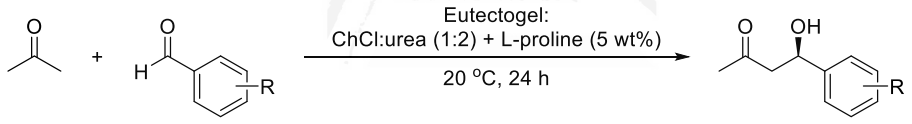
Entry	Eutectogel [ChCl:urea (1:2) + amino acid]	T (°C)	Yield (%)[b]	*ee* (%)[c]
1	L-Serine (3 wt%)	20	0	-
2	*Trans*-4-hydroxy-L-proline (3 wt%)	20	<5	50
3	L-Prolinamide (5 wt%)	20	50	20
4	L-Proline (5 wt%)	20	87	68
5	L-Proline (5 wt%)	15	21	68
6	L-Proline (5 wt%)	4	7	56
7	L-Proline (5 wt%)	35	90	55

[a] Reaction conditions: acetone (1 equiv.) and *p*-nitrobenzaldehyde (5 equiv.) for 24 h; [b] Yield calculated by ^{1}H NMR; [c] Enantioselectivities determined by chiral HPLC.

An increase of the temperature (entry 7) led to the destruction of the gel phase (in general this systems have a T_{gel} lower than 35 ºC), so the reaction temperature was set at 20 ºC. In order to prove the virtue of the catalytic system, the results obtained with L-proline eutectogel were compared to the literature, observing that the same aldol reaction performed in ChCl:urea (1:2) mixture gave lower results in terms of both yield and enantioselectivity.[175e] This fact could be imputed to the best entrapment of substrate induced by the precise distribution of L-proline, which induces a higher enantioselectivity in the aldol reaction.

With the optimum reaction conditions established (Table 30, entry 4), the substrate scope was next studied (Table 31). Different aromatic aldehydes were tested, observing that the electronic nature of the substituents attached to the aromatic ring had a notable impact, observing lower yields with electron-rich substituents (entries 1-7 and entry 8). However, similar enantioselectivities were achieved with aldehydes bearing electron-withdrawing or electron-donating substituents.

Table 31. Scope aldol reaction with different aldehydes in L-proline based eutectogel.[a]



32a **33** **34**

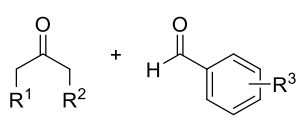
Entry	R	Product	Yield (%)[b]	*ee* (%)[c]
1	4-NO_2	**34a**	87	68
2	3-NO_2	**34b**	93	70
3	2-NO_2	**34c**	95	72
4	4-CN	**34d**	94	72
5	4-CF_3	**34e**	97	46
6	2-Cl	**34f**	98	61
7	H	**34g**	93	53
8	4-CH_3	**34h**	22 (80)[d]	59 (65)[d]

[a] Reaction conditions: acetone (1 equiv.) and **33** (5 equiv.) at 20 ºC for 24 h; [b] Yield calculated by ^{1}H NMR; [c] Enantioselectivities determined by chiral HPLC; [d] Reaction time: 5 days.

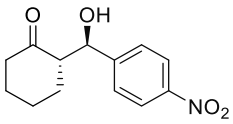
Furthermore, the versatility of this transformation was evaluated using different ketones and aldehydes (Table 32). When cyclohexanone was used as a nucleophile, the majorly achieved diastereoisomer has an *anti*-configuration but with low diastereoselectivities (20-30%) except for the 2-chlorobenzaldehyde that gave 86% *de*. Moderate to good

enantioselectivities were obtained depending on the aldehyde employed. Then, cyclopentanone was employed obtaining the *syn*-product with moderate results. Also, α-alkoxy/hydroxy ketones can be used as nucleophiles with moderate diastereoselectivities but excellent enantioselectivities.

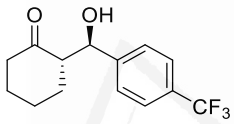
Table 32. Aldol reaction using different ketones and aldehydes in L-proline based eutectogel.[a]



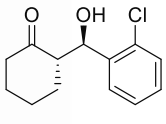
32 **33** **34**



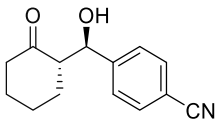
anti-**34i** (95%)
28% *de*, 97% *ee*



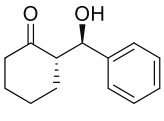
anti-**34j** (85%)
31% *de*, 55% *ee*



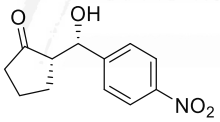
anti-**34k** (80%)
86% *de*, 67% *ee*



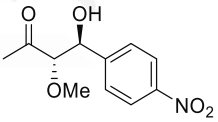
anti-**34l** (85%)
17% *de*, 62% *ee*



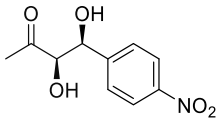
anti-**34m** (53%)
20% *de*, 45% *ee*



syn-**34n** (39%)
46% *de*, 45% *ee*



anti-**34o** (90%)
62% *de*, 97% *ee*



syn-**34p** (20%)
64% *de*, 84% *ee*

[a] Reaction conditions: **32** (1 equiv.) and **33** (5 equiv.) at 20 °C for 24 h. Yield calculated by ^{1}H NMR (yield%). Diastereoselectivities/enantioselectivities determined by chiral HPLC.

Additionally, the recyclability of the system was studied since it is considered to be a crucial point for the sustainability of the process (Figure 28).

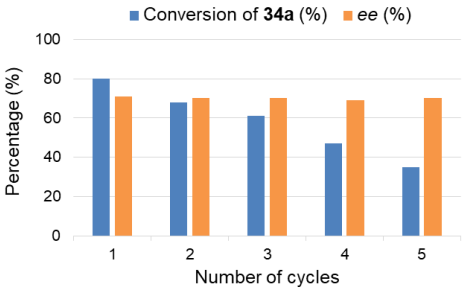
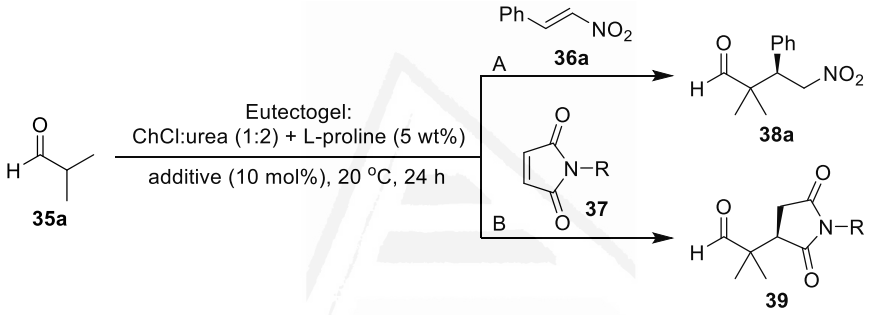


Figure 28. Recyclability of the eutectogel system in aldol reaction.

For this purpose, after the completion of the reaction, the formed product **34a** was extracted with a small amount of a renewable VOC solvent (2- MeTHF), the remaining solvent into the eutectogel was evaporated and finally, the eutectogel material could be recycled for five consecutive cycles, maintaining the enantioselectivity in all cycles, although a decrease in the yield was observed.

In order to prove the versatility of the eutectogel material as an organocatalyst medium, different enantioselective Michael reactions were tested (Table 33).

Table 33. Michael reaction performed in L-proline based eutectogel.[a]



Entry	Alkene	Additive	Product	Yield (%)[b]	*ee* (%)[c]
1	*Trans*-β-nitrostyrene	-	**38a**	8	-
2	*Trans*-β-nitrostyrene	DMAP	**38a**	>99	23
3	*Trans*-β-nitrostyrene	DABCO	**38a**	>99	19
4	*Trans*-β-nitrostyrene	Imidazole	**38a**	>99	20
5	*Trans*-β-nitrostyrene	DBU	**38a**	>99	16
6	*Trans*-β-nitrostyrene	Pyridine	**38a**	53	24
7	*Trans*-β-nitrostyrene	Benzoic acid	**38a**	44	24
8	*Trans*-β-nitrostyrene	*p*-Nitrobenzoic acid	**38a**	36	27
9	*Trans*-β-nitrostyrene	Adipic acid	**38a**	27	25
10	*Trans*-β-nitrostyrene	Imidazole	**38a**	43[d]	9
11	*N*-phenylmaleimide	-	**39a**	4	-
12	*N*-phenylmaleimide	Pyridine	**39a**	10	-
13	*N*-phenylmaleimide	2,6-Lutidine	**39a**	3	-
14	*N*-phenylmaleimide	*p*-Nitrobenzoic acid	**39a**	<1	-
15	Maleimide	Imidazole	**39b**	11	-

[a] Reaction conditions A: *trans*-β-nitrostyrene (0.2 mmol) and **35a** (0.8 mmol) at 20 °C for 24 h; Reaction conditions B: **37** (0.2 mmol) and **35a** (0.4 mmol) at 20 °C for 24 h; [b] Yield calculated by ^{1}H NMR; [c] Enantioselectivities determined by chiral HPLC;[d] Reaction performed at -10 °C.

Isobutyraldehyde (**35a**) was employed as the nucleophilic source in the Michael reaction with *trans*-β-nitrostyrene (**36a**) and different maleimides **37** as electrophiles. When *trans*-β-nitrostyrene (**36a**) was used without any additive, the yield of the reaction was very low (entry 1). Then, different bases were used obtaining excellent yields but low enantioselectivities (entries 2-6). Different acid additives were tested, observing both lower yields and enantioselectivities (entries 7-9). Decreasing the temperature led to worse results than at 20 ^{o}C (entry 10). Also, cyclohexanone was used as substrate, observing 73% yield but low enantioselectivities in its reaction with *trans*-β-nitrostyrene (96% *de*, *syn* 29% *ee*). Then, a different Michael reaction was tested using various maleimides as electrophiles, but lower yields were obtained in all the cases (entries 11-15). Although these results are in the range of those obtained using L-proline in different solvents.[179]

[179] a) Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3*, 3737-3740; b) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423-2425; c) Kotrusz, P.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2004**, 1577-1583.

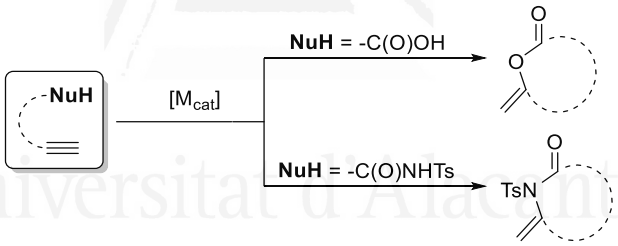
CHAPTER II

C-O bond formation reactions

2.1 CYCLOISOMERIZATION OF ALKYNOIC ACID DERIVATIVES

2.1.1 Precedents

Cycloisomerization reactions constitute extremely valuable transformations according to the Green Chemistry standards, since these transformations occur with quantitative atom economy.[180] In particular, lactones and lactams are widespread motifs in natural and pharmaceutical products,[181] as well as useful synthetic intermediates.[182] Therefore, several synthetic routes have been developed over the years, making use of electrophilic reagents,[183] organic acids/bases,[184] transition metals[185] or even biocatalysts.[186] Among the synthetic routes to form lactones and lactams, the intramolecular cycloaddition of heteroatomic nucleophiles (O-H, N-H functionalities) to an alkyne moiety comprises a straightforward and highly selective method for the synthesis of these heterocycles. Such cycloisomerization reactions have been extensively employed for the synthesis of cyclic enol lactones and lactams, with palladium species being the most used catalyst (Scheme 29).



Scheme 29. Metal-catalyzed cycloisomerization of alkynoic acids or alkynyl amides.

[180] a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079-3159; b) Patil, N. T.; Kavthe, R. D.; Shinde, V. S. *Tetrahedron* **2012**, *68*, 8079-8146.

[181] Janecki, T. (Ed.) *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*, Wiley-VCH, Weinheim, 2013.

[182] a) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921-1949; b) Lima, C. G.; Monteiro, J. L.; de Melo Lima, T.; Weber Paixão, M.; Correa, A. G. *ChemSusChem* **2018**, *11*, 25-47.

[183] Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937-2980.

[184] a) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517-5520; b) Kanazawa, C.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 933-935.

[185] El Ali, B.; Alper, H. *Synlett* **2000**, 161-171.

[186] Hollmann, F.; Kara, S.; Opperman, D. J.; Wang, Y. *Chem. Asian J.* **2018**, *13*, 3601-3610.

Although homogeneous palladium catalysts were initially used,[187] there are several examples in the literature which employ different heterogeneous palladium catalysts.[188] However, most of these procedures require high catalyst loadings, additives such as co-catalysts or bases, and the use of toxic VOCs.

The increasing awareness of environmental concerns has stimulated the development of metal-catalyzed reactions in sustainable media. Thus, various catalytic systems were able to carry out the cycloisomerization of alkynoic acid derivatives using green solvents with water being the most employed reaction medium in these metal-catalyzed cyclization reactions.[189] Further, DESs have been efficiently applied as solvent and also, as catalyst in these transformations.[190] In addition, the use of these polar solvents in many cases allows an easy catalyst/product separation, thus allowing the effective recycling of the catalytically active species.

One of the crucial point to bear in mind when designing catalytic green chemical processes is the easy isolation and recycling of the catalyst.[191] Homogeneous catalysts have been broadly employed in organic synthesis. Although these catalysts have several advantages, such as requiring a low quantity of catalyst and the use of well-defined and

[187] a) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323-5326; b) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533-2545; c) Nebra, N.; Monot, J.; Shaw, R.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2013**, *3*, 2930-2934; d) Conde, N.; SanMartín, R.; Herrero, M. T.; Domínguez, E. *Adv. Synth. Catal.* **2016**, *358*, 3283-3292; e) Brunel, P.; Monot, J.; Kefalidis, C. E.; Maron, L.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2017**, *7*, 2652-2660.

[188] a) Rambabu, D.; Bhavani, S.; Nalivela, K. S.; Mukherjee, S.; Rao, M. V. B.; Pal, M. *Tetrahedron Lett.* **2013**, *54*, 2151-2155; b) Nagendiran, A.; Verho, O.; Haller, C.; Johnston, E. V.; Bäckvall, J.-E. *J. Org. Chem.* **2014**, *79*, 1399-1405; c) Verho, O.; Gao, F.; Johnston, E. V.; Wan, W.; Nagendiran, A.; Zheng, H.; Bäckvall, J.-E.; Zou, X. *APL Mater.* **2014**, *2*, 113316; d) Goerbe, T.; Gustafson, K. P. J.; Verho, O.; Kervefors, G.; Zheng, H.; Zou, X.; Johnston, E. V.; Bäckvall, J.-E. *ACS Catal.* **2017**, *7*, 1601-1605; e) Oschmann, M.; Placais, C.; Nagendiran, A.; Baeckvall, J.-E.; Verho, O. *Chem. Eur. J.* **2019**, *25*, 6295-6299.

[189] a) Francos, J.; Cadierno, V. *Catalysts* **2017**, *7*, 328; b) Iben Ayad, A.; Belda Marin, C.; Colaco, E.; Lefevre, C.; Methivier, C.; Ould Driss, A.; Landoulsi, J.; Guenin, E. *Green Chem.* **2019**, *21*, 6646-6657; c) Fernández, G.; Bernardo, L.; Villanueva, A.; Pleixats, R. *New. J. Chem.* **2020**, *44*, 6130-6141.

[190] a) Rodríguez-Álvarez, M. J.; Vidal, C.; Díez, J.; García-Álvarez, J. *Chem. Commun.* **2014**, *50*, 12927-12929; b) Curti, F.; Tiecco, M.; Pirovano, V.; Germani, R.; Caselli, A.; Rossi, E.; Abbiati, G. *Eur. J. Org. Chem.* **2019**, 1904-1914.

[191] Benaglia, M. (Ed.) *Recoverable and Recyclable Catalysts*, John Wiley & Sons, Chichester, UK, 2009.

characterized active species compared to heterogeneous catalysts, its recovery after the reaction is nearly impossible. Conversely, heterogeneous catalysts are preferred due to their robustness and lower operational cost, through its facile recovery and reuse.

Metal nanoparticles (MNPs) unite the advantages of homogeneous and heterogeneous catalytic systems.[192] The catalytic activity and other properties, can be modified as for homogeneous catalysts, by increasing the surface/volume ratio. Besides, supported metal nanoparticles comprise an attractive methodology for the recyclability of this heterogeneous catalytic species. In this sense, using magnetite (Fe_3O_4) as support is a particularly efficient strategy for catalyst recovery, since their magnetic properties allow easy separation of the catalysts from the reaction mixture, just using an external magnet (magnetic decantation), avoiding tedious, time-consuming and waste-production steps (filtration, centrifugation or membrane separation).[193]

Numerous approaches to support metal catalyst in the surface of a solid support have been described. However, among those, the impregnation method is the most straightforward, simple and less expensive methodology. It consists in the precipitation or evaporation of a solution which contains the dissolved metal or metal oxide precursors and the preformed solid support, followed by a drying process. Different metal oxides have been impregnated on magnetite following this procedure and they have been applied in wide variety of organic reactions (Figure 29).[194]

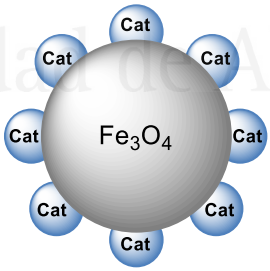


Figure 29. General scheme for metal-impregnated magnetite catalyst.

[192] Astruc, D.; Lu, F.; Aranzaes, J. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 7852-7872.
[193] Gawande, M. B.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev.* **2013**, *42*, 3371-3393.
[194] Ramón, D. J. *Johnson Matthey Technol. Rev.* **2015**, *59*, 120-122.

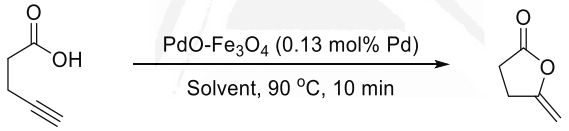
In particular, palladium(II) oxide nanoparticles supported on magnetite have been successfully applied for the synthesis of 4-arylcoumarins *via* Heck-arylation/cyclization process, the direct arylation of various heterocycles, the multicomponent reductive amination of aldehydes and different cross-coupling reactions, among others.[137,195]

With all these precedents in mind, we decided to test palladium(II) oxide nanoparticles supported on magnetite as a simple and heterogeneous catalyst for the cycloisomerization of alkynoic acid derivatives in neoteric media.[196]

2.1.2 Results

The cycloisomerization reaction was optimized using PdO-Fe_3O_4 as catalyst and 4-pentynoic acid (**40a**) as model reaction (Table 34). Different DESs were used as sustainable solvents, obtaining the best result with ChCl:urea (1:2) eutectic mixture (entries 1-6).

Table 34. Solvent optimization for the cycloisomerization reaction.[a]



40a **41a**

Entry	Solvent	Yield (%)[b]
1	ChCl:urea (1:2)	81
2	ChCl:glycerol (1:2)	32
3	ChCl:ethylene glycol (1:2)	36
4	AcChCl:urea (1:2)	67
5	ChCl:resorcinol (1:1)	65
6	ChCl:acetamide (1:2)	25
7	H_2O	100

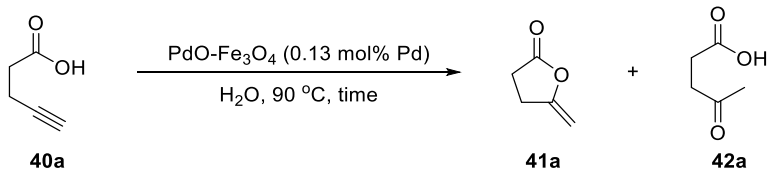
[a] Reaction conditions: compound **40a** (0.1 mmol), 0.5 mg of catalyst (0.13 mol% Pd) in 0.2 mL of solvent at 90 °C for 10 min; [b] Yield determined by GC using tridecane as internal standard.

[195] a) Baeza, A.; Guillena, G.; Ramón, D. J. *ChemCatChem* **2016**, *8*, 49-67; b) Pérez, J. M.; Cano, R.; McGlacken, G. P.; Ramón, D. J. *RSC Adv.* **2016**, *6*, 36932-36941.

[196] This work has been carried out in collaboration with research group of Prof. Dr. García-Álvarez in Oviedo (Spain).

However, the yield was substantially improved using pure water as solvent (entry 7), what drives our research to the use of this neoteric medium.

During the optimization studies, it was noticed that the enol-lactone **41a** could be hydrolyzed in a further step affording the corresponding ketoacid **42a** (Scheme 30).



Scheme 30. Hydrolysis of enol-lactone **41a** to afford the corresponding ketoacid **42a**.

Thus, a study of the evolution of the reaction was carried out at different temperatures under the optimal reaction conditions (Figure 30). Ketoacid **42a** was obtained as sole product after 7 days at room temperature, 4 days at 50 ºC and 7 hours at 90 ºC.

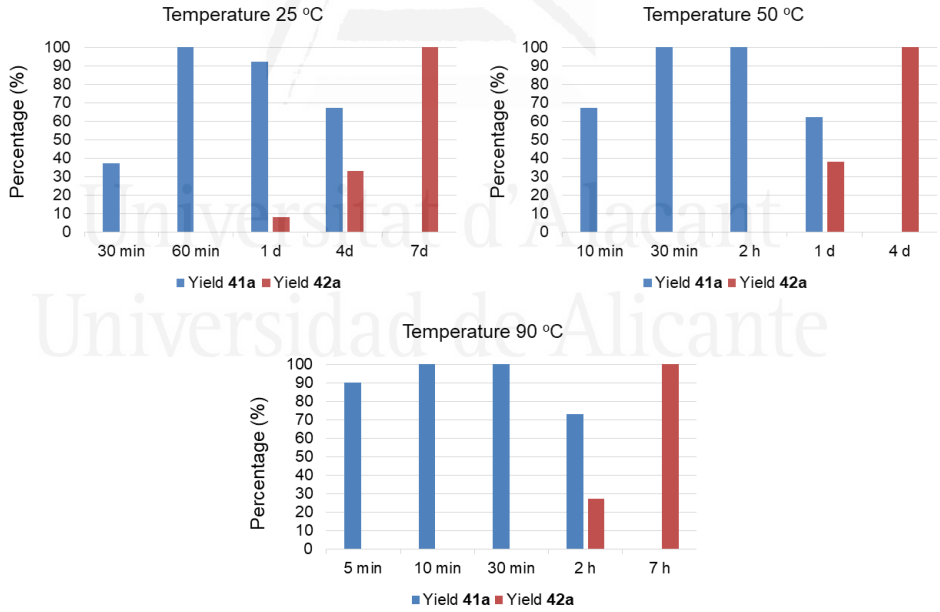


Figure 30. Evolution of the cycloisomerization/hydrolysis reactions at different temperatures.

So, the temperature of the reaction was set at 90 ºC and the reaction time 10 min for the initial cycloisomerization and 7 h for the following hydrolysis using pure water as solvent, which is an indication of the high activity of the catalyst under this conditions. It should be highlighted that this reaction time (10 min) for the cycloisomerization transformation is one of the lowest reported so far in the literature. The complete hydrolysis of previously isolated compound **41a** took place after 17 h without PdO-Fe_3O_4 catalyst, while in the presence of catalyst the whole process took only 7 h as aforementioned, indicating that PdO-Fe_3O_4 also catalyzed the hydrolysis step.

Additionally, a complete kinetic plot was performed under the optimized reaction conditions, observing that the hydrolysis transformation did not take place until the cycloisomerization process was completed (Figure 31). These results showed the selectivity of the palladium catalyst, capable of performing the 5-*exo-dig* cyclization regioselectively with no hydrolysis.

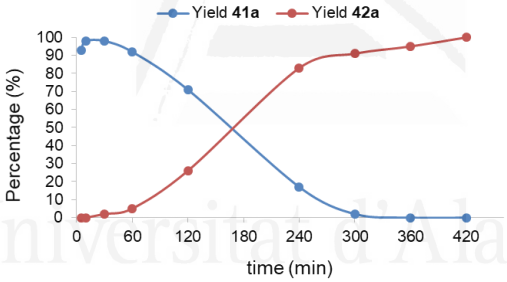
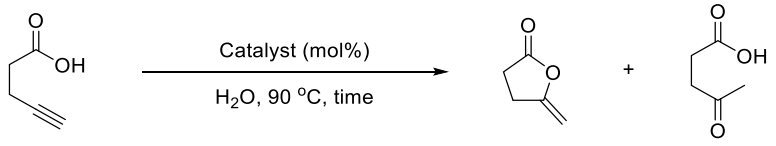


Figure 31. Plot time-yield product **41a** and **42a** at 90 ºC.

Other catalysts were tested in order to optimize the catalytic system (Table 35). Firstly, different blank experiments were performed (entries 2-4). The palladium catalyst was found to be essential for the reaction since the transformation did not occur without PdO-Fe_3O_4 (entry 2). Then, the possible catalytical activity of the magnetite support (micro- and nanoparticles of magnetite) was evaluated, but any activity was detected (entries 3-4). After that, an array of different metal oxides impregnated on magnetite were tested (entries 5-16), but only PtO/Pt_2O-Fe_3O_4 and PdO/Cu-Fe_3O_4 were active catalysts (entries 5 and 16). However, these catalysts presented poor selectivity, since ketoacid **42a** was detected without a full conversion of compound **41a**, as the results obtained with PdO-Fe_3O_4 catalyst.

Table 35. Optimization of the catalyst.[a]



40a **41a** **42a**

Entry	Catalyst (metal%)	time	Yield 41a (%)[b]	Yield 42a (%)[b]
1	PdO-Fe_3O_4 (0.13)	10 min	100	0
2	-	10 min	0	0
3	Micro-Fe_3O_4 (6.48)	10 min	0	0
4	Nano-Fe_3O_4 (6.48)	10 min	0	0
5	PtO/Pt_2O-Fe_3O_4 (0.13)	10 min	40	7
6	Au_2O_3-Fe_3O_4 (0.13)	10 min	0	0
7	Cu/CuO-Fe_3O_4 (0.13)	10 min	0	0
8	Ru_2O_3-Fe_3O_4 (0.13)	10 min	0	0
9	IrO_2-Fe_3O_4 (0.13)	10 min	0	0
10	CoO-Fe_3O_4 (0.13)	10 min	0	0
11	NiO-Fe_3O_4 (0.13)	10 min	0	0
12	Rh_2O_3-Fe_3O_4 (0.13)	10 min	0	0
13	Ag_2O/Ag-Fe_3O_4 (0.13)	10 min	0	0
14	$OsO_2/OsO_2(OH)_2$-Fe_3O_4 (0.13)	10 min	0	0
15	NiO/Cu-Fe_3O_4 (0.19/0.22)	10 min	0	0
16	PdO/Cu-Fe_3O_4 (0.17/0.13)	10 min	76	22
17	Pd/C (1.18)	10 min	100	0
18	Pd/C (1.10)	7 h	70	30
19	$PdO{\cdot}H_2O$ (1.85)	10 min	100	0
20	$PdO{\cdot}H_2O$ (2.06)	7 h	0	100
21	$PdCl_2$ (3.87)	10 min	100	0
22	$PdCl_2$ (4.05)	7 h	0	100
23	$Pd(AcO)_2$ (0.10)	10 min	100	0
24	$Pd(AcO)_2$ (0.10)	7 h	100	0
25	$Pd(MeCN)_2Cl_2$ (0.10)	10 min	100	0
26	$Pd(MeCN)_2Cl_2$ (0.10)	7 h	100	0

[a] Reaction conditions: compound **40a** (0.1 mmol) in 0.2 mL of solvent at 90 °C; [b] Yield determined by GC using tridecane as internal standard.

Once palladium was found to be the most active metal, other commercially available palladium catalysts were evaluated (entries 17-26). In most of the employed palladium catalysts, the required amount of metal catalyst loading to obtain a quantitative yield of compounds **41a** or **42a**, was superior in comparison with the initial PdO-Fe_3O_4 (compare

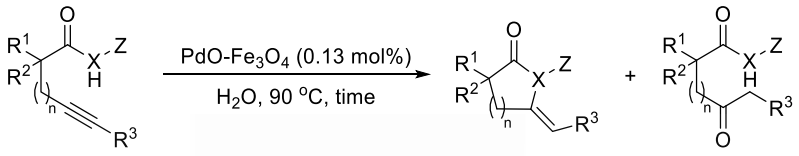
entry 1 and entries 17-26). Although homogeneous palladium catalysts [$Pd(OAc)_2$ and $Pd(MeCN)_2Cl_2$] presented a high catalytical activity, these palladium catalysts were unable to promote the hydrolysis reaction at longer reaction times (entries 24 and 26). Thus, all these results pointed out that $PdO\text{-}Fe_3O_4$ is the most active palladium catalyst and even recyclable.

Once the best catalytic system and reaction conditions were established, the scope of the cycloisomerization/hydrolysis transformation was evaluated (Table 36). The protocol showed a wide applicability and tolerance to different functional groups at α position with one of the lowest metal catalyst loading reported. Lower temperatures (50 ^oC) were needed for the cycloisomerization of α-substituted alkynoic acids in order to perform the reaction selectively (entry 3), and almost complete hydrolysis was achieved after 1 day at 90 ^oC (entry 4). The length of the aliphatic chain was also studied, observing that the cycloisomerization process was slower in the presence of an ethylene unit (n = 2) compared with the final hydrolysis, since the only product detected was the ketoacid **42c** (entry 5). Alkynoic acids containing a longer aliphatic chain (n = 3) were inactive substrates toward cycloisomerization as previously reported (entry 6).[188-190] A more challenging internal alkynoic acid gave the expected cyclic compound **41e** in an excellent yield (entry 7), although the reaction time should be increased. This observed experimental fact is consistent with the *trans* addition of the acid/imide group on the alkyne, which is activated by π-coordination to Pd. It should be pointed out that the addition was regioselective, since only the *Z*-product was observed and the corresponding 6-membered ring, resulting from an *endo* instead of an *exo* cyclization, was not detected. Later, the corresponding ketoacid **42e** was obtained just by increasing the reaction time (entry 8). After the good results obtained in the cycloisomerization of alkynoic acids, different alkynyl sulfonylimides were used to afford the corresponding alkylidene lactams (Scheme 29). Cycloisomerization of alkynyl imides[197] is usually more challenging in comparison with their corresponding carboxylic acid counterparts since it typically demands the employment of organic solvents as reaction media. Only a few examples in the literature

[197] a) Wu, H.; He, Y.-P.; Gong, L.-Z. *Adv. Synth. Catal.* **2012**, *354*, 975-980; b) Espinosa-Jalapa, N. A.; Ke, D.; Nebra, N.; Le Goanvic, L.; Mallet-Ladeira, S.; Monot, J.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2014**, *4*, 3605-3611; c) Ke, D.; Espinosa-Jalapa, N. A.; Mallet-Ladeira, S.; Monot, J.; Martin-Vaca, B.; Bourissou, D. *Adv. Synth. Catal.* **2016**, *358*, 2324-2331.

describe the cycloisomerization of alkynyl imides using water as solvent and under aerobic conditions.[198] Fortunately, the PdO-Fe_3O_4 catalyst proved to be compatible with *N*-tosyl derivatives (Table 36, entries 9-15). Cyclization of **41f** (entry 9) proceed slowly in comparison with the hydrolysis reaction (entry 10) as only 30% of compound **41f** could be isolated after 8 h, with the starting material and ketoacid derivative **42f** being detected in the crude mixture.

Table 36. Scope of the cyclization of alkynoic acids and derivatives.[a]



40 **41** **42**

Entry	R^1	R^2	R^3	X-Z	n	time	Product	Yield (%)[b]
1	H	H	H	O	1	10 min	**41a**	>99
2	H	H	H	O	1	7 h	**42a**	>99
3	Me	Me	H	O	1	1 d	**41b**	55[c]
4	Me	Me	H	O	1	1 d	**42b**	92
5	H	H	H	O	2	45 h	**42c**	98
6	H	H	H	O	3	3 d	**42d**	0[d]
7	H	H	Ph	O	1	1 d	**41e**	96
8	H	H	Ph	O	1	4 d	**42e**	75
9	H	H	H	*N*-Ts	1	8 h	**41f**	30[e]
10	H	H	H	*N*-Ts	1	1 d	**42f**	95
11	CO_2Me	H	H	*N*-Ts	1	5 h	**41g**	95[f]
12	CO_2Me	H	H	*N*-Ts	1	2 d	**42g**	83
13	CO_2Me	Allyl	H	*N*-Ts	1	2 d	**41h**	97
14	CO_2Et	Me	H	*N*-Ts	1	5 h	**41i**	95[f]
15	CO_2Et	Me	Et	*N*-Ts	1	4 d	**41j**	76

[a] Reaction carried out using compounds **40a-j** (0.1 mmol), 0.5 mg of catalyst (0.13 mol% Pd) in 0.2 mL of water at 90 °C; [b] Isolated yield after flash column chromatography; [c] Reaction carried out at 25 °C; [d] Starting material **40d** recovered unchanged; [e] 25% of **42f** and 40% of starting **40f** were detected by ^{1}H NMR of crude mixture; [f] Reaction carried out at 50 °C.

[198] a) Belger, K.; Krause, N. *Org. Biomol. Chem.* **2015**, *13*, 8556-8560; b) Rodríguez-Álvarez, M. J.; Vidal, C.; Schumacher, S.; Borge, J.; García-Álvarez, J. *Chem. Eur. J.* **2017**, *23*, 3425-3431.

Functional groups such as esters (entries 11 and 14) and allyls (entry 13) were compatible with the cyclization, finding that in these examples the process was totally selective. Note that most of the substrates (either cyclic lactones or lactams) underwent the hydrolysis reaction successfully (entries 2, 4, 5, 8, 10 and 12), but when the bulkiness of substitution at α position was increased, the hydrolysis process did not occur (entries 13-15). Then, the recyclability of the system was evaluated taking into account the important advantage of the magnetite based catalyst since the magnetic properties of magnetite allows an easy separation of the catalyst from the reaction mixture just by using an external magnet.

For this purpose, after completion of the reaction, all the organic compounds were extracted with ethyl acetate, and the mixture of water and catalyst was reused under the same reaction conditions. Meanwhile, the recyclability of the PdO-Fe_3O_4 catalyst, separated by magnetic decantation, was also investigated using fresh water in the next reaction. In both cases, the catalytic system could be recycled up to 4 consecutive cycles without any decrease in catalytic activity or selectivity (Figure 32).

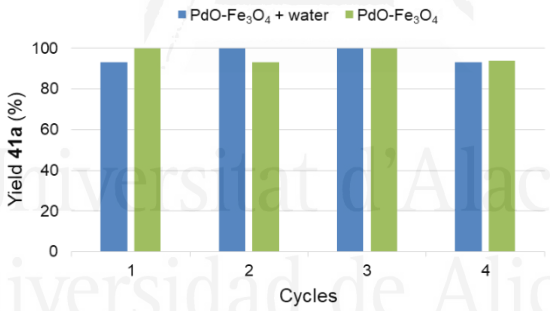


Figure 32. Recyclability of the catalytic system.

The particle size distribution of the heterogeneous palladium catalyst was measured after the recycling process (first cycle). A small overall increase of the nanoparticles was detected, observing that after the reaction the PdNPs tend to sinter, giving a mean value of 4.0±1.1 nm, in comparison with the initial mean value of 3.1±1.0 nm (Figure 33).

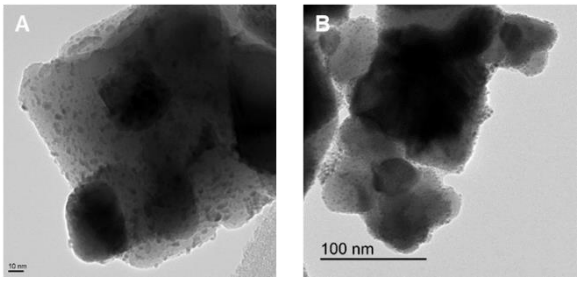


Figure 33. TEM images of PdO-Fe_3O_4 catalyst before (A) and after (B) the reaction.

In order to study the heterogeneity of the catalyst, a simple hot-filtration experiment was performed. The cycloisomerization reaction of **40e** was performed under standard reaction conditions and, after 5 h the catalyst was recovered by magnetic decantation and the alkynoic acid **40a** was added to the water solution. After 10 minutes, the GC analysis of the crude mixture showed the presence of compounds **41e** (40%) and **41a** (37%). So, this result seems to indicate that a partial lixiviation of the active species from the surface of the catalyst to the water solution occurs.

Furthermore, the ICP-MS analysis of the water solution after the reaction showed leaching of a small amount of palladium (7.1% of the initial amount) and iron (0.1% of the initial amount), which is in consonance with the hot-filtration results. It should be noted that when Pd/C was used as catalyst under the standard reaction conditions a similar leaching of palladium was observed in the water solution (6.4% of the initial amount). However, no leaching was observed when PdO-Fe_3O_4 was treated with an acid compound (butyric acid) and alkyne substrate (1-hexyne; 1:1 proportion) in water or only in the presence of the water solvent at 90 ^oC. All these facts seem to indicate that the leached palladium is due to the solubility of *in situ* formed vinyl palladium intermediate.

To prove the applicability of this methodology, the model reaction was set up on a gram-scale (Figure 34). Specifically, the reaction was performed with 4-pentynoic acid (**40a**; 10 mmol) in 20 mL of water at 90 ^oC for 7 h. Then, the organic compounds were extracted with 2-MeTHF (3 x 5 mL) and the organic phase was evaporated until dry to afford 1.07 g of pure product **42a** (92% yield) without the need of further purification steps.

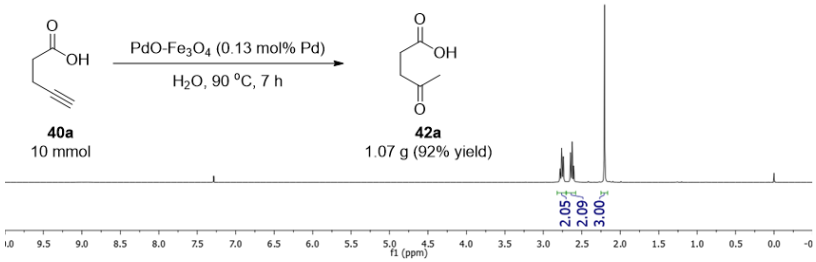


Figure 34. Gram-scale reaction.

Finally, XPS analysis was performed to confirm the oxidation state of the palladium species after the reaction. As shown in Figure 35, a portion of initial palladium(II) is oxidized to palladium(IV) species, but this partial oxidation of the catalyst seemed to not affect the catalytic activity of the palladium catalyst.

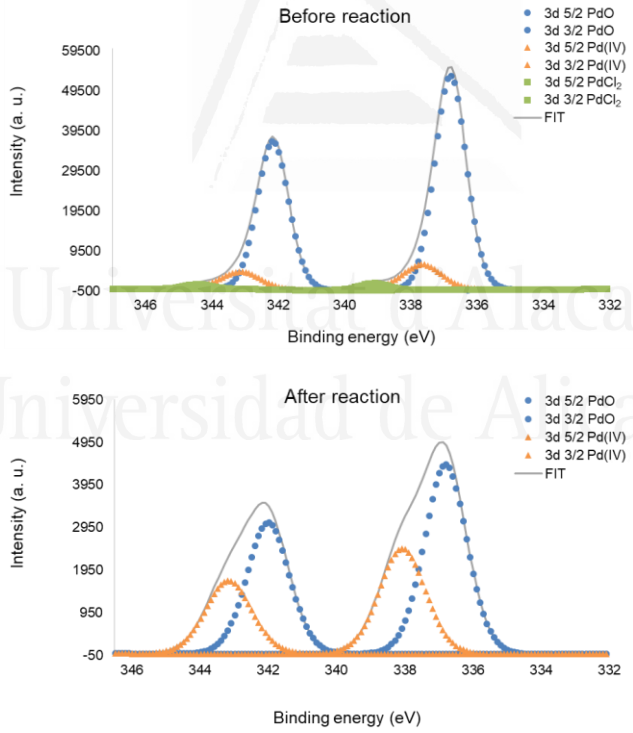


Figure 35. XPS of fresh and recycled palladium catalyst.

CHAPTER III

C-S bond formation reactions

3. 1 SULFONE SYNTHESIS AND RELATED DERIVATIVES

3.1.1 Precedents

Organosulfur compounds such as sulfides, sulfoxides and sulfones are important building blocks in synthetic organic chemistry due to their unique chemical, biological and pharmaceutical properties (Figure 36).[199]

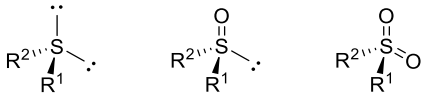


Figure 36. Sulfur-derived functional groups left to right: sulfides, sulfoxides and sulfones.

In particular, sulfones feature in a broad range of applications ranging from bioactive ingredients in agrochemicals and pharmaceuticals[200] to versatile intermediates in organic synthesis.[201] Owing to their widespread use, the efficient synthesis of sulfones has received considerable attention during the past few years.[202]

Conventionally, the common approaches to prepare sulfones relies on the exhaustive oxidation of the corresponding sulfides, which usually requires thiol substrates and harsh oxidative conditions.[203] The use of this methodology has some restrictions due to the unpleasant odor of thiols, their relatively limited commercial availability, as well as, the incompatibility with the presence of oxidation-sensitive functional groups in the starting materials.

[199] a) Feng, M.; Tang, B.; H Liang, S.; Jiang, X. *Curr. Top. Med. Chem.* **2016**, *16*, 1200-1216; b) Devendar, P.; Yang, G.-F. Sulfur-Containing Agrochemicals, in *Sulfur Chemistry*, Springer, Cham, 2019, pp. 35-78.

[200] a) Krämer, W.; Schirmer, U. *Modern Crop Protection Compounds*, Wiley-VCH: Weinheim, 2007; b) Scott, K. A.; Njardarson, J. T. *Top. Curr. Chem.* **2018**, *376*, 1-34; c) Zhao, C.; Rakesh, K. P.; Ravidar, L.; Fang, W.-Y.; Qin, H.-L. *Eur. J. Med. Chem.* **2019**, *162*, 679-734.

[201] a) Simpkins, N. S. *Sulphones in Organic Synthesis*, Pergamon, Oxford; New York, 1993; b) El-Awa, A.; Noshi, M. N.; du Jourdin, X. M.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315-2349; c) Trost, B. M.; Kalnmals, C. A. *Chem. Eur. J.* **2019**, *25*, 11193-11213.

[202] Li, Y.; Fan, Y. *Synth. Commun.* **2019**, *49*, 3227-3264.

[203] Matavos-Aramyan, S.; Soukhakian, S.; Jazebizadeh, M. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2020**, *195*, 181-193.

Another widely used strategy to synthesize sulfones is the transition-metal catalyzed sulfonylation with sulfinic acids/salts, sulfonyl halides or sulfonyl hydrazides,[204] including sulfonyl-type radicals.[205] Nonetheless, all these protocols employ sulfur-containing reagents, which are often difficult to prepare and therefore of limited availability.

More recently, multicomponent procedures for the direct insertion of sulfur dioxide into small molecules have been proved to be an attractive alternative to traditional protocols toward these valuable compounds. Gaseous SO_2 can be applied for the synthesis of various sulfonyl derived compounds.[206] However, this methodology entails important limitations, such as toxicity and the issues associated with handling gaseous sulfur dioxide. Thus, the application of SO_2 (g) for transition metal-catalyzed insertion reactions is limited.

These limitations could be overcome by the introduction of bench-stable and easy-to-handle solid SO_2 surrogates.[207] In 2010, the research group of Prof. Willis reported the use of DABSO, a bench-stable complex formed between 1,4-diazabicyclo[2.2.2]octane (DABCO) and two sulfur dioxide molecules,[208] as a convenient SO_2 surrogate.[209] Since then, DABSO has been combined with preformed organometallic reagents to generate metal sulfinates which can then undergo *in situ* conversion into sulfones (Scheme 31).[210]

[204] a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 4719-4721; b) Bandgar, B.; Bettigeri, S. V.; Phopase, J. *Org. Lett.* **2004**, *6*, 2105-2108; c) Kar, A.; Sayyed, I. A.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Org. Lett.* **2007**, *9*, 3405-3408; d) Liu, N.-W.; Liang, S.; Manolikakes, G. *Synthesis* **2016**, *48*, 1939-1973; e) Yang, F.-L.; Tian, S.-K. *Tetrahedron Lett.* **2017**, *58*, 487-504; f) Liu, N. W.; Liang, S.; Margraf, N.; Shaaban, S.; Luciano, V.; Drost, M.; Manolikakes, G. *Eur. J. Org. Chem.* **2018**, 1208-1210; g) Liu, J.; Zheng, L. *Adv. Synth. Catal.* **2019**, *361*, 1710-1732.

[205] Zhu, J.; Yang, W.-C.; Wang, X.-d.; Wu, L. *Adv. Synth. Catal.* **2018**, *360*, 386-400.

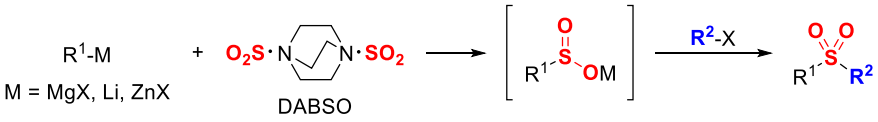
[206] Deeming, A. S.; Emmett, E. J.; Richards-Taylor, C. S.; Willis, M. C. *Synthesis* **2014**, *46*, 2701-2710.

[207] Emmett, E. J.; Willis, M. C. *Asian J. Org. Chem.* **2015**, *4*, 602-611.

[208] Santos, P. S.; Mello, M. T. S. *J. Mol. Struct.* **1988**, *178*, 121-133.

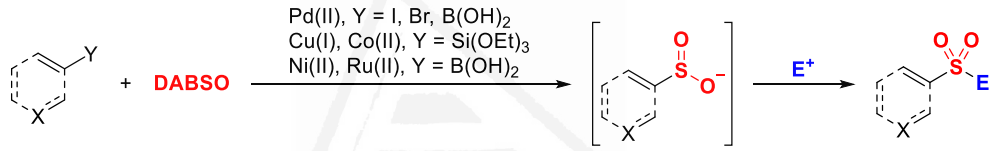
[209] Nguyen, B.; Emmett, E. J.; Willis, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 16372-16373.

[210] a) Emmett, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 12679-12683; b) Deeming, A. S.; Russell, C. J.; Hennessy, A. J.; Willis, M. C. *Org. Lett.* **2014**, *16*, 150-153; c) Rocke, B. N.; Bahnck, K. B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A. *Org. Lett.* **2014**, *16*, 154-157.



Scheme 31. Sulfone synthesis using an organometallic reagent, DABSO and an electrophile.

The use of organometallic reagents can be avoided by means of using palladium catalysts to generate a sulfinate from (hetero)aryl/vinyl halides, as well as boronic acids, and DABSO, with a subsequent alkylation step.[211] Additionally, the transmetalation-sulfination approach by the combination of boronic acids or aryl triethoxysilanes with DABSO has also proved to be successful using other transition metal catalysts (Cu,[212] Co,[213] Ni[214] or Ru;[215] Scheme 32).



Scheme 32. Synthesis of sulfones *via* transition-metal-catalyzed sulfonylation using DABSO.

Alternatively, sulfite salts, such as $K_2S_2O_5$ and $Na_2S_2O_5$, have been widely applied as sulfur dioxide surrogates.[216] These inexpensive and non-toxic inorganic compounds are known to release SO_2 under heating or in the presence of water, only generating Na_2SO_3 as a non-harmful by-product. In 2012, the first sulfonylation reaction employing inorganic sulfites as SO_2 surrogate for the synthesis of various sulfonamides was reported.[217] Inspired by this result, a series of sulfonylations derived from metabisulfite were developed. Aryl halides and boronic acids have been coupled with the *in situ* generated SO_2 affording

[211] a) Emmett, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 10204-10208; b) Richards-Taylor, C. S.; Blakemore, D. C.; Willis, M. C. *Chem. Sci.* **2014**, *5*, 222-228; c) Deeming, A. S.; Russell, C. J.; Willis, M. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 747-750.

[212] a) Mao, R.; Zheng, D.; Xia, H.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 693-696; b) Zheng, D.; Mao, R.; Li, Z.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 359-363; c) Chen, Y.; Willis, M. C. *Chem. Sci.* **2017**, *8*, 3249-3253.

[213] Zheng, D.; Chen, M.; Yao, L.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 985-988.

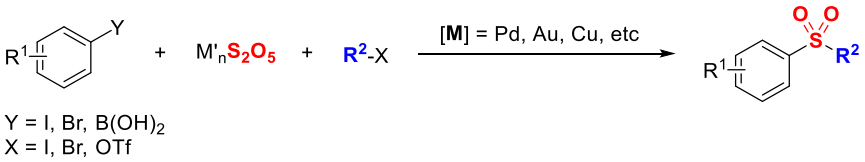
[214] Lo, P. K. T.; Chen, Y.; Willis, M. C. *ACS Catal.* **2019**, *9*, 10668-10673.

[215] Gulbe, K.; Turks, M. r. *J. Org. Chem.* **2020**, *85*, 5660-5669.

[216] Ye, S.; Yang, M.; Wu, J. *Chem. Commun.* **2020**, *56*, 4145-4155.

[217] Ye, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 10037-10039.

sulfinates, which could be treated with various electrophiles including alkyl halides and tosylates to lead sulfones (Scheme 33).[218]



Scheme 33. Multicomponent synthesis of sulfones using metabisulfite salts as SO_2 surrogate.

More recently, thiourea dioxide and sodium dithionite were employed as SO_2 surrogates for the synthesis of alkyl alkyl and aryl alkyl sulfones *via* a three-component cross-coupling protocol of halides, sulfur dioxides surrogates and phosphate esters.[219]

Notwithstanding, several aspects of the above methodologies should be improved, such as the use of specialized and expensive ligands and catalysts, generally in high loadings. Other limitations are the requirement for stoichiometric phase-transfer additives, air-sensitive reagents, poor solubility of the inorganic sulfites in organic media and the use of volatile and harmful solvents. As a consequence, the access of sulfones under green conditions is still unresolved.

In this respect, the multicomponent synthesis of sulfur-containing compounds from triarylbismuthines (Ar_3Bi) and $Na_2S_2O_5$ in DESs was envisaged as an environmentally friendly protocol, based on a few precedents of organosulfur compounds synthesis in different eutectic mixtures.[220] Due to the high dissolution power of DESs, all the inorganic salts and organic reagents would become soluble, increasing the effectiveness of the sodium metabisulfite as SO_2 source. Moreover, the high solubility of SO_2 (g) in this class of solvents was also a potential benefit for using them as a reaction medium for this transformation.[221]

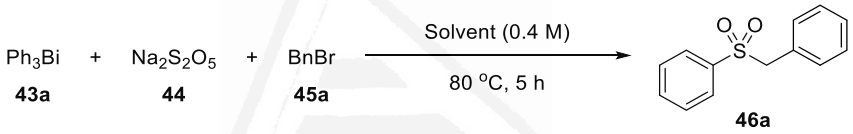
[218] Ye, S.; Qiu, G.; Wu, J. *Chem. Commun.* **2019**, *55*, 1013-1019.
[219] Chen, S.; Li, Y.; Wang, M.; Jiang, X. *Green Chem.* **2020**, *22*, 322-326.
[220] a) Dilauro, G.; Cicco, L.; Perna, F. M.; Vitale, P.; Capriati, V. *C. R. Chimie* **2017**, *20*, 617-623; b) Marset, X.; Guillena, G.; Ramón, D. J. *Chem. Eur. J.* **2017**, *23*, 10522-10526; c) Marset, X.; Torregrosa-Crespo, J.; Martínez-Espinosa, R. M.; Guillena, G.; Ramón, D. J. *Green Chem.* **2019**, *21*, 4127-4132.
[221] Yang, D.; Hou, M.; Ning, H.; Zhang, J.; Ma, J.; Yang, G.; Han, B. *Green Chem.* **2013**, *15*, 2261-2265.

Also, triarylbismuthines are particularly attractive since they are non-toxic, air stable and they can transfer their three aryl moieties, increasing the atom economy of the process.[222]

3.1.2 Results

The study started by optimizing the reaction conditions using triphenylbismuthine (**43a**), $Na_2S_2O_5$ (**44**) and benzyl bromide (**45a**) as the model reaction (Table 37). Conventional organic solvents were used with no success (entries 1-5). In the case of protic solvents, only methanol gave a good yield (70% yield; entries 6-8). Then, eutectic mixtures were tested as reaction media (entries 9-11), obtaining a quantitative yield using the non-toxic DES acetylcholine chloride:acetamide (1:2; entry 11).[111b]

Table 37. Solvent optimization of the sulfonylation reaction.[a]



Entry	Solvent	Yield (%)[b]
1	Toluene	0
2	$CHCl_3$	0
3	Acetonitrile	7
4	DMSO	27
5	DMF	56
6	MeOH	70
7	EtOH	55
8	H_2O	9
9	ChCl:glycerol (1:2)	57
10	ChCl:acetamide (1:2)	30
11	AcChCl:acetamide (1:2)	99

[a] Reaction conditions: Ph_3Bi (0.1 mmol), $Na_2S_2O_5$ (0.66 mmol) and BnBr (0.60 mmol) in 0.75 mL of solvent were stirred at 80 °C for 5 h; [b] Yield determined by GC using tridecane as an internal standard.

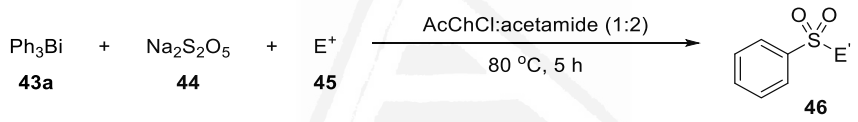
These results highlighted the ability of DESs to modulate reactivity properties fitting to requirements of the reaction, such as activation role or solubility of inorganic salts ($Na_2S_2O_5$) and solubility of the *in situ* generated SO_2. Also, the rest of organic compounds and

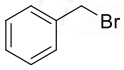
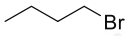
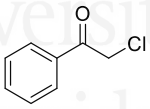
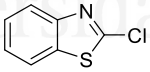
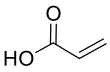
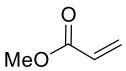
[222] Suzuki, H.; Matano, Y. *Organobismuth Chemistry*, Elsevier, Amsterdam, 2001.

intermediates formed during the reaction between Ph_3Bi and the SO_2-surrogate are totally dissolved in the DES mixture.

Once the optimal conditions were determined (Table 37, entry 11), the scope of this sustainable multicomponent transformation was evaluated. Firstly, different electrophiles were evaluated (Table 38). Various alkyl halides were employed with good to excellent yields (entries 1-3). 2-Chlorobenzo[*d*]thiazole afforded product **46d** in 85% yield (entry 4). Less conventional electrophiles as diaryliodonium salts could be also employed (entry 5). Electron poor olefins were used as electrophiles in the sulfonylation reaction obtaining moderate to good yields (entries 6-7). It is worth noting that the reaction conditions tolerated a wide number of functionalities, including carboxylic acids.

Table 38. Scope of the electrophiles in the sulfonylation reaction.[a]

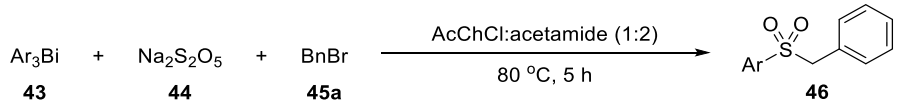


Entry	Electrophile (E^+)	Product	Yield (%)[b]
1		**46a**	90
2		**46b**	83
3		**46c**	75
4		**46d**	85
5	Ph_2IBF_4	**46e**	40
6		**46f**	80
7		**46g**	41

[a] Reaction conditions: Ph_3Bi (0.2 mmol), $Na_2S_2O_5$ (1.32 mmol) and E^+ (1.2 mmol) in 1.5 mL of solvent were stirred at 80 °C for 5 h; [b] Yield of compounds isolated by column chromatography and calculated assuming that all three aryl moieties are transferred.

After that, different triarylbismuthines **43** were evaluated (Table 39). Regarding the electronic nature of the aromatic ring of triarylbismuthines, slightly better yields were obtained using neutral triarylbismuthines (entries 1-2), but in general, no significant effects were observed in the results (entries 3-8).

Table 39. Scope of the triarylbismuthines in the sulfonylation reaction.[a]



43 **44** **45a** **46**

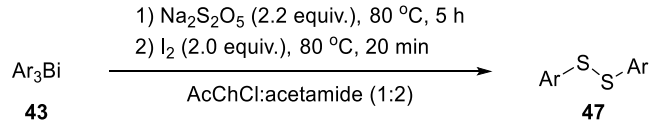
Entry	Ar	Product	Yield (%)[b]
1	Ph	**46a**	90
2	1-naphthyl	**46h**	76
3	4-MeC_6H_4	**46i**	62
4	4-$(MeO)C_6H_4$	**46j**	70
5	3,4,5-$(MeO)C_6H_2$	**46k**	63
6	4-$(Me_2N)C_6H_4$	**46l**	83
7	4-FC_6H_4	**46m**	82
8	4-BrC_6H_4	**46n**	67

[a] Reaction conditions: Ar_3Bi (0.2 mmol), $Na_2S_2O_5$ (1.32 mmol) and BnBr (1.2 mmol) in 1.5 mL of solvent were stirred at 80 °C for 5 h; [b] Yield of compounds isolated by column chromatography and calculated assuming that all three aryl moieties are transferred.

In terms of the possible mechanism pathway, an aryl sulfinate salt is postulated to be generated after the first reaction step. Thus, inspired by the previous results in the reduction of different organic sulfonic acids and sodium sulfonates with iodine for disulfides synthesis,[223] we tested the addition of iodine to the reaction mixture in order to investigate the versatility of the methodology. In this way, a radical process could also take place in this new reaction medium for the synthesis of different disulfides in the absence of any other reagent (Table 40). Particularly, the electronic nature of the aromatic ring (Ar_3Bi) had a notable impact in this reaction. Triarylbismuthines bearing neutral or electron-withdrawing groups gave good results (entries 1-2 and 5-6). However, a significant drop in the reaction yield was noticed with electron donor substituents, such as methyl or methoxy groups (entries 3-4).

[223] Shigeru, O.; Hideo, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3813-3817.

Table 40. Scope of the aryl disulfides.[a]



Entry	Ar	Product	Yield (%)[b]
1	Ph	**47a**	65
2	1-naphthyl	**47b**	51
3	4-MeC_6H_4	**47c**	27
4	4-$(MeO)C_6H_4$	**47d**	36
5	4-FC_6H_4	**47e**	80
6	4-BrC_6H_4	**47f**	70

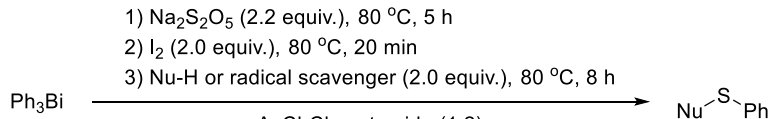
[a] Reaction conditions: Ph_3Bi (0.2 mmol), $Na_2S_2O_5$ (1.32 mmol) in 1.5 mL of solvent were stirred at 80 °C for 5 h, then I_2 was added and the mixture was stirred for 20 min; [b] Yield of compounds isolated by column chromatography. Yield calculated assuming that all three aryl moieties are transferred and two of them are in the final product.

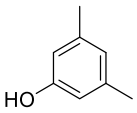
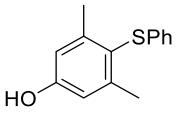
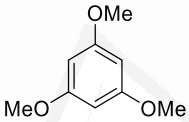
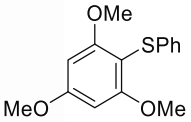
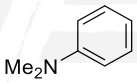
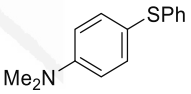
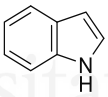
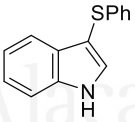
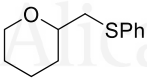
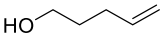
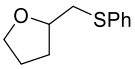
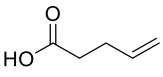
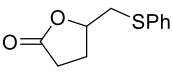
Iodine was also employed together with sulfinate salts for the synthesis of different sulfides *via* direct C-H functionalization in the literature.[224] In view of these precedents, a three step process in a one-pot manner was proposed for the synthesis of various sulfides (formation of the sulfinate salt, transformation to thiol derivative and its reaction with nucleophile/radical scavenger). As shown in Table 41, moderate to good yields were obtained when phenol/anisole derivatives (entries 1-2), *N*,*N*-dimethylaniline (entry 3) or indole (entry 4) were used as a nucleophile/radical scavenger. In the presence of a nucleophilic functionalized olefin, it was observed that the double bond initially reacts with the *in situ* generated radical thiol, being then the radical trapped by the hydroxyl functionality affording cyclic products **48e-g** (entries 5-7).

Then, we decided to study the recyclability of the system. Once the reaction was finished, the organic compounds were extracted with 2-MeTHF, and the remaining DES could be reused up to 5 consecutive cycles under the same reaction conditions, with only a slight decrease in the yields after the first cycle (Figure 37).

[224] a) Wang, D.; Zhang, R.; Lin, S.; Yan, Z.; Guo, S. *RSC Adv.* **2015**, *5*, 108030-108033; b) Gao, Y.; Gao, Y.; Tang, X.; Peng, J.; Hu, M.; Wu, W.; Jiang, H. *Org. Lett.* **2016**, *18*, 1158-1161; c) Xiao, F.; Chen, S.; Tian, J.; Huang, H.; Liu, Y.; Deng, G.-J. *Green Chem.* **2016**, *18*, 1538-1546.

Table 41. Scope of the aryl sulfides.[a]



Entry	Nu-H or radical scavenger	Product	Yield (%)[b]
1		 **48a**	72
2		 **48b**	79
3		 **48c**	67
4		 **48d**	81
5		 **48e**	52
6		 **48f**	77
7		 **48g**	73

[a] Reaction conditions: Ph_3Bi (0.2 mmol), $Na_2S_2O_5$ (1.32 mmol) in 1.5 mL of solvent were stirred at 80 °C for 5 h, then I_2 was added and the mixture was stirred for 20 min. Finally, Nu-H or radical scavenger (1.2 mmol) was added and the mixture was stirred for another 8 h at 80 °C; [b] Yield of compounds isolated by column chromatography and calculated assuming that all three aryl moieties are transferred.

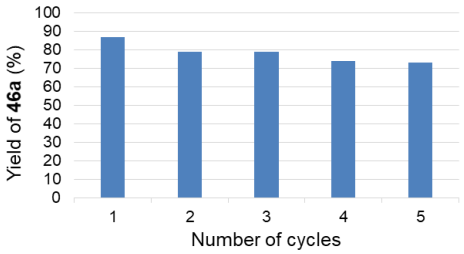
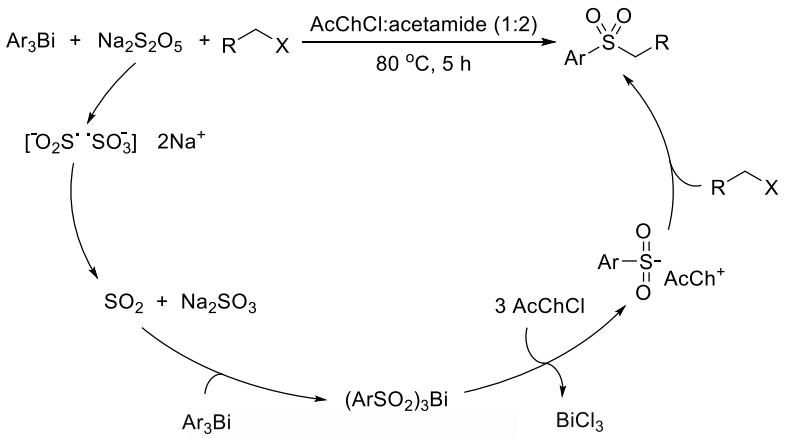


Figure 37. Recyclability of the system.

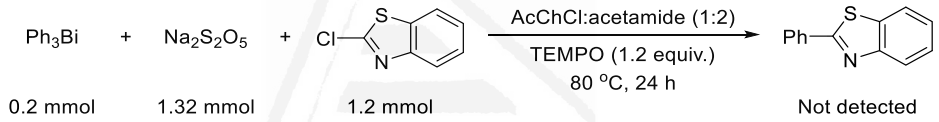
Another important aspect to be controlled in a sustainable process is the waste materials. In this process, the amount of wasted bismuth compounds could be controlled just by adjusting the pH of the aqueous work-up. When the standard reaction (see Table 37, entry 11) was quenched with only water, this water solution contained 0.1% of the initial bismuth (ICP-OES analysis). However, if the presence of bismuth impurities in the desired product are not allowed for some purposes, for instance in medicinal chemistry, HCl 2.0 M could be added instead of water, with 99% of the initial bismuth (ICP-OES analysis) remaining in the aqueous layer, highlighting the possibility of controlling the waste bismuth salts.

A plausible mechanism for the synthesis of sulfones has been proposed (Scheme 34). First, $Na_2S_2O_5$ disaggregation occurs through homolytic cleavage of the S-S bond. This step includes radical intermediates,[225] which is in consonance with radical-trapping experiments (Scheme 35). Note that any TEMPO-derived trapping products were detected, only the hydroxylamine or amine TEMPO derived compounds were detected by GC-MS while Ph_3Bi remained unchanged. Then, these radical intermediates suffer a disproportionation to afford SO_2, which later undergoes insertion between C-Bi bond.[226] The excess of chlorides in DES, might favor the $BiCl_3$ released, affording the corresponding sulfinate. The generation of the sulfinate intermediate could be detected monitoring the reaction by reversed-phase HPLC, as has been proven in a related process.[220b] Finally, the sulfinate reacts with an electrophile to give the desired sulfone product.

[225] Janzen, E. G. *J. Phys. Chem.* **1972**, *76*, 157-162.
[226] Smith, B. C.; Waller, C. B. *J. Organomet. Chem.* **1971**, *32*, C11-C12.

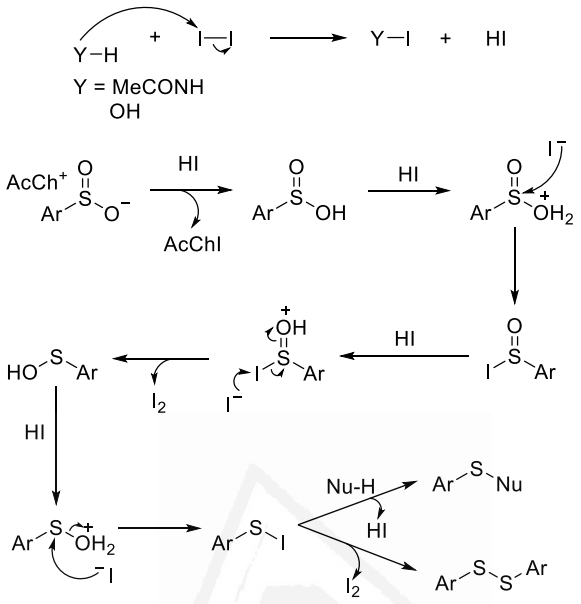


Scheme 34. Proposed mechanism for the synthesis of sulfones.



Scheme 35. Radical trapping experiment (TEMPO).

A possible mechanism for the sulfide and disulfides synthesis is also proposed in Scheme 36. Acetamide, one of the DES components, or also other proton sources in the media, such as moisture, reacts with I_2 to get hydrogen iodide. Then, the *in situ* generated sulfinate (see Scheme 34), reacts repeatedly with HI to give the corresponding hypoiodothioite (ArS-I), which could react with a nucleophile to afford different sulfides or suffer a recombination to give symmetrical disulfides.[223]



Scheme 36. Proposed mechanism for the synthesis of sulfides and disulfides synthesis.

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, Alfa Aesar, Fluka, Fluorochem, Merck, Sigma Aldrich,* 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 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-Microtech 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*.

Melting points were obtained with a *Reichert Thermovar* apparatus.

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_{254} light.

FT-IR spectra were obtained on a *JASCO 4100LE* (*Pike Miracle* ATR) spectrophotometer.

UV-Vis spectra were recorded in a *SHIMAZDU UV-1603* spectrophotometer.

Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon (^{13}C 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 ^{1}H and 100/75 MHz for ^{13}C). $CDCl_3$, MeOD-d_4 and DMSO-d_6 were used as solvents (unless otherwise indicated) and tetramethylsilane (TMS) as an internal standard for ^{1}H NMR. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hz.

Low-resolution mass spectra were 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). *Agilent 5973 Network* spectrometer with a Direct Insertion Probe (73DIP-1) or *Agilent Model 1100* Series High Performance Liquid Chromatograph coupled simultaneously to a UV-Visible Variable Wavelength Detector and a Mass Trap Spectrometer with Ion Trap Analyzer (*Agilent Model 1100 Series LC / MSD Trap SL*) were also used for low-resolution mass spectra analysis. High-resolution mass spectra (EI) were recorded at 70 eV on an *Agilent 7200 flight* (Q-TOF) spectrometer with a Direct Insertion Probe (73DIP-1). 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 inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis were performed in the units Technical Services Research at the University of Alicante with an inductively coupled plasma optical emission spectroscopy (*Perkin Elmer, Optima 4300DV, Dual vision*).

Column chromatography was performed in 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 with 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 different chiral columns, using mixtures of n-hexane/isopropyl alcohol (IPA) as the mobile phase, at 25 °C.

1.3 DES preparation

General procedure for the preparation of DESs: A mixture of hydrogen-bond donor and hydrogen-bond acceptor, with the selected molar ratio, was added in a round bottom flask under an inert atmosphere. The mixture was stirred for 30 minutes in a T range between 65 and 80 °C obtaining the corresponding DES.

1.4 Eutectogel preparation

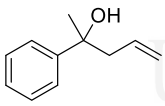
General procedure for the preparation of eutectogels: To a previously synthesized DES, the gelator (3-5 wt%) was added. The mixture was heated to 80 ^{0}C for 30 min. After that, the

clear solution was placed in a fridge (4 ^{o}C) during a 24 h period to obtain the corresponding eutectogel.

2. INDIUM MEDIATED ALLYLATION OF CARBONYL COMPOUNDS

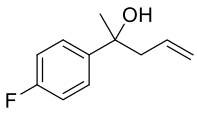
General procedure: To a solution of carbonyl compound (0.5 mmol), indium (1 mmol) and ammonium chloride (28 mol%) in 1 mL of DES, 1 mmol of the corresponding allyl chloride was added and the mixture was stirred at room temperature for 12 hours. The mixture was quenched with water and extracted with AcOEt (3×5 mL). The combined organic layers were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. Products were purified by chromatography on silica gel (hexane/ethyl acetate, usually hexane to 10% of ethyl acetate in hexane) to give the corresponding products.

General procedure for recycling experiments: The reaction was performed according to the general procedure. Once the reaction was completed, 2-MeTHF (3×2 mL) was added to the reaction vessel. The biphasic mixture was stirred for 5 min, and the upper phase (VOC-phase, mainly unreacted organic reagents and products) was separated by decantation and analyzed by GC using 4,4'-di-*tert*-butyl-1,1'-biphenyl (DTBB) as the internal standard. The eutectic mixture (bottom phase) was dried under vacuum and was charged again with fresh reagents, repeating the process.

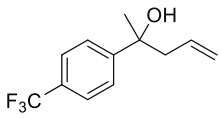


2-Phenylpent-4-en-2-ol (3a):[227] Colorless oil; R_f = 0.5 (hexane/ethyl acetate 8/2); t_r = 9.93 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50-7.40 (m, 2H, ArH), 7.40-7.30 (m, 2H, ArH), 7.27 (dt, J = 9.4, 4.3 Hz, 1H, ArH), 5.75-5.55 (m, 1H, CH_2CHCH_2), 5.20-5.10 (m, 2H, CH_2CHCH_2), 2.72 (dd, J = 13.7, 6.4 Hz, 1H, CH_2CHCH_2), 2.53 (dd, J = 13.7, 8.3 Hz, 1H, CH_2CHCH_2), 2.09 (s, 1H, OH), 1.57 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.8, 133.818, 128.3, 126.8, 124.9, 119.6, 73.8, 48.6, 30.1 ppm; IR (ATR) ν = 3425, 3070, 2974, 2927, 1639, 764, 694 cm^{-1}; MS (EI) *m/z* (%): 144 (M^+ - H_2O, 1%), 121 (100), 105 (16), 77 (20), 51 (9).

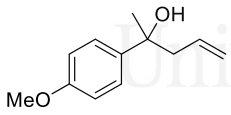
[227] Fandrick, K. R.; Fandrick, D. R.; Gao, J. J.; Reeves, J. T.; Tan, Z.; Li, W.; Song, J. J.; Lu, B.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 3748-3751.



2-(4-fluorophenyl)pent-4-en-2-ol (3b):[228] Yellowish oil; R_f = 0.43 (hexane/ethyl acetate 8/2); t_r = 10.00 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50-7.35 (m, 2H, ArH), 7.10-6.95 (m, 2H, ArH), 5.70-5.50 (m, 1H, CH_2CHCH_2), 5.25-5.00 (m, 2H, CH_2CHCH_2), 2.75-2.60 (m, 1H, CH_2CHCH_2), 2.55-2.45 (m, 1H, CH_2CHCH_2), 2.37 (s, 1H, OH), 1.54 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.8 (d, J = 244.7 Hz), 143.4, 133.5, 126.7, 126.6, 119.9, 114.9 (d, J = 21.2 Hz), 73.6, 48.7, 30.1 ppm; IR (ATR) ν = 3413, 3074, 2977, 1666, 1604, 1508 1157, 921, 833 cm^{-1}; MS (EI) *m/z* (%): 162.1 (M^+ - H_2O, 1%), 139 (100), 123 (16), 95 (11).

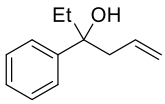


2-(4-(trifluoromethyl)phenyl)pent-4-en-2-ol (3c):[229] Yellowish oil; R_f = 0.43 (hexane/ethyl acetate 8/2); t_r = 8.73 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (dt, J = 9.0, 4.5 Hz, 4H, ArH), 5.70-5.45 (m, 1H, CH_2CHCH_2), 5.20-5.10 (m, 2H, CH_2CHCH_2), 2.75-2.60 (m, 1H, CH_2CHCH_2), 2.60-2.45 (m, 1H, CH_2CHCH_2), 2.10 (s, 1H, OH), 1.56 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.7, 133.0, 128.8 (m), 125.4 (m) 123.0, 120.3, 73.7, 48.4, 30.0 ppm; IR (ATR) ν = 3429, 3086, 2981, 2939, 1624, 1119, 1010, 840 cm^{-1}; MS (EI) *m/z* (%): 212 (M^+ - H_2O, 3%), 189 (100), 173 (22), 145 (18).

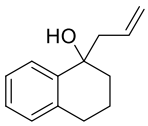


2-(4-methoxyphenyl)pent-4-en-2-ol (3d):[230] Colorless oil; R_f = 0.33 (hexane/ethyl acetate 8/2); t_r = 12.25 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 (d, J = 8.9 Hz, 2H, ArH), 6.87 (d, J = 8.9 Hz, 2H, ArH), 5.63 (dddd, J = 16.9, 10.3, 8.2, 6.5 Hz, 1H, CH_2CHCH_2), 5.20-5.00 (m, 2H, CH_2CHCH_2), 3.80 (s, 3H, OCH_3), 2.70-2.60 (m, 1H, CH_2CHCH_2), 2.60-2.40 (m, 1H, CH_2CHCH_2), 1.85 (s, 1H, OH), 1.53 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.0, 133.8, 126.9, 126.3, 116.9, 113.77, 113.7, 113.6, 55.4, 16.1 ppm; IR (ATR) ν = 2954, 2835, 1608, 1508, 1246, 1176, 1034, 825, 737 cm^{-1}; MS (EI) *m/z* (%): 174.1 (M^+ - H_2O, 10%), 151 (100), 77 (22).

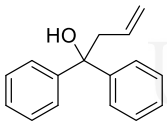
[228] Lee, B. S.; Jang, D. O. *Eur. J. Org. Chem.* **2013**, 3123-3130.
[229] Yin, J.; Stark, R. T.; Fallis, I. A.; Browne, D. L. *J. Org. Chem.* **2020**, *85*, 2347-2354.
[230] Cui, Y.; Yamashita, Y.; Kobayashi, S. *Chem. Commun.* **2012**, *48*, 10319-10321.



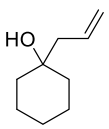
3-Phenylhex-5-en-3-ol (3e):[227] Colorless oil; R_f = 0.4 (hexane/ethylacetate 9/1); t_r = 11.25 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50-7.30 (m, 4H, ArH), 7.30-7.10 (m, 1H, ArH), 5.57 (dddd, J = 17.1, 10.1, 8.7, 6.0 Hz, 1H, CH_2CHCH_2), 5.20-5.00 (m, 2H, CH_2CHCH_2), 2.80-2.60 (m, 1H, CH_2CHCH_2), 2.49 (dd, J = 13.7, 8.7 Hz, 1H, CH_2CHCH_2), 1.96 (s, 1H, OH), 1.90-1.78 (m, 2H, CH_2CH_3), 0.76 (t, J = 7.4 Hz, 3H, CH_2CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.8, 133.7, 128.2, 126.5, 125.5, 119.7, 76.1, 47.0, 35.4, 7.9 ppm; IR (ATR) ν = 3741, 3066, 2970, 2931, 1639, 1450, 914, 760, 702 cm^{-1}; MS (EI) *m/z* (%): 158 (M^+ - H_2O, 3%) 135 (100), 115 (9), 105 (42), 91 (9), 77 (25), 57 (43).



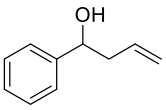
1-Allyl-1,2,3,4-tetrahydronaphthalen-1-ol (3f):[227] Colorless oil; R_f = 0.24 (hexane/ethyl acetate 9/1); t_r = 13.58 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (dd, J = 7.7, 1.4 Hz, 1H, ArH), 7.30-7.10 (m, 2H, ArH), 7.07 (dd, J = 7.7, 1.4 Hz, 1H, ArH), 6.00-5.70 (m, 1H, CH_2CHCH_2), 5.13 (dtd, J = 11.5, 2.0, 1.3 Hz, 2H, CH_2CHCH_2), 2.90-2.65 (m, 2H, CH_2CHCH_2), 2.60 (dt, J = 7.3, 1.1 Hz, 2H, CyH), 2.03 (ddd, J = 10.5, 4.8, 3.5 Hz, 1H, OH), 1.95-1.70 (m, 4H, CyH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.9, 136.9, 134.1, 129.0, 127.3, 126.5, 126.4, 118.8, 72.1, 47.1, 36.2, 29.9, 19.9 ppm; IR (ATR) ν = 3429, 3066, 2935, 1485, 1003, 737 cm^{-1}; MS (EI) *m/z* (%): 170 (M^+-H_2O, 59%), 147 (100), 129 (93), 115 (28), 91 (38).



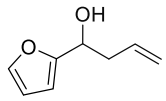
1,1-Diphenylbut-3-en-1-ol (3g):[230] Colorless oil; R_f = 0.4 (hexane/ethyl acetate 9/1); t_r = 14.80 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50-7.40 (m, 4H), 7.40-7.25 (m, 5H), 7.25-7.10 (m, 2H), 5.65 (ddt, J = 17.3, 10.1, 7.2 Hz, 1H), 5.30-5.10 (m, 2H), 3.15-3.01 (m, 2H), 2.39 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.5 (2C), 133.5 (2C), 128.2 (2C), 126.9 (2C), 126.0 (2C), 120.6 (2C), 76.9, 46.7 ppm; IR (ATR) ν = 3556, 3066, 3031, 1493, 995, 760, 694 cm^{-1}; MS (EI) *m/z* (%): 206 (M^+- H_2O, 62%), 183 (100), 105 (77), 91 (16), 77 (41), 51 (9).



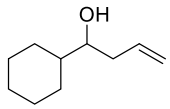
1-Allylcyclohexan-1-ol (3h):[227] Colorless oil; R_f = 0.43 (hexane/ethyl acetate 4/1); t_r = 8.20 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.89 (ddt, J = 17.0, 10.3, 7.5 Hz, 1H, CH_2CHCH_2), 5.25-5.00 (m, 2H, CH_2CHCH_2), 3.59 (s, 1H, OH), 2.30-2.15 (m, 2H, CH_2CHCH_2), 1.70-1.35 (m, 10H, CyH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 134.1, 119.0, 71.4, 47.1, 37.8, 30.1, 26.2, 22.6 ppm; IR (ATR) ν = 3614, 2924, 2854, 1458, 1064, 737cm^{-1}; MS (EI) *m/z* (%): 122 (M^+- H_2O, 1%), 99 (100), 81 (86), 55 (37).



1-Phenylbut-3-en-1-ol (3i):[229] Colorless oil; R_f = 0.5 (hexane/ethyl acetate 4/1); t_r = 9.70 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50-7.15 (m, 5H, ArH), 5.84 (ddt, J = 17.2, 10.1, 7.5 Hz, 1H, CH_2CHCH_2), 5.30-5.05 (m, 2H, CH_2CHCH_2), 4.76 (dd, J = 7.5, 5.4 Hz, 1H, $PhCHOHCH_2$), 3.61 (s, 1H, OH), 2.70-2.40 (m, 2H, CH_2CHCH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.9, 134.6, 128.5, 127.7, 125.9, 118.5, 73.4, 43.9 ppm; IR (ATR) ν = 3070, 2920, 2862, 1643, 1003, 733 cm^{-1}; MS (EI) *m/z* (%):148 (M^+, 0.1%), 107 (100), 79 (65), 77 (41), 51 (10).



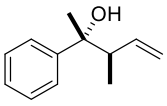
1-(furan-2-yl)but-3-en-1-ol (3j):[231] Colorless oil; R_f = 0.55 (hexane/ethyl acetate 7/3); t_r = 8.20 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50-7.30 (m, 1H, furylH), 6.40-6.30 (m, 1H, furylH), 6.30-6.15 (m, 1H, furylH), 6.00-5.65 (m, 1H, furyl$CH(OH)CH_2$), 5.25-5.00 (m, 2H, CH_2CHCH_2), 4.85-4.60 (m, 1H, CH_2CHCH_2), 3.59 (bs, 1H, OH), 2.70-2.55 (m, 2H, CH_2CHCH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.2, 142.0, 133.9, 118.6, 110.2, 106.1, 67.0, 40.2 ppm; IR (ATR) ν = 3367, 2923, 2866, 1635, 910 cm^{-1}; MS (EI) *m/z* (%): 138 (M^+, 3%), 97 (100), 69 (10).



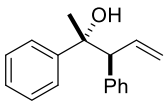
1-Cyclohexylbut-3-en-1-ol (3k):[229] Colorless oil; R_f 0.4 = (hexane/ethyl acetate 4/1); t_r = 9.70 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.90-5.75 (m, 1H, CH_2CHCH_2), 5.25-5.10 (m, 2H, CH_2CHCH_2), 3.39 (ddd, J = 9.1, 5.8, 3.5 Hz, 1H, $CH(OH)$), 2.40-2.20 (m, 1H, CH_2CHCH_2), 2.20-2.00 (m, 1H, CH_2CHCH_2), 1.95-1.80 (m, 1H, OH), 1.75 (ddt, J = 10.7, 8.9, 4.7 Hz, 2H, Cy), 1.75-1.60 (m, 3H, Cy), 1.45-1.30 (m, 1H, Cy), 1.30-0.90 (m, 6H, Cy) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.6, 118.1, 74.9,

[231] Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827-3830.

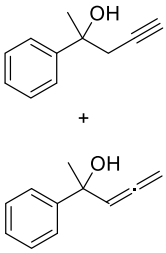
43.2, 38. 9, 29.2, 28.2, 26.6, 26.4, 26.3 ppm; IR (ATR) ν = 2927, 2857, 906, 725 cm^{-1}; MS (EI) *m/z* (%): 154 (M^+, 0.1%), 113 (28), 95 (100), 67 (17), 55 (15).



(2*R,3*R**)-3-Methyl-2-phenylpent-4-en-2-ol (3l):**[227] Colorless oil; R_f = 0.6 (hexane/ethyl acetate 4/1); t_r = 11.03 (*anti* isomer), 11.12 (*syn* isomer) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.60-7.10 (m, 5H, ArH), 5.82 (ddd, *J* = 16.4, 11.1, 8.3 Hz, 1H, CHC*H*CH_2), 5.25-5.00 (m, 2H, CHCHC*H*$_2$), 2.70-2.40 (m, 1H, C*H*CHCH_2), 1.83 (s, 1H, OH), 1.53 (s, 3H, COHC*H*$_3$), 0.97 (d, *J* = 6.9 Hz, 1H, *syn* isomer), 0.86 (d, *J* = 6.9 Hz, 3H, CH_3 *anti* isomer) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.1, 140.0, 128.0, 126.6, 125.6, 125.3, 116.5, 75.9, 49.1, 28.6, 14.9 ppm; IR (ATR) ν = 3864, 3741, 2927, 2861, 1724, 1547, 1454, 1072, 736 cm^{-1}; MS (EI) *m/z* (%): 144 (M^+- H_2O, 0.4%), 121 (100), 105 (13), 77 (14).



(2*R,3*S**)-2,3-Diphenylpent-4-en-2-ol (3m):**[227] Yellowish oil; R_f = 0.66 (hexane/ethyl acetate 4/1); t_r = 14.02 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45-7.00 (m, 10H, ArH), 6.12 (ddd, *J* = 17.1, 10.3, 8.6 Hz, 1H, CHC*H*CH_2), 5.05 (ddd, *J* = 10.3, 1.7, 1.2 Hz, 1H, CHCHC*H*$_2$), 4.93 (ddd, *J* = 17.1, 1.7, 1.2 Hz, 1H, CHCHC*H*$_2$), 3.63 (d, *J* = 8.6 Hz, 1H, C*H*CHCH_2), 2.04 (dd, *J* = 15.1, 8.6 Hz, 1H, OH), 1.43 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.5, 140.2, 137.5, 129.7, 128.2, 127.9, 127.8, 126.9, 126.7, 125.6, 118.1, 76.4, 61.9, 28.6 ppm; IR (ATR) ν = 3741, 3062, 3028, 2978, 1689, 917 694 cm^{-1}; MS (EI) *m/z* (%): 220 (M^+ - H_2O, 0.2%), 121 (100), 105 (11), 91 (10), 77 (13).



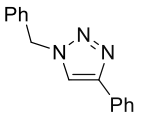
2-Phenylpent-4-yn-2-ol + 2-phenylpenta-3,4-dien-2-ol (5, 6):[232] Colorless oil; R_f = 0.4 (hexane/ethyl acetate 4/1); t_r = 10.37 (**6** isomer), 10.92 (**5** isomer) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (ddd, *J* = 8.8, 2.3, 0.9 Hz, 2H, ArH), 7.40-7.30 (m, 2H, ArH), 7.30-7.15 (m, 1H, ArH), 5.55 (t, *J* = 6.6 Hz, 1H, C*H*CCH_2), 4.96 (dd, *J* = 6.6, 3.2 Hz, 2H, CHCC*H*$_2$), 2.72 (qd, *J* = 16.7, 2.6 Hz, 1H, OH), 1.65 (s, 3H, CH_3, **6** isomer), 1.64 (s, 1H, CH_3, **5** isomer) ppm; ^{13}C RMN (101 MHz, $CDCl_3$) δ = 29.3 (**5** isomer), 30.5

[232] Schneekloth Jr., J. S.; Pucheault, M.; Crews, C. M. *Eur. J. Org. Chem.* **2007**, 40-43.

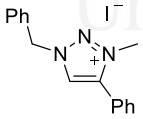
(**6** isomer), 34.7, 71. 9, 73.1, 73.3, 79.2, 80.5, 100.2, 124.8, 125.0, 127.1, 127.2, 128.3, 128.4, 126.4, 147.2, 205.9 (**6** isomer) IR (ATR) ν = 3386, 2981, 2923, 1955, 1446, 1369, 1064, 848, 763, 694 cm^{-1}; MS (EI) *m/z* (%; **5** isomer): 142 (M^+ - H_2O, 0.3%), 121 (100), 105 (20), 77 (22) and MS (EI) *m/z* (%; **6** isomer): 142 (M^+ - H_2O,10%), 141, (20) 121 (100), 105 (12), 77 (20).

3. CROSS-COUPLING REACTIONS

3.1 Palladium mesoionic carbene catalyst preparation



1-Benzyl-4-phenyl-1H-1,2,3-triazole (10):[233] To a water solution of sodium ascorbate (30 mol%) and $CuSO_4 \cdot 5H_2O$ (5 mol%), benzyl bromide (10 mmol), sodium azide (10 mmol) and phenylacetylene (10 mmol) were added. The mixture was heated at 50 ºC for 24 h. The product was extracted with AcOEt (3 x 25 mL). The organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The obtained solid was washed with hexane to obtain compound **10** (1.30 g, 55% yield). White solid; R_f = 0.57 (hexane/ethyl acetate 1/1); m.p. 124-126 °C; t_r = 18.67; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.80 (d, J = 7.3 Hz, 2H, ArH), 7.68 (s, 1H, CH-N), 7.45-7.25 (m, 8H, ArH), 5.55 (s, 2H, CH_2Ph) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.3, 134.8, 130.6, 129.2 (2C), 128.9 (2C), 128.8, 128.3, 128.2 (2C), 125.8 (2C), 119.7, 54.3 ppm; IR (ATR) ν = 1450, 1223, 767 cm^{-1}; MS (EI) *m/z* (%): 235 (M^+, 26), 207 (74), 206 (73), 180 (11), 116 (100), 106 (12), 105 (16), 104 (24), 91(80), 89 (26), 77 (20), 65 (14).

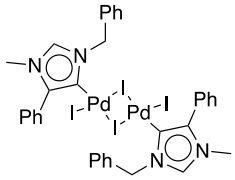


1-Benzyl-3-methyl-4-phenyl-1*H*-1,2,3-triazolium chloride (11):[234] Previously synthesized compound **10** (2.1 mmol) was dissolved in 20 mL MeCN and then, MeI (31.9 mmol) was added. The mixture was heated at 80 ºC for 24 h. Once the reaction was finished, the solvent was removed under reduce pressure and the solid was washed with Et_2O to obtain compound **11** (0.610 g, 75% yield). Brown solid; R_f = 0.43 (ethyl acetate/methanol 2/1); m.p. 127-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.42 (s, 1H, CH-N), 7.80-7.35 (m, 10H, ArH), 6.04 (s, 2H, CH_2Ph), 4.32 (s, 3H, NCH_3) ppm;

[233] Guisado-Barrios, G.; Bouffard, J.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4759-4762.

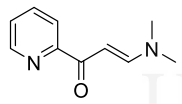
[234] Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc.* **2008**, *130*, 13534-13535.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.1, 132.1, 131.3, 130.1 (2C), 130.0, 129.8 (2C), 129.7 (2C), 129.5 (2C), 129.4, 121.7, 57.7, 39.6 ppm; IR (ATR) ν = 3038, 1157, 764 cm^{-1}.



Complex 12:[234] Triazolium salt **11** (1.0 mmol), $PdCl_2(SMe)_2$ (1.0 mmol) and *t*-BuOK (1.0 mmol) were dissolved in 20 mL DCM (dry) under inert atmosphere. The mixture was stirred at room temperature for 24 h. After that, water was added (3 x 10 mL) and the aqueous layers were extracted with DCM (x3) and concentrated under reduced pressure to 1-2 mL of volume. NaI (5 mmol) was added to the DCM solution and the mixture was stirred at room temperature for 24 h. Then, the mixture was added to a vigorously stirred solution of hexane, obtaining a precipitate which was filtered and washed with hexane to afford complex **12** (122 mg, 20% yield). Brown solid; R_f = 0.57 (ethyl acetate/methanol 2/1); m.p. 140 °C (decompose); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.00-7.95 (m, 4H, ArH), 7.65-7.55 (m, 10H, ArH), 7.45-7.35 (m, 6H, ArH), 5.90 (s, 4H, 2xCH_2Ph), 4.04 (s, 6H, 2xNCH_3) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ = 142.9, 133.8, 129.9 (2C), 129.7, 129.6 (2C), 129.3, 128.5 (2C), 128.4 (2C), 127.0, 58.7, 38.2 (C_{trz}-Pd not observerd) ppm; IR (ATR) ν = 3028, 1323, 1078, 771 cm^{-1}.

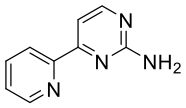
3.2 Bipyridine palladium catalyst preparation



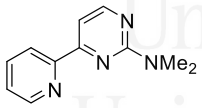
(*E*)-3-(dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one (23):[235] 1-acetylpyride **22** (1.70 mL, 15 mmol) and 1,1-dimethoxy-*N,N*-dimethylmethanamide (2.0 mL, 15 mmol) were heated under reflux for 6 h. After the reaction mixture was cooled down to room temperature, the precipitated was filtered off, washed with hexane and a mixture of hexane:Et_2O (2:1) and dried under vacuum. Dark green solid (2.20 g, 83% yield); R_f = 0.2 (AcOEt); m.p. 116.0-120.7 ºC; t_r = 13.70 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.66 (d, *J* = 4.8 Hz, 1H, ArH), 8.19 (d, *J* = 7.9 Hz, 1H, ArH), 7.95 (d, *J* = 12.6 Hz, 1H, CH=C*H*-N), 7.90-7.85 (m, 1H, ArH), 7.45-7.40 (m, 1H, ArH), 6.51 (d, *J* = 12.6 Hz, 1H, C*H*=CH-N), 3.20 (s, 3H, N-CH_3), 3.03 (s, 3H, N-CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.7, 156.1, 154.8, 148.2, 136.8, 125.4, 122.0, 91.0, 45.2, 37.4 ppm; IR

[235] Kerner, C.; Straub, S.-D.; Sun, Y.; Thiel, W. R. *Eur. J. Org. Chem.* **2016**, 3060-3064.

(ATR) ν = 2922, 2822, 1723, 1697, 1635, 1564, 1531, 901, 771, 749 cm^{-1}; MS (EI) *m/z* (%): 176 (M^+, 11%), 161 (18), 133 (75), 98 (100), 78 (31), 70 (14), 55 (38).



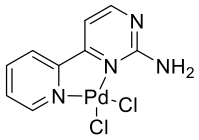
4-(pyridin-2-yl)pyrimidin-2-amine (24a):[236] 0.25 g of sodium were dissolved in 10 mL of ethanol under argon atmosphere. Then, a solution of the guanidine hydrochloride (6.28 mmol) in 10 mL of ethanol was added to **23** (5.0 mmol) in 10 mL of ethanol (79 ºC) and the mixture was stirred for 20 minutes. After this, sodium solution was added under argon atmosphere and it was refluxed 16 h. The solvent was removed under vacuum and the residue was dissolved in NaOH 2M. The product was extracted with AcOEt (3 x 5 mL). The organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure to obtain compound **24a** (0.65 g, 76% yield). Light yellow solid ; R_f = 0.4 (AcOEt); m.p. 128.8-130.0 ºC; t_r = 12.79 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.71 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, ArH), 8.44 (d, *J* = 5.2 Hz, 1H, ArH), 8.34 (d, *J* = 7.9 Hz, 1H, ArH), 7.83 (td, *J* = 7.9, 1.8 Hz, 1H, ArH), 7.66 (d, *J* = 5.2 Hz, 1H, ArH), 7.39 (ddd, *J* = 7.9, 4.8, 1.2 Hz, 1H, ArH), 5.38 (s, 2H, NH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.3, 157.8, 154.0, 149.7, 137.2, 125.6, 121.9, 108.2 ppm; IR (ATR) ν = 3473, 3301, 3138, 3059, 1565, 1543, 1463, 780 cm^{-1}; MS (EI) *m/z* (%): 172 (M^+, 100%), 145 (9), 131 (10), 103 (12), 79 (13).



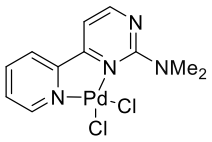
***N*,*N*-Dimethyl-4-(pyridin-2-yl)pyrimidin-2-amine (24b):**[235] 0.25 g of sodium were dissolved in 10 mL of ethanol under argon atmosphere. Then, a solution of *N*,*N*-dimethylguanidine sulfate (6.28 mmol) in 10 mL of ethanol was added to **23** (5.0 mmol) in 10 mL of ethanol (79 ºC) and the mixture was stirred for 20 minutes. After this, sodium solution was added under argon atmosphere and it was refluxed for 16 h. The solvent was removed under vacuum and the residue was dissolved in NaOH 2M. The product was extracted with AcOEt (3 x 5 mL). The organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure to obtain compound **24b** (0.80 g, 80% yield). Light yellow solid; R_f = 0.4 (hexane/AcOEt 6/4); t_r = 14.88 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.70-8.65 (m, 1H, ArH), 8.48 (d, *J* = 5.0 Hz, 1H, ArH), 8.39 (d, *J* = 7.8 Hz, 1H, ArH), 7.95 (td, *J* = 7.8, 1.8 Hz, 1H, ArH), 7.50 (ddd, *J* = 7.8, 4.7, 1.2

[236] Bejan, E.; Haddou, H. A.; Daran, J. C.; Balavoine, G. G. A. *Synthesis* **1996**, 1012-1018.

Hz, 1H, ArH), 7.47 (d, *J* = 5.0 Hz, 1H, ArH), 3.18 (s, 6H, $N(CH_3)_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ = 162.3, 161.9, 159.0, 154.1, 149.3, 137.3, 125.4, 120.9, 104.7, 36.6 ppm; IR (ATR) ν = 1559, 1546, 1403, 1348, 990, 781 cm^{-1}; MS (EI) *m/z* (%): 200 (M^+, 100%), 185 (59), 172 (12), 171 (83), 158 (13), 157, (26), 156 (38), 130 (21), 100 (10), 79 (15), 78 (13).



4-(pyridin-2-yl)pyrimidin-2-aminepaladium(II) chloride (25a):[237] $PdCl_2$ (0.23 g, 1.3 mmol) and ligand **24a** (1.3 mmol) were added to 20 mL of methanol and this mixture was stirred overnight at room temperature. Then, the precipitated was filtered off and dried under vacuum to obtain **25a** (0.28 g, 61% yield). Light brown solid; m.p. (decomposition) 335 ºC; ^1H NMR (300 MHz, DMSO-d_6) δ = 9.18 (s, 1H), 9.00 (s, 1H), 8.69 (d, *J* = 4.6 Hz, 1H), 8.55 (d, *J* = 8.1 Hz, 1H), 8.32 (t, *J* = 7.9 Hz, 2H), 7.81 (t, *J* = 6.5 Hz, 1H), 7.64 (d, *J* = 5.0 Hz, 1H) ppm; IR (ATR) ν = 3268, 3128, 3105, 1592, 1565, 771 cm^{-1}; MS (EI) *m/z* (%): 665 (M_2^+-Cl); Anal. Calcd for $C_9H_8Cl_2N_4Pd$ (%): C 30.93, H 2.31, N 16.03; found C 30.32, H 2.12, N 16.44.



***N*,*N*-Dimethyl-4-(pyridin-2-yl)pyrimidin-2-aminepaladium(II) chloride (25b):**[237] $PdCl_2$ (0.23 g, 1.3 mmol) and ligand **24b** (1.3 mmol) were added to 20 mL of methanol and this mixture was stirred overnight at room temperature. Then, the precipitated was filtered off and dried under vacuum to obtain **25b** (0.36 g, 73% yield). Orange solid; ^1H NMR (300 MHz, DMSO-d_6) δ = 8.73 (dd, *J* = 4.8, 1.8 Hz, 1H, ArH), 8.51 (d, *J* = 5.1 Hz, 1H, ArH), 8.44 (d, *J* = 7.9 Hz, 1H, ArH), 8.04 (td, *J* = 7.9, 1.8 Hz, 1H, ArH), 7.59 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H, ArH), 7.51 (d, *J* = 5.1 Hz, 1H, ArH), 3.23 (s, 6H, $N(CH_3)_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ = 158.3, 153.4, 151.0, 149.2, 138.0, 125.9, 123.3, 121.3, 104.7, 37.3, 36.8 ppm; IR (ATR) ν = 1596, 1359, 1221, 988, 760 cm^{-1}; MS (EI) *m/z* (%): 721 (M_2^+-Cl), 684 (M_2^+-2Cl); Anal. Calcd for $C_{11}H_{12}Cl_2N_4Pd$ (%): C 34.99, H 3.20, N 14.84; found C 34.41, H 2.99, N 14.74.

[237] Jadhav, B. D.; Pardeshi, S. K. *Appl. Organometal. Chem.* **2017**, *31*, e3591.

3.3 General procedure for cross-coupling reactions

3.3.1 Suzuki-Miyaura and Hiyama cross-coupling reactions

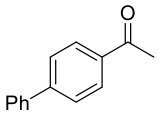
Suzuki-Miyaura cross-coupling reaction using palladium mesoionic carbene catalyst: To a solution of aryl halide (0.2 mmol), potassium carbonate (0.30 mmol), catalyst **12** (0.5 mol%) in 2 mL of DES and H_2O (36 µL, 10 equiv.), 0.21 mmol of boronic acid was added and the resulting mixture was stirred at 25 °C for 3 h. 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.

Hiyama cross-coupling reaction using palladium mesoionic carbene catalyst: To a solution of aryl bromide (0.5 mmol), sodium bicarbonate (0.75 mmol), catalyst **12** (1 mol%) in 1 mL of DES, 0.75 mmol of organosilane was added and the resulting mixture was stirred at 100 °C for 24 h. 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.

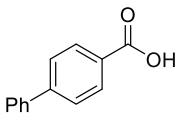
Suzuki-Miyaura cross-coupling reaction using bipyridine palladium catalyst: To a solution of aryl halide (0.5 mmol), potassium carbonate (0.75 mmol), catalyst **25a** (1 mol%) in 2 mL of DES, 0.55 mmol of boronic acid was added and the resulting mixture was stirred at 100 °C for 4 h. The mixture was 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.

Hiyama cross-coupling reaction using bipyridine palladium catalyst: To a solution of aryl halide (0.5 mmol), sodium bicarbonate (1 mmol), catalyst **25a** (1 mol%) in 1 mL of DES, 0.75 mmol of organosilane was added and the resulting mixture was stirred at 100 °C for 16 h. 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

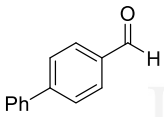
remove the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products.



1-([1,1'-biphenyl]-4-yl)ethanone (15a):[125] White solid; R_f = 0.33 (hexane/ethyl acetate 4/1); m.p. 109-113°C; t_r =15.53 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.05-8.00 (m, 2H, ArH), 7.70-7.60 (m, 4H, ArH), 7.50-7.40 (m, 3H, ArH), 2.64 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.9, 145.9, 140.0, 135.9, 129.1 (2C), 129.0 (2C), 128.3 (2C), 127.4 (2C), 127.3, 26.8 ppm; IR (ATR) ν = 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).



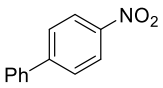
1-([1,1'-biphenyl]-4-carboxylic acid (15b):[238] White solid; R_f = 0.47 (hexane/ethyl acetate 1/1); m.p. 225-227 °C; t_r = 15.65; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.96 (s, 1H, CO_2H), 8.10-7.95 (m, 2H, ArH), 7.85-7.80 (m, 2H, ArH), 7.80-7.70 (m, 2H, ArH), 7.55-7.45 (m, 2H, ArH), 7.45-7.40 (m, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.1, 144.3, 139.0, 129.9 (2C), 129.6, 129.0 (2C), 128.2, 126.9 (2C), 126.8 (2C); IR (ATR) ν = 3346, 2918, 1675, 1607, 1287 cm^{-1}; MS (EI) *m/z* (%): 198 (M^+, 19), 190 (84), 177 (48), 152 (14), 96 (100), 78 (55).



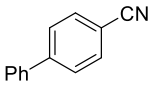
1-([1,1'-biphenyl]-4-carbaldehyde (15c):[239] White solid; R_f = 0.47 (hexane/ethyl acetate 4/1); m.p. 59-61 °C; t_r = 14.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.06 (s, 1H, CHO), 7.95 (d, J = 8.2 Hz, 2H, ArH), 7.75 (d, J = 8.2 Hz, 2H, ArH), 7.70-7.60 (m, 2H, ArH), 7.55-7.40 (m, 3H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.0, 147.2, 139.8, 135.3, 130.3 (2C), 129.1 (2C), 128.6, 127.8 (2C), 127.4 (2C); IR (ATR) ν = 2839, 2743, 1696, 1601 cm^{-1}; MS (EI) *m/z* (%): 183 (M^+ + 1, 13), 182 (M^+, 99), 181 (100), 153 (33), 152 (59), 151 (17), 76 (13).

[238] Bunda, S.; Udvardy, A.; Voronova, K.; Joó, F. *J. Org. Chem.* **2018**, *83*, 15486-15492.

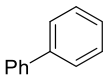
[239] Karimi, B.; Tavakolian, M.; Mansouri, F.; Vali, H. *ACS Sustainable Chem. Eng.* **2018**, *7*, 3811-3823.



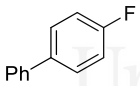
4-Nitro-1,1'-biphenyl (15d):[125] Yellow solid; R_f = 0.17 (hexane); m.p. 98-100 °C; t_r =15.81 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.35-8.25 (m, 2H, ArH), 7.75-7.70 (m, 2H, ArH), 7.65-7.60 (m, 2H, ArH), 7.55-7.45 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.8, 147.2, 138.9, 129.3 (2C), 129.1, 127.9 (2C), 127.5 (2C), 124.3 (2C) ppm; IR (ATR) ν = 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).



[1,1'-biphenyl]-4-carbonitrile (15e):[240] White solid; R_f = 0.53 (hexane/ethyl acetate 4/1); m.p. 69-71 °C; t_r = 14.46; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75-7.65 (m, 4H, ArH), 7.60-7.55 (m, 2H, ArH), 7.50-7.40 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.8, 139.3, 132.7 (2C), 129.3 (2C), 128.8, 127.9 (2C), 127.4 (2C), 119.1, 111.1; IR (ATR) ν = 2921, 2851, 2224, 1482 cm^{-1}; MS (EI) *m/z* (%): 180 (M^++1, 32), 179 (M^+, 100), 178 (53), 177 (19), 152 (14), 151 (25).



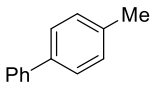
1,1'-Biphenyl (15f):[125] White solid; R_f = 0.57 (hexane); m.p. 68-70 °C; t_r =11.52 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.0-7.55 (m, 4H), 7.50-7.40 (m, 4H), 7.35-7.30 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.4 (2C), 128.9 (4C), 127.4 (2C), 127.3 (4C) ppm; IR (ATR) ν = 3033, 1477, 725 cm^{-1}; MS (EI) *m/z* (%): 155 (M^++1, 14%), 154 (M^+, 100), 153 (40), 152 (26), 76 (13).



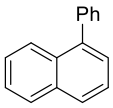
4-Fluoro-1,1'-biphenyl (15g):[241] White solid; R_f = 0.47 (hexane); m.p. 71-73 °C; t_r =11.48 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.60-7.50 (m, 4H), 7.45-7.40 (m, 2H), 7.35-7.30 (m, 1H), 7.15-7.10 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.6 (d, *J* = 243.8 Hz), 140.4, 137.5 (d, *J* = 3.3 Hz), 128.9 (2C), 128.8 (d, *J* = 8.3 Hz, 2C), 127.4, 127.2 (2C), 115.7 (d, *J* = 21.0 Hz, 2C) ppm; IR (ATR) ν = 3062, 1231, 756 cm^{-1}; MS (EI) *m/z* (%): 172 (M^+, 100%), 171 (M^+-1, 35), 170 (25).

[240] Stevens, P. D.; Fan, J.; Gardimalla, H. M.; Yen, M.; Gao, Y. *Org. Lett.* **2005**, *7*, 2085-2088.

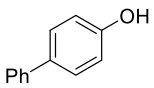
[241] Iranpoor, N.; Rahimi, S.; Panahi, F. *RSC Adv.* **2016**, *6*, 3084-3090.



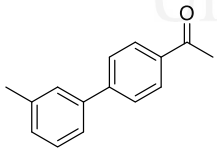
4-Methyl-1,1'-biphenyl (15h):[242] White solid; R_f = 0.47 (hexane); m.p. 43-45 °C; t_r =12.65 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.60-7.55 (m, 2H, ArH), 7.50-7.45 (m, 2H, ArH), 7.40-7.35 (m, 2H, ArH), 7.30-7.25 (m, 1H, ArH), 7.25-7.20 (m, 2H, ArH), 2.38 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.3, 138.5, 137.2, 129.6 (2C), 128.8 (2C), 127.1 (5C) ppm, 21.2 ppm; IR (ATR) ν = 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).



1-Phenylnaphtalene (15i):[243] White solid; R_f = 0.77 (hexane/ethyl acetate 4/1); m.p. 43-45 °C; t_r = 17.86; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.00-7.85 (m, 3H, ArH), 7.60-7.45 (m, 9H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.9, 140.4, 133.9, 131.8, 130.2, 128.4, 127.8, 127.4, 127.1, 126.2, 125.9, 125.5 ppm; IR (ATR) ν = 3055, 1395, 776 cm^{-1}; MS (EI) *m/z* (%): 169 (M^+ + 1, 13), 168 (M^+, 100), 167 (66), 165 (25), 153 (15), 152 (20).



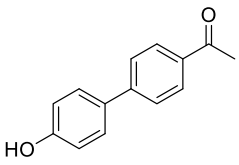
4-Phenylphenol (15j):[244] White solid; R_f = 0.40 (hexane/ethyl acetate 4/1); m.p. 160.0-161.1 °C; t_r =14.60 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55-7.50 (m, 2H, ArH), 7.50-7.45 (m, 2H, ArH), 7.45-7.40 (m, 2H, ArH), 7.35-7.30 (m, 1H, ArH), 6.95-6.85 (m, 2H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.2, 140.9, 134.2, 128.9, 128.5, 126.8 (2C), 115.8 ppm; IR (ATR) ν = 3415, 3062, 3038, 2925, 2851, 1595, 1520, 1484, 1458, 1423, 1373, 1235, 1198, 1112, 831, 756, 684 cm^{-1}; MS (EI) *m/z* (%): 170 (M^+, 100%), 141 (18), 115 (13).



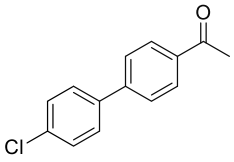
1-(3'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one (15k):[245] White solid; R_f = 0.5 (hexane/ethyl acetate 4/1); m.p. 89.0-90.3 ºC; t_r = 15.72 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.10-7.90 (m, 2H, ArH), 7.70-7.60 (m, 2H, ArH), 7.43 (d, *J* = 7.3 Hz, 2H, ArH), 7.40-7.30 (m, 1H, ArH), 7.23 (dd, *J* = 7.7, 7.1 Hz, 1H, ArH), 2.64 (s, 3H, $COCH_3$), 2.44 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (101

[242] Pradhan, S.; John, R. P. *RSC Adv.* **2016**, *6*, 12453-12460.
[243] Zhang, Z.; Wang, Z. *J. Org. Chem.* **2006**, *71*, 7485-7487.
[244] Bai, L.; Wang, J.-X. *Adv. Synth. Catal.* **2008**, *350*, 315-320.
[245] Li, Q.; Zhang, L.-M.; Bao, J.-J.; Li, H.-X.; Xie, J.-B.; Lang, J.-P. *Appl. Organometal. Chem.* **2014**, *28*, 861-867.

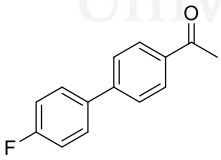
MHz, $CDCl_3$) δ = 197.9, 146.1, 139.9, 138.7, 135.9, 129.1 (2C), 128.2, 127.4 (2C), 124.5, 26.8, 21.7 ppm; IR (ATR) ν = 2921, 2852, 1685, 1598, 1170 cm^{-1}; MS (EI) *m/z* (%): 210 (M^+, 48%), 195 (100), 152 (29).



1-(4'-hydroxy-[1,1'-biphenyl]-4-yl)ethan-1-one (15l):[246] White solid; R_f = 0.2 (hexane/ethyl acetate 2/1); m.p. 195.0-198.1 ºC; t_r = 17.32 min; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.10-7.95 (m, 2H, ArH), 7.70-7.60 (m, 2H, ArH), 7.60-7.50 (m, 2H, ArH), 6.70-6.85 (m, 2H, ArH), 6.80-6.60 (m, 1H, -OH), 2.65 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (101 MHz, MeOD-d_4) δ = 200.0, 159.1, 147.1, 136.0, 131.9, 129.9 (2C), 129.2 (2C), 127.2 (2C), 116.7, (2C), 26.5 ppm; IR (ATR) ν = 3286, 2922, 2854, 1653, 1598, 1583, 1295, 1268, 1198, 955, 819 cm^{-1}; MS (EI) *m/z* (%): 212 (M^+, 63%), 197 (100), 169 (11), 139 (15), 115 (12), 99 (4), 84 (7).



1-(4'-chloro-[1,1'-biphenyl]-4-yl)ethan-1-one (15m):[247] White solid; R_f = 0.43 (hexane/ethyl acetate 4/1); m.p. 97-98 ºC; t_r = 15.95; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.05-8.00 (m, 2H), 7.65-7.60 (m, 2H, ArH), 7.55-7.50 (m, 2H, ArH), 7.45-7.35 (m, 2H, ArH), 2.62 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.6, 144.5, 138.4, 136.2, 134.5, 129.2 (2C), 129.1 (2C), 128.6 (2C), 127.1 (2C), 26.7 ppm; IR (ATR) ν = 1671, 1416, 1266 cm^{-1}; MS (EI) *m/z* (%): 232 (M^+Cl^{37}, 17), 230 (M^+Cl^{35}, 50), 217 (33), 216 (15), 215 (100), 152 (62), 151 (14), 76 (12).



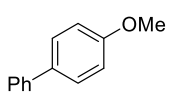
1-(4'-fluoro-[1,1'-biphenyl]-4-yl)ethan-1-one (15n):[248] Light brown solid (55.8 mg, 57% yield); R_f = 0.5 (hexane/ethyl acetate 4/1); m.p 95.6-97.0 ºC; t_r = 14.94 min; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.05-8.00 (m, 2H, ArH), 7.70-7.60 (m, 2H, ArH), 7.60-7.55 (m, 2H, ArH), 7.20-7.10 (m, 2H, ArH), 2.63 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.8, 163.1 (d, *J* = 248.2 Hz) 144.8, 136.1 (d, *J* = 3.2 Hz), 136.0, 129.0 (d, *J* = 9.3 Hz), 127.2, 116.0 (d,

[246] Monguchi, Y.; Fujita, Y.; Hashimoto, S.; Ina, M.; Takahashi, T.; Ito, R.; Nozaki, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* **2011**, *67*, 8628-8634.

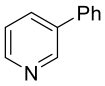
[247] Kylmälä, T.; Kuuloja, N.; Xu, Y.; Rissanen, K.; Franzén, R. *Eur. J. Org. Chem.* **2008**, 4019-4024.

[248] Kienle, M.; Knochel, P. *Org. Lett.* **2010**, *12*, 2702-2705.

J = 21.8 Hz), 26.8 ppm; IR (ATR) ν = 2923, 2855, 1681, 1599, 1528, 1494, 1360, 1251, 1195, 1161, 960, 818 cm^{-1}; MS (EI) *m/z* (%): 214 (M^+, 53%), 199 (100), 170 (48), 151 (5), 85 (9).



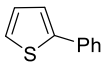
4-Methoxy-1,1'-biphenyl (15o):[125] White solid; R_f = 0.57 (hexane/ethyl acetate 9:1); m.p. 76-78 °C; t_r =14.13 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55-7.50 (m, 4H, ArH), 7.41 (t, *J*= 7.5 Hz, 2H, ArH), 7.30-7.25 (m, 1H, ArH), 6.98 (d, *J*= 8.8 Hz, 2H, ArH), 3.85 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3, 141.0, 133.9, 128.9 (2C), 128.3 (2C), 126.9 (2C), 126.8, 114.3 (2C), 55.5 ppm; IR (ATR) ν = 3070, 1604, 1523, 1271, 756 cm^{-1}; MS (EI) *m/z* (%):185 (M^+ +1, 14%), 184 (M^+, 100), 169 (44), 141 (39), 115 (25).



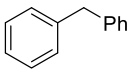
3-Phenylpyridine (15p):[249] Yellow oil; R_f = 0.23 (hexane/ethyl acetate 7:3); t_r =12.35 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.85 (d, *J* = 1.7 Hz, 1H), 8.59 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.89 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.65-7.55 (m, 2H), 7.50-7.45 (m, 2H), 7.45-7.35 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.2, 148.1, 137.8, 136.9, 134.7, 129.2 (2C), 128.3, 127.3 (2C), 123.8 ppm; IR (ATR) ν = 3029, 1473, 710 cm^{-1}; MS (EI) *m/z* (%): 155 (M^+, 100%), 154 (M^+-1, 52), 127 (13).

3-Phenylfuran (15q):[250] White solid; R_f = 0.33 (hexane); m.p. 53.2-54.3 °C; t_r =9.95 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75-7.70 (m, 1H, O-C*H*=C), 7.49 (dt, *J* = 7.3, 1.6 Hz, 3H, ArH), 7.40-7.35 (m, 2H, ArH), 7.30-7.20 (m, 1H, HC=C*H*-O) 6.71 (dd, *J* = 1.9, 0.9 Hz, 1H, *H*C=CH-O) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.8, 138.6, 132.6, 128.9 (2C), 127.1, 126.6, 126.0 (2C), 109.0 ppm; IR (ATR) ν = 3127, 3030, 2924, 1605, 1510, 1451, 1367, 1162, 1054, 1017, 870, 751, 690 cm^{-1}; MS (EI) *m/z* (%): 145 (M^+ +1, 11%), 144 (M^+, 100), 115 (84).

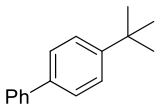
[249] Ilie, A.; Roiban, G. D.; Reetz, M. T. *ChemistrySelect* **2017**, *2*, 1392-1397.
[250] Kumar Manian, R.; Park, K.; Lee, S. *Adv. Synth. Catal.* **2010**, *352*, 3255-3266.



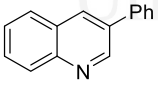
2-Phenylthiophene (15r):[251] White solid; R_f = 0.4 (hexane); m.p. 30.0-32.0 ºC; t_r = 11.70 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.60 (m, 2H, ArH), 7.50-7.30 (m, 2H, ArH), 7.30-7.10 (m, 3H, ArH), 7.08 (dd, J = 5.1, 3.6 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.6, 134.5, 129.0, 128.1, 127.6, 126.1, 124.9, 123.2 ppm; IR (ATR) ν = 2922, 2850, 1730, 1664, 1596, 1484, 1446, 1210, 1076, 850, 826, 690 cm^{-1}; MS (EI) *m/z* (%): 160 (M^+, 100%), 128 (8), 115 (25).



Diphenylmethane (15s):[252] Colorless oil; R_f = 0.60 (hexane); t_r =12.04 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30-7.25 (m, 4H, ArH), 7.20-7.15 (m, 6H, ArH), 3.97 (s, 2H, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.2, 129.1 (2C), 128.6 (2C), 126.2, 42.1 ppm; IR (ATR) ν = 3083, 3061, 3026, 2905, 2841, 1600, 1492, 1450, 1076, 1029, 729, 694 cm^{-1}; MS (EI) *m/z* (%): 169 (M^+ +1, 13%), 168 (M^+, 100), 167 (100), 166 (12), 165 (38), 153 (20), 152 (21), 91 (15).



4-*Tert*-butyl-1,1'-biphenyl (15t):[253] White solid; R_f = 0.5 (hexane); m. p 50.0-51.2 ºC; t_r = 14.28 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.60-7.50 (m, 3H, ArH), 7.55-7.45 (m, 3H, ArH), 7.45-7.40 (m, 2H, ArH), 7.40-7.30 (m, 1H, ArH), 1.37 (s, 9H, *tert*-butyl) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 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) ppm; IR (ATR) ν = 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-Phenylquinoline (15u):[254] Yellow oil; R_f = 0.5 (hexane/ethyl acetate 2/1); t_r = 16.38 min**;** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.18 (d, J = 2.1 Hz, 1H, ArH), 8.28 (s, 1H, ArH), 8.15 (d, J = 8.1 Hz, 1H, ArH), 7.86 (d, J = 8.1 Hz, 1H, ArH), 7.72 (dd, J = 11.9, 4.6 Hz, 3H, ArH), 7.60-7.45 (m, 3H, ArH), 7.50-7.35 (m, 1H, ArH)

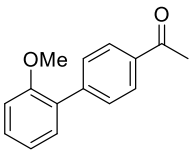
[251] Lois, S.; Florès, J.-C.; Lère-Porte, J.-P.; Serein-Spirau, F.; Moreau, J. J. E.; Miqueu, K.; Sotiropoulos, J.-M.; Baylère, P.; Tillard, M.; Belin, C. *Eur. J. Org. Chem.* **2007**, 4019-4031.

[252] Pena-López, M.; Ayan-Varela, M.; Sarandeses, L. A.; Pérez Sestelo, J. *Chem. Eur. J.* **2010**, *16*, 9905-9909.

[253] Li, H.; Sun, C.-L.; Yu, M.; Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Chem. Eur. J.* **2011**, *17*, 3593-3597.

[254] Hogan, A.-M. L.; O'Shea, D. F. *Org. Lett.* **2006**, *8*, 3769-3772.

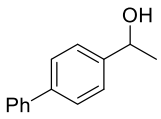
ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.9, 147.2, 137.9, 133.9, 133.4, 129.5, 129.3, 129.2 (2C), 128.2, 128.1, 127.5 (2C), 127.1 ppm; IR (ATR) ν = 3062, 2985, 2937, 2892, 1496, 1450, 1418, 1343, 1127, 1022, 955, 907 cm^{-1}; MS (EI) *m/z* (%): 205 (M^+, 100%), 176 (10), 151 (4), 102 (5), 76 (7).



1-(2'-methoxy-[1,1'-biphenyl]-4-yl)ethan-1-one (15v):[255] White solid; R_f = 0.3 (Hxane/AcOEt 4/1); m.p. 96.0-97.0 ºC; t_r = 16.14 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06-7.94 (m, 2H, ArH), 7.70-7.55 (m, 2H, ArH), 7.40-7.30 (m, 2H, ArH), 7.04 (m, 2H, ArH), 3.83 (s, 3H, -OCH_3), 2.64 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.1 156.6, 143.7, 135.6, 130.8, 129.8, 129.6 (2C), 128.1(2C), 121.1, 111.4, 55.7, 26.8 ppm; IR (ATR) ν = 2951, 2922, 1670, 1601, 1483, 1458, 1267, 1236 cm^{-1}; MS (EI) *m/z* (%): 226 (M^+, 60%), 211 (100), 168 (38), 139 (16), 106 (6).

3.3.2 Organometallic addition to carbonyl compounds

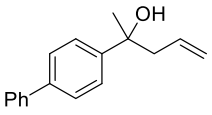
General procedure: To a vigorously stirred solution of product **15a** or **15c** (0.2 mmol) in 0.3 mL of ChCl:ethylene glycol (1:2) at 0 ºC, 0.5 mmol of the corresponding organometallic reagent **16** was added. After that, the solution was stirred at room temperature for 30 min. The mixture was quenched 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 **17**.



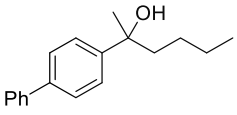
1-([1,1'-biphenyl]-4-yl)ethan-1-ol (17a):[256] White solid; R_f = 0.30 (hexane/ethyl acetate 4/1); m.p. 57-59 °C; t_r = 15.02; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.55 (m, 4H, ArH), 7.50-7.40 (m, 4H, ArH), 7.36 (ddd, *J* = 6.1, 3.8, 1.3 Hz, 1H, ArH), 4.96 (q, *J* = 6.4 Hz, 1H, CH_3CHOH), 2.11 (br s, 1H, CH_3CHOH), 1.55 (d, *J* = 6.4 Hz, 3H, CH_3CHOH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.9, 141.0, 140.5, 128.9 (2C), 127.4 (3C), 127.2 (2C), 126.0 (2C), 70.3, 25.2 ppm; IR (ATR) ν = 3313,

[255] Zhang, G. *Synthesis* **2005**, 537-542.
[256] Wang, C.; Luo, Q.; Sun, H.; Guo, X.; Xi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 3094-3095.

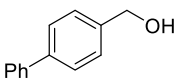
3040, 1343, 1085 cm^{-1}; MS (EI) *m*/*z* (%): 198 (M^+, 7), 183 (11), 181 (23), 180 (100), 179 (21), 178 (27), 165 (14), 155 (11), 152 (16).



2-([1,1'-biphenyl]-4-yl)pent-4-en-2-ol (17b):[257] Yellowish oil; R_f = 0.30 (hexane/ethyl acetate 4/1); t_r = 15.02; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65-7.55 (m, 4H, ArH), 7.55-7.50 (m, 2H, ArH), 7.50-7.40 (m, 2H, ArH), 7.40-7.30 (m, 1H, ArH), 5.68 (dddd, *J* = 16.7, 10.2, 8.3, 6.4 Hz, 1H, CH_2=C*H*), 5.20-5.10 (m, 2H, C*H*$_2$=CH), 2.74 (dd, *J* = 13.7, 6.4 Hz, 1H, C*H*HCH=CH_2), 2.55 (dd, *J* = 13.7, 8.3 Hz, 1H, CH*H*CH=CH_2), 2.09 (br s, 1H, OH), 1.59 (s, 3H, CCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.9, 140.9, 139.6, 133.8, 128.9 (2C), 127.3, 127.2 (2C), 127.0 (2C), 125.4 (2C), 119.8, 73.7, 48.6, 30.1 ppm; IR (ATR) ν = 3443, 2976, 1486, 1006, 998, 915 cm^{-1}; MS (EI) *m*/*z* (%): 220 (M^+-H_2O, 100), 219 (27), 206 (15), 205 (84), 203 (24), 202 (20), 198 (10), 197 (63), 196 (17), 181 (38), 179 (43), 178 (49), 165 (14), 153 (18), 152 (39), 151 (13), 128 (10).



2-([1,1'-biphenyl]-4-yl)hexan-2-ol (17c): Colorless oil; R_f = 0.37 (hexane/ethyl acetate 4/1); t_r = 16.97; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65-7.55 (m, 4H, ArH), 7.55-7.50 (m, 2H, ArH), 7.50-7.40 (m, 2H, ArH), 7.35-7.30 (m, 1H, ArH), 1.90-1.75 (m, 2H, HOCC*H*$_2$), 1.70 (br s, 1H, OH), 1.60 (s, 3H, C*H*$_3$COH), 1.35-1.15 (m, 4H, CH_3C*H*$_2$C*H*$_2$), 0.87 (t, *J* = 5.8 Hz, 3H, C*H*$_3$$CH_2CH_2$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.3, 141.0, 139.5, 128.9 (2C), 127.3, 127.2 (2C), 127.0 (2C), 125.4 (2C), 74.8, 44.1, 30.3, 26.3, 23.2, 14.2 ppm; IR (ATR) ν = 3404, 3028, 2931, 1486, 1006 cm^{-1}; MS (EI) *m*/*z* (%): 254 (M^+, 1), 237 (13), 236 (66), 221 (10), 207 (80), 197 (33), 195 (25), 194 (100), 192 (16), 191 (15), 179 (52), 178 (38), 165 (47); HRMS calcd. for $C_{18}H_{22}O$: 254.1671; found: 254.1678.

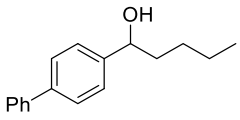


[1,1'-biphenyl]-4-ylmethanol (17d):[258] White solid; R_f = 0.2 (hexane/ethyl acetate 4/1); m. p. 96-98 ºC; t_r = 14.92; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.55 (m, 4H, ArH), 7.50-7.40 (m, 4H, ArH), 7.40-7.30 (m, 1H, ArH), 4.73 (s, 2H,

[257] Li, S.; Wang, J.-X.; Wen, X.; Ma, X. *Tetrahedron* **2011**, *67*, 849-855.

[258] Furuyama, T.; Yonehara, M.; Arimoto, S.; Kobayashi, M.; Matsumoto, Y.; Uchiyama, M. *Chem.Eur. J.* **2008**, *14*, 10348-10356.

C*H*$_2$OH), 1.78 (br s, 1H, CH$_2$O*H*) ppm;^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.0, 140.8, 140.0, 128.9 (2C), 127.6 (2C), 127.5 (3C), 127.2 (2C) ppm; IR (ATR) ν = 3321, 1428, 1038, 751 cm^{-1}; MS (EI) m/z (%): 184 (M$^+$, 88), 183 (37), 182 (97), 181 (100), 167 (19), 165 (24), 155 (60), 154 (60), 153 (51), 152 (85), 151 (24), 77 (20), 76 (17).



1-([1,1'-biphenyl]-4-yl)pentan-1-ol (17e):[259] White solid; R_f = 0.40 (hexane/ethyl acetate 4/1); m.p. 69-71 °C; t_r = 16.96; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.60 (m, 4H, ArH),7.50-7.40 (m, 4H, ArH), 7.40-7.35 (m, 1H, ArH), 4.72 (dd, *J* = 7.2, 6.1 Hz, 1H, C*H*OH), 2.03 (br s, 1H, CHO*H*), 1.95-1.70 (m, 2H, C*H*$_2$CHOH), 1.50-1.25 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$), 0.93 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$CH$_2$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.1, 141.0, 140.5, 128.9 (2C), 127.4, 127.3 (2C), 127.2 (2C), 126.5 (2C), 74.6, 38.9, 28.1, 22.8, 14.2 ppm; IR (ATR) ν = 3290, 2930, 2857, 1406, 1005 cm^{-1}; MS (EI) *m*/*z* (%): 240 (M$^+$, 6), 222 (32), 194 (17), 193 (100), 191 (14), 183 (60), 178 (82), 167 (14), 165 (33), 155 (20), 153 (11), 152 (21), 115 (12).

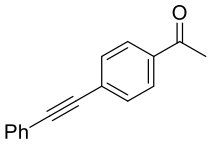
3.3.3 Sonogashira cross-coupling reaction

Sonogashira cross-coupling reaction using palladium mesoionic carbene catalyst: To a solution of aryl iodide (0.2 mmol), iPrNH$_2$ (1 mmol), catalyst **12** (1 mol%) in 0.2 mL of DES, 0.4 mmol of phenylacetylene was added and the resulting mixture was stirred at rt for 2 h. 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.

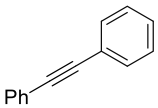
Sonogashira cross-coupling reaction using bipyridine palladium catalyst: To a solution of aryl halide (0.5 mmol), iPr$_2$NH (1 mmol), catalyst **25a** (3 mol%) in 2 mL of DES, 0.60 mmol of phenylacetylene was added and the resulting mixture was stirred at 60 °C for 16 h. The mixture was quenched with 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

[259] Brekan, J. A.; Chernyak, D.; White, K. L.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 1205-1210.

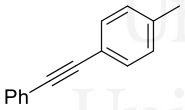
remove the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products.



1-(4-(phenylethynyl)phenyl)ethan-1-one (18a):[261] White solid; R_f = 0.54 (hexane/ethyl acetate 4/1); m.p. 93-95 °C; t_r = 15.26 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.00-7.95 (m, 2H, ArH), 7.65-7.60 (m, 2H, ArH), 7.60-7.55 (m, 2H, ArH), 7.40-7.35 (m, 3H, ArH), 2.64 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.4, 136.3, 131.9, 131.8, 129.0, 128.6, 128.4, 128.3, 122.8, 92.8, 88.7, 26.8 ppm; IR (ATR) ν = 1676, 1600, 1403, 1359, 1261, 955, 831, 7556, 689 cm^{-1}; MS (EI) *m/z* (%): 221 (M^++1, 12%), 220 (M^+, 74%), 206 (18), 205 (100), 177 (13), 176 (49), 151 (15), 150 (11).

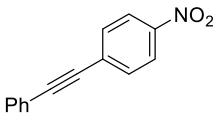


1,2-Diphenylethyne (18b):[260] White solid; R_f = 0.5 (hexane); m.p. 59-61 °C; t_r = 12.43 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55-7.50 (m, 4H, ArH), 7.40-7.30 (m, 6H, ArH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 131.8, 128.5, 128.4, 123.4, 89.5 ppm; IR (ATR) ν = 3063, 2921, 2851, 1950, 1882, 1806, 1758, 1674, 1599, 1492, 1442, 1312, 1280, 1156, 11069, 1025, 916 cm^{-1}; MS (EI) *m/z* (%): 179 (M^+ +1, 15%) 178 (M^+, 100%), 177 (10), 176 (22).

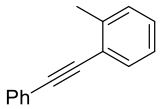


1-Methyl-4-(phenylethynyl)benzene (18c):[261] Yellowish solid; R_f = 0.47 (hexane); m.p. 63-65 °C; t_r = 13.47 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55-7.50 (m, 2H, ArH), 7.45-7.40 (m, 2H, ArH), 7.35-7.30 (m, 3H, ArH), 7.20-7.15 (m, 2H, ArH), 2.37 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.5, 131.7, 131.6, 129.2, 128.4, 128.2, 123.6, 120.3, 89.7, 88.8, 21.6 ppm; IR (ATR) ν = 3029, 2919, 2853, 1593, 1507, 1484, 1439, 1260, 1017, 816, 753, 689 cm^{-1}; MS (EI) *m/z* (%): 193 (M^++1, 21%), 192 (M^+, 100%), 191 (M^+-1, 57%), 190 (14), 189 (30), 165 (14).

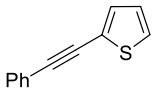
[260] Bong Park, S.; Alper, H. *Chem. Commun.* **2004**, 1306-1307.



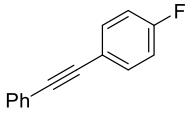
1-Nitro-4-(phenylethynyl)benzene (18d):[261] Yellow solid; R_f = 0.43 (hexane/ethyl acetate 98/2); m.p. 111-113 °C; t_r= 15.71 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25-8.20 (m, 2H, ArH), 7.70-7.65 (m, 2H, ArH), 7.60-7.55 (m, 2H, ArH), 7.45-7.40 (m, 3H, ArH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.1, 132.4, 132.0, 130.4, 129.4, 128.7, 123.8, 122.2, 94.8, 87.7 ppm; IR (ATR) ν = 2213, 1590, 1509, 1344, 1334, 1105, 856, 763, 687 cm^{-1}; MS (EI) *m/z* (%): 224 (M^+ +1, 11%), 223 (M^+, 100%), 193 (23), 177 (18), 176 (63), 165 (24), 150 (11), 88 (12).



1-Methyl-2-(phenylethynyl)benzene (18e):[262] Yellow oil; R_f = 0.37 (hexane); t_r= 14.35 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.60-7.40 (m, 3H, ArH), 7.40-7.30 (m, 3H, ArH), 7.25-7.20 (m, 2H, ArH), 7.20-7.15 (m, 1H, ArH), 2.52 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.3, 132.0, 131.6, 129.6, 128.5, 128.4, 128.3, 125.7, 123.7, 123.2, 93.5, 88.5, 20.9 ppm; IR (ATR) ν = 3020, 2918, 1606, 1566, 1498, 1447, 751, 713, 688 cm^{-1}; MS (EI) *m/z* (%): 193 (M^++1, 15%), 192 (M^+, 100%), 191 (M^+-1, 94%), 190 (18), 189 (34), 165 (20), 115 (10).



2-(Phenylethynyl)thiophene (18f):[263] White solid; R_f = 0.56 (hexane); m.p. 44-46 °C; t_r= 13.95 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55-7.50 (m, 2H, ArH), 7.35-7.30 (m, 3H, ArH), 7.30-7.25 (m, 2H, ArH), 7.00-6.95 (m, 1H, ArH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.0, 131.6, 128.5 (2C), 127.4, 127.2, 123.4, 123.1, 93.2, 82.8 ppm; IR (ATR) ν = 2912, 2853, 1595, 1520, 1484, 1425, 1214, 853, 754, 687 cm^{-1}; MS (EI) *m/z* (%): 185 (M^++1, 12%), 184 (100), 152 (11), 139 (17).



1-Fluoro-4-(phenylethynyl)benzene (18g):[264] White solid; R_f = 0.6 (hexane); m.p. 103-106 °C; t_r= 13.55 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55-7.45 (m, 4H, ArH), 7.40-7.30 (m, 3H, ArH), 7.10-7.00 (m, 2H, ArH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.6 (d, *J* = 249.6 Hz), 161.4, 133.6 (d, *J* = 8.4 Hz),

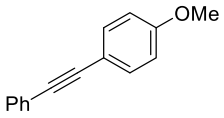
[261] Gholap, A. R.; Venkatesan, K.; Pasricha, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2005**, *70*, 4869-4872.

[262] Kakusawa, N.; Yamaguchi, K.; Kurita, J. *J. Organomet. Chem.* **2005**, *690*, 2956-2966.

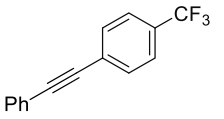
[263] Kim, H.; Lee, P. H. *Adv. Synth. Catal.* **2009**, *351*, 2827-2832.

[264] Döbele, M.; Vanderheiden, S.; Jung, N.; Bräse, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 5986-5988.

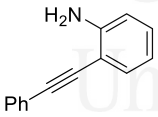
131.7, 128.5 (2C), 123.4, 119.5 (d, *J* = 3.4 Hz), 115.8 (d, *J* = 22.1 Hz), 89.2, 88.4 ppm; IR (ATR) ν = 2926, 2858, 1590, 1214, 1158, 835, 756, 686 cm^{-1}; MS (EI) *m/z* (%): 197 (M^++1, 15%), 196 (M^+, 100%), 194 (14), 175 (10).



1-Methoxy-4-(phenylethynyl)benzene (18h):[260] White solid; R_f = 0.47 (hexane/ethyl acetate 98/2); m.p. 61-62.5 °C; t_r= 17.64 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55-7.45 (m, 4H, ArH), 7.35-7.30 (m, 3H, ArH), 6.85-6.80 (m, 2H, ArH), 3.85 (s, 3H, OCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.7, 133.2, 131.6, 128.4, 128.0, 123.7, 115.5, 114.1, 89.5, 88.2, 55.4 ppm; IR (ATR) ν = 2919, 2852, 2213, 1603, 1594, 1506, 1244, 1024, 835, 753, 688 cm^{-1}; MS (EI) *m/z* (%): 209 (M^++1, 16%), 208 (M^+, 100%), 193 (42), 165 (30), 164 (11).

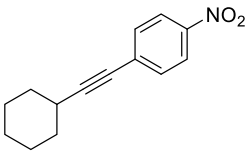


1-(Phenylethynyl)-4-(trifluoromethyl)benzene (18i):[265] White solid; R_f = 0.6 (hexane); m.p. 99-101 °C; t_r= 13.2 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.60 (m, 4H, ArH), 7.55-7.50 (m, 2H, ArH), 7.40-7.35 (m, 3H, ArH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 132.0, 131.9, 130.0 (d, *J* = 32.2 Hz), 129.0, 128.6, 127.3, 125.4 (q, *J* = 3.8 Hz), 124.1 (d, *J* = 272.2 Hz), 122.7, 91.9, 88.1ppm; IR (ATR) ν = 3379, 2980, 2221, 1603, 1323, 1102, 1060, 844, 754, 690 cm^{-1}; MS (EI) *m/z* (%): 247 (M^++1, 17%), 246 (M^+, 100%).



2-(Phenylethynyl)aniline (18j):[266] Brown solid; R_f = 0.43 (hexane/ethyl acetate 4/1); m.p. 83-85 °C; t_r= 16.06 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55–7.50 (m, 2H, ArH), 7.40–7.30 (m, 4H, ArH), 7.20–7.10 (m, 1H, ArH), 6.80–6.70 (m, 2H, ArH), 4.56 (brs, 2H, NH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 132.3, 131.6, 129.8, 128.5, 128.4, 123.3, 118.9, 115.2, 108.9, 95.1, 85.8.ppm; IR (ATR) ν = 3466, 3369, 3049, 3029, 2205, 1611, 1494, 1482, 1453, 1309, 744, 689 cm^{-1}; MS (EI) *m/z* (%): 194 (M^++1, 15%) , 193 (M^+, 100%), 192 (16), 165 (27).

[265] Busacca, C. A.; Farber, E.; DeYoung, J.; Campbell, S.; Gonnella, N. C.; Grinberg, N.; Haddad, N.; Lee, H.; Ma, S.; Reeves, D.; Shen, S.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5594-5597.
[266] Cao, Z.; Bassani, D. M.; Bibal, B. *Chem. Eur. J.* **2018**, *24*, 18779-18787.



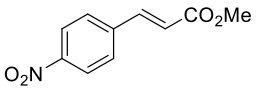
1-(cyclohexylethynyl)-4-nitrobenzene (18k):[267] Orange oil; R_f = 0.40 (hexane); t_r= 16.57 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 9.0 Hz, 2H, ArH), 7.52 (d, *J* = 9.0 Hz, 2H, ArH), 2.70–2.55 (m, 1H, C≡C-C*H*(CH_2)$_2$), 1.95–1.85 (m, 2H, -CH_2-), 1.80–1.70 (m, 2H, -CH_2-), 1.65–1.50 (m, 3H, -CH_2-), 1.45–1.30 (m, 3H, -CH_2-) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.7, 132.4, 131.4, 123.6, 100.8, 79.4, 32.5, 30.0, 26.0, 25.0 ppm; IR (ATR) ν = 2926, 2852, 2228, 1592, 1516, 1447, 1340, 1107, 853, 750 cm^{-1}; MS (EI) *m/z* (%): 229 (M^+, 100%), 214 (13), 213 (19), 212 (43), 201 (28), 188 (13), 187 (31), 186 (31), 183 (45), 182 (67), 175 (13), 173 (13), 170 (13), 168 (24), 167 (31), 165 (11), 155 (28), 154 (64), 153 (47), 152(29), 143 (19), 142 (31), 141 (93), 140 (21), 139 (37), 129 (27), 128 (50), 127 (40), 126 (21), 116 (13), 115 (68), 114 (15), 102 (14), 101 (18), 93 (31), 91 (17), 89 (13), 82 (20), 81 (19), 80 (20), 79 (16), 77 (32), 76 (11), 75 (16), 67 (39), 63 (19), 55 (10), 54 (10), 51 (11).

3.3.3 Heck cross-coupling reactions

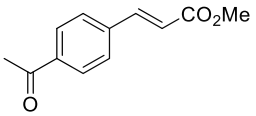
Heck cross-coupling reaction using palladium mesoionic carbene catalyst: To a solution of aryl iodide (0.2 mmol), methyl acrylate (0.25 mmol), NaOAc (0.3 mmol) and catalyst **12** (1 mol%) in 0.2 mL of DES were stirred at 120 ^{o}C for 16 h. The mixture was quenched with water and extracted with EtOAc (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.

Heck cross-coupling reaction using bipyridine palladium catalyst: To a solution of aryl halide (0.5 mmol), sodium acetate (0.75 mmol), catalyst **25a** (1 mol%) in 1 mL of DES, 0.60 mmol of methyl acrylate was added, and the resulting mixture was stirred at 120 °C for 6 h. 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.

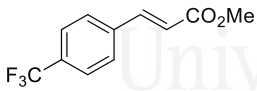
[267] Kim, S.; Rojas-Martin, J.; Toste, F. D. *Chem. Sci.* **2016**, *7*, 85-88.



Methyl (*E*)-3-(4-nitrophenyl)acrylate (20a):[268] Off-white solid, R_f = 0.43 (hexane/ethyl acetate 4/1); m.p. 131-133°C; t_r =13.95 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.30-8.20 (m, 2H, ArH), 7.72 (d, *J* = 16.0 Hz, 1H, *H*C=CH), 7.70-7.65 (m, 2H, ArH), 6.56 (d, *J* = 16.0 Hz, 1H, HC=C*H*), 3.84 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.6, 148.6, 142.0, 140.6, 128.8, 124.3, 122.2, 52.2 ppm; IR (ATR) ν = 2920, 2855, 1719, 1598, 1510, 1339, 1311, 1170, 849 cm^{-1}; MS (EI) *m/z* (%): 207 (M^+, 63%), 206 (18), 186 (14), 177 (25), 176 (100), 146 (24), 130 (35), 118 (23), 102 (23), 91 (10), 89 (15), 76 (20), 63 (10), 50 (14).



Methyl (*E*)-3-(4-acetylphenyl)acrylate (20b):[269] White solid, R_f = 0.25 (hexane/ethyl acetate 4/1); m.p. 104.4-104.7 °C; t_r =15.21 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.00-7.95 (m, 2H, ArH), 7.71 (d, *J* = 16.1 Hz, 1H, *H*C=CH), 7.65-7.60 (m, 2H, ArH), 6.53 (d, *J* = 16.1 Hz, 1H, HC=C*H*), 3.83 (s, 3H, OCH_3), 2.62 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.4, 167.1, 143.4, 138.8, 138.2, 129.0, 128.3, 120.5, 52.1, 26.8 ppm; IR (ATR) ν = 2959, 2922, 2852, 1707, 1680, 1638, 1429, 1325, 1314, 1205, 1172, 988, 824 cm^{-1}; MS (EI) *m/z* (%): 204 (M^+, 31%), 190 (12), 189 (100), 102 (10).

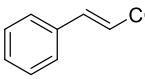


Methyl (*E*)-3-(4-(trifluoromethyl)phenyl)acrylate (20c):[270] White solid, R_f = 0.50 (hexane/ethyl acetate 4/1); m.p. 73.1-73.4 °C; t_r =11.43 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 16.0 Hz, 1H, *H*C=CH), 7.65-7.60 (m, 4H), 6.52 (d, *J* = 16.0 Hz, 1H, HC=C*H*), 3.83 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.0, 143.1, 137.9, 132.4-131.4 (q, *J* = 32.4 Hz), 128.3, 126.1-125.3 (q, *J* = 3.8 Hz), 128.0-119.9 (q, *J* = 271.8 Hz), 120.5, 52.1 ppm; IR (ATR) ν = 2957, 2923, 2850, 1708, 1639, 1316, 1159, 1107, 1064, 834 cm^{-1}; MS (EI) *m/z* (%): 230 (M^+, 39%), 229 (15), 220 (11), 199 (100), 171 (34), 151 (38).

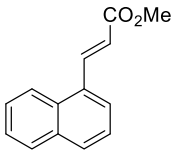
[268] Evangelisti, C.; Panziera, N.; Pertici, P.; Vitulli, G.; Salvadori, P.; Battocchio, C.; Polzonetti, G. *J. Catal.* **2009**, *262*, 287-293.

[269] Bernini, R.; Cacchi, S.; Fabrizi, G.; Forte, G.; Niembro, S.; Petrucci, F.; Pleixats, R.; Prastaro, A.; Sebastián, R. M.; Soler, R.; Tristany, M.; Vallribera, A. *Org. Lett.* **2008**, *10*, 561-564.

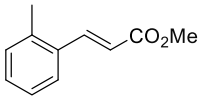
[270] O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6836-6839.



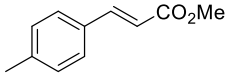
Methyl cinnamate (20d):[271] White solid; R_f = 0.50 (hexane/ethyl acetate 4/1); m.p. 33-35 °C; t_r =11.54 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 16.0 Hz, 1H, *H*C=CH), 7.55-7.50 (m, 2H, ArH), 7.40-7.35 (m, 3H, ArH), 6.45 (d, *J* = 16.0 Hz, 1H, HC=C*H*), 3.81 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.6, 145.0, 134.5, 130.4, 129.0, 128.2, 117.9, 51.8 ppm; IR (ATR) ν = 2944, 1711, 1636, 771 cm^{-1}; MS (EI) *m/z* (%): 162 (M^+, 55%), 161 (M^+-1, 29), 131 (100), 103 (57), 102 (15), 77 (30), 51 (15).



Methyl (*E*)-3-(naphthalen-1-yl)acrylate (20e):[271] Yellowish oil; R_f = 0.46 (hexane/ethyl acetate 4/1); t_r =16.32 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.55 (d, *J* = 15.8 Hz, 1H, *H*C=CH), 8.20 (dd, *J* = 8.2, 1.0 Hz, 1H, ArH), 7.90-7.85 (m, 2H, ArH), 7.75 (d, *J* = 7.2 Hz, 1H, ArH), 7.60-7.45 (m, 3H, ArH), 6.54 (d, *J* = 15.8 Hz, 1H, HC=C*H*), 3.87 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.4, 142.0, 133.8, 131.8, 131.5, 130.6, 128.8, 127.0, 126.3, 125.6, 125.1, 123.5, 120.5, 51.9 ppm; IR (ATR) ν = 2947, 1709, 1630, 1165, 799 cm^{-1}; MS (EI): *m/z* (%): 212 (M^+, 29%), 181 (14), 154 (13), 153 (100), 152 (76), 151 (17), 76 (13).



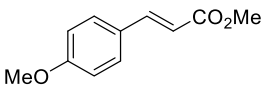
Methyl (*E*)-3-(*o*-tolyl)acrylate (20f):[271] Yellowish oil; R_f = 0.50 (hexane/ethyl acetate 4/1); t_r =12.40 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 15.9 Hz, 1H, *H*C=CH), 7.50-7.45 (m, 1H, ArH), 7.25-7.10 (m, 3H, ArH), 6.29 (d, *J* = 15.9 Hz, 1H, HC=C*H*), 3.73 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.6, 142.7, 137.8, 133.5, 130.9, 130.2, 126.5, 126.5, 119.0, 51.8, 19.9 ppm; IR (ATR) ν = 2948, 1714, 1433, 1168, 761 cm^{-1}; MS (EI): *m/z* (%): 176 (M^+, 34%), 161 (29), 146 (13), 145 (100), 144 (29), 117 (46), 116 (86), 115 (95), 91 (26), 65 (10).



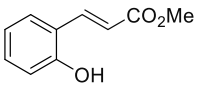
Methyl (*E*)-3-(*p*-tolyl)acrylate (20g):[271] Yellowish oil; R_f = 0.43 (hexane/ethyl acetate 4/1); t_r =12.70 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 16.0 Hz, 1H, *H*C=CH), 7.42 (d, *J* = 8.0 Hz, 2H, ArH), 7.19 (d, *J* = 8.0 Hz, 2H, ArH), 6.40 (d, *J* = 16.0 Hz, 1H, HC=C*H*), 3.80 (s, 1H, OCH_3), 2.37 (s, 1H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.8, 145.0, 140.9, 131.8, 129.8, 128.2,

[271] Yang, L.; Zhang, X.; Mao, P.; Xiao, Y.; Bian, H.; Yuan, J.; Mai, W.; Qu, L. *RSC Adv.* **2015**, *5*, 25723-25729.

116.8, 51.8, 21.6 ppm; IR (ATR) ν = 2945, 1703, 1604, 815 cm^{-1}; MS (EI): *m*/*z* (%): 176 (M^+, 65%), 175 (M^+-1, 15), 146 (11), 145 (100), 117 (28), 116 (16), 115 (51), 91 (18).



Methyl (*E*)-3-(4-methoxyphenyl)acrylate (20h):[271] White solid; R_f = 0.40 (hexane/ethyl acetate 4/1); m.p. 83-84 °C**;** t_r =14.23 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 16.0 Hz, 1H, *H*C=CH), 7.50-7.45 (m, 2H, ArH), 6.95-6.90 (m, 2H, ArH), 6.31 (d, *J* = 16.0 Hz, 1H, HC=C*H*), 3.84 (s, 3H, OCH_3), 3.79 (s, 3H, CO_2CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.9, 161.5, 144.7, 129.9, 127.2, 115.4, 114.5, 55.5, 51.7 ppm; IR (ATR) ν = 2038, 1711, 1600, 819 cm^{-1}; MS (EI): *m*/*z* (%): 192 (M^+, 74%), 162 (11), 161 (100), 134 (13), 133 (28), 118 (12), 90 (11), 89 (16).



Methyl (*E*)-3-(2-hydroxyphenyl)acrylate (20i):[272] White solid; R_f = 0.17 (hexane/ethyl acetate 4/1); m.p. 129.7-130.5 °C; t_r =14.04 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 16.2 Hz, 1H, *H*C=CH), 7.47 (dd, *J* = 7.8, 1.6 Hz, 1H, ArH), 7.30-7.15 (m, 1H, ArH), 7.00-6.80 (m, 2H, ArH), 6.64 (d, *J* = 16.2 Hz, 1H, HC=C*H*), 3.83 (s, 3H, OCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.9, 155.5, 140.9, 131.6, 129.4, 121.8, 120.9, 118.2, 116.6, 52.0 ppm; IR (ATR) ν = 3383, 1688, 1624, 1456, 1325, 1197, 1174, 990, 752 cm^{-1}; MS (EI): *m*/*z* (%): 178 (M^+, 18%), 147 (21), 146 (87), 119 (10), 118 (100), 103 (13), 91 (21), 90 (22), 89 (22), 63 (13).

3.4 General prodecure for recycling experiments

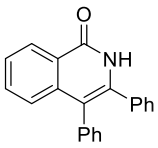
General procedure for recycling experiments: The reaction was performed according to the general procedure. Once the reaction was completed, the reaction mixture was cooled to room temperature, and 2-MeTHF (3 x 3 mL) was added to the reaction vessel. The biphasic mixture was stirred for 5 min, and the upper phase (VOC-phase, mainly unreacted organic reagents and products) was separated by decantation and analyzed by GC using tridecane as the internal standard. The eutectic mixture with the remaining PdNPs (bottom

[272] Kauch, M.; Snieckus, V.; Hoppe, D. *J. Org. Chem.* **2005**, *70*, 7149-7158.

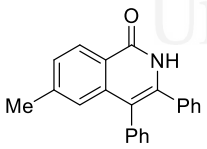
phase) was dried under vacuum and was charged again with fresh reagents and base, repeating the process.

4. RUTHENIUM CATALYZED C-H ACTIVATION

General procedure for the synthesis of isoquinolones: N-methoxybenzamide derivative **26** (0.2 mmol), terminal alkyne **27** (0.24 mmol), NaOAc (20 mol%) and $[RuCl_2(p\text{-cymene})]_2$ (3 mol%) were stirred in 1.0 mL DES at 70 ºC for 16 h. 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 purified by chromatography on silica gel (usually with 1/1 hexane/ethyl acetate elution) or by precipitation with Et_2O.

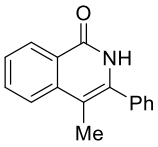


3,4-Diphenylisoquinolin-1(2*H*)-one (28a):[273] White solid, R_f = 0.36 (hexane/ethyl acetate 1/1); m.p. 252.8-255.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.56 (s, 1H, NH), 8.32 (dd, J = 8.0, 1.1 Hz, 1H, ArH), 7.70-7.60 (m, 1H, ArH), 7.60-7.50 (m, 1H, ArH), 7.30-7.20 (m, 8H, ArH), 7.20-7.10 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 161.7, 138.5, 138.1, 135.8, 134.6, 132.5, 131.7, 129.8, 128.2 (2C), 127.7, 127.0, 126.8, 126.2, 125.0, 124.9, 115.5 ppm; IR (ATR) ν = 3155, 3023, 2888, 1643, 1608, 1346, 694 cm^{-1}; MS (EI): m/z (%): 297 (M^+, 100%), 296 (46), 278 (13), 165 (11).

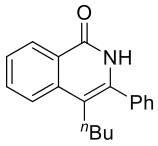


6-Methyl-3,4-diphenylisoquinolin-1(2*H*)-one (28b):[273] White solid, R_f = 0.30 (hexane/ethyl acetate 1/1); m.p. 276.8-279.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.45 (s, 1H, NH), 8.21 (d, J = 8.1 Hz, 1H, ArH), 7.34 (dd, J = 8.1, 1.1 Hz, 1H, ArH), 7.30-7.25 (m, 3H, ArH), 7.25-7.20 (m, 5H, ArH), 7.20-7.10 (m, 2H, ArH), 6.92 (s, 1H, ArH), 2.31 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ = 161.6, 142.5, 138.7, 138.2, 135.9, 134.7, 131.8, 129.8, 128.2, 128.2, 127.8, 127.7, 127.1, 126.9, 124.5, 122.9, 115.3, 21.6 ppm; IR (ATR) ν = 3166, 3023, 2857, 1639, 1619, 1488, 1149, 694 cm^{-1}; MS (EI): m/z (%): 311 (M^+, 100%), 310 (47).

[273] Yang, F.; Ackermann, L. *J. Org. Chem.* **2014**, *79*, 12070-12082.



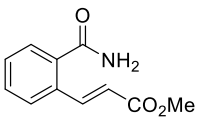
4-Methyl-3-phenylisoquinolin-1(2*H*)-one (28c):[274] White solid, R_f = 0.30 (hexane/ethyl acetate 1/1); m.p. 208.6-210.2 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.26 (s, 1H, NH), 8.35-8.20 (m, 1H, ArH), 7.85-7.70 (m, 2H, ArH), 7.60-7.40 (m, 6H, ArH), 2.05 (s, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 161.4, 138.2, 137.8, 134.8, 132.5, 129.6, 128.6, 128.2, 126.9, 126.1, 125.4, 123.7, 107.1, 13.5 ppm; IR (ATR) ν = 3035, 2915, 1643, 1489. 1350, 1157, 759, 698 cm^{-1}; MS (EI): *m*/*z* (%): 235 (M^+, 100%), 234 (72), 216 (16), 77 (13).



4-Butyl-3-phenylisoquinolin-1(2*H*)-one (28d):[273] White solid, R_f = 0.36 (hexane/ethyl acetate 1/1); m.p. 153.5-154.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.79 (s, 1H, NH), 8.45-8.45 (m, 1H, ArH), 7.85-7.70 (m, 2H, ArH), 7.60-7.40 (m, 6H, ArH), 2.75-2.55 (m, 2H, C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.60-1.50 (m, 2H, CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.35-1.20 (m, 2H, (CH$_2$)$_2$C*H*$_2$CH$_3$), 0.90-0.75 (m, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ = 161.3, 138.2, 137.4, 135.0, 132.5, 129.3, 128.7, 128.3, 127.1, 126.0, 125.8, 123.7, 112.2, 32.2, 26.2, 22.1, 13.5 ppm; IR (ATR) ν = 3162, 2950, 2873, 1643, 1612, 1469, 1157, 760 cm^{-1}; MS (EI): *m*/*z* (%): 277 (M^+, 33%), 236 (19), 235 (100), 216 (17).

General procedure for N-methoxybenzamides olefination: N-methoxybenzamide derivative **26** (0.2 mmol), methyl acrylate (0.24 mmol), NaOAc (20 mol%) and [RuCl$_2$(*p*-cymene)]$_2$ (3 mol%) were stirred in 1.0 mL DES at 70 ^{o}C for 16 h. 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 purified by chromatography on silica gel (usually with 1/1 hexane/ethyl acetate elution).

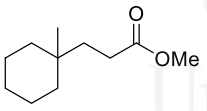
[274] Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548-6551.



Methyl (*E*)-3-(2-carbamoylphenyl)acrylate (29a):[275] White solid, R_f = 0.13 (hexane/ethyl acetate 1/1); m.p. 153.0-155.2 °C; t_r =14.69 min; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ = 8.00-7.95 (m, 2H, *H*C=CHCO$_2$Me + NH), 7.95-7.85 (m, 1H, ArH), 7.70-7.55 (m, 1H, NH), 7.55-7.40 (m, 3H, ArH), 6.59 (d, J = 16.0 Hz, 1H, HC=C*H*CO$_2$Me), 3.72 (s, 1H, CO$_2$CH$_3$) ppm; ^{13}C NMR (101 MHz, DMSO-d$_6$) δ = 170.1, 166.6, 142.3, 138.1, 131.5, 129.9, 129.8, 127.6, 126.8, 119.0, 51.6 ppm; IR (ATR) ν = 378, 3197, 1693, 1654, 1623, 1388, 1299, 1253, 1207, 1033, 979, 759 cm^{-1}; MS (EI): *m*/*z* (%): 205 (M$^+$, 14%), 177 (12), 146 (15), 145 (24), 132 (100), 104 (12).

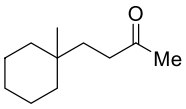
5. IRON CATALYZED RADICAL CONJUGATED ADDITION OF OLEFINS

General procedure for the reductive olefin coupling: To a solution of donor olefin **30** (1.0 equiv.), acceptor olefin **19** (intermolecular reactions only, 3.0 equiv.), and Fe(acac)$_3$ (10 mol%) in DES, PMHS (5.0 equiv.) was added. The resulting mixture was heated to 60 °C with stirring for 2-5 h. Once the reaction was completed, water was added to dissolve the DES phase. That aqueous suspension was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. Products were purified by chromatography on silica gel (hexane/ethyl acetate, typically 9/1).

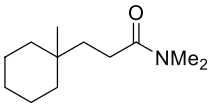


Methyl 3-(1-methylcyclohexyl)propanoate (31a):[276] Colorless oil; t_r = 10.13 min; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 3.67 (s, 3H, OCH$_3$), 2.30-2.20 (m, 2H, CH$_2$CO), 1.60-1.55 (m, 2H, COCH$_2$C*H$_2$*), 1.50-1.40 (m, 5H, CyH), 1.30-1.20 (m, 5H, CyH), 0.85 (s, 3H, CCH$_3$) ppm; ^{13}C NMR (101 MHz, CDCl$_3$) δ = 175.2, 51.6, 37.6, 36.8, 32.4, 28.9, 26.5, 24.6, 22.1 ppm; IR (ATR) ν = 2923, 2854, 1739, 1442, 1164 cm^{-1}; MS (EI): *m*/*z* (%): 184 (M$^+$, 0.6%), 153 (13), 97 (100), 96 (33), 95 (11), 88 (27), 87 (44), 81 (13), 69 (16), 67 (12), 55 (54).

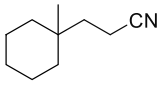
[275] Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736-739.
[276] Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342-15345.



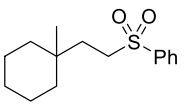
4-(1-methylcyclohexyl)butan-2-one (31b):[276] Colorless oil; t_r = 9.80 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.40-2.30 (m, 2H, $COCH_2$), 2.15 (s, 3H, $COCH_3$), 1.55-1.50 (m, 2H, $COCH_2CH_2$), 1.50-1.35 (m, 5H, CyH), 1.30-1.15 (m, 5H, CyH), 0.84 (s, 3H, CCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.1, 38.5, 37.8, 35.6, 32.3, 30.1, 26.6, 24.7, 22.1 ppm; IR (ATR) ν = 2923, 2854, 1712, 1450, 1361, 1160, 906 cm^{-1}; MS (EI) *m*/*z* (%): 168 (M^+, 1%), 97 (100), 96 (23), 95 (14), 81 (12), 72 (44), 69 (15), 67 (11), 55 (58).



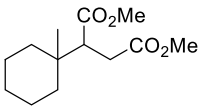
***N*,*N*-Dimethyl-3-(1-methylcyclohexyl)propanamide (31c):**[276] Colorless oil; t_r = 12.84 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.98 (s, 6H, $N(CH_3)_2$), 2.30-2.25 (m, 2H, $COCH_2$), 1.60-1.50 (m, 2H, $COCH_2CH_2$), 1.50-1.40 (m, 5H, CyH), 1.30-1.20 (m, 5H, CyH), 0.87 (s, 3H, CCH_3) ppm;^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.7, 37.7 (2C), 37.2, 32.6, 27.8, 26.6, 24.7, 22.2 ppm; IR (ATR) ν = 2923, 2857, 1639, 1454, 790 cm^{-1}; MS (EI) *m*/*z* (%): 197 (M^+, 1%), 101 (16), 100 (100), 87 (11), 72 (22), 55 (16).



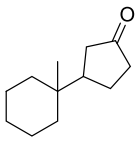
3-(1-methylcyclohexyl)propanenitrile (31d):[276] Colorless oil; t_r = 9.71 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.30-2.20 (m, 2H, CH_2CN), 1.70-1.60 (m, 2H, CH_2CH_2CN), 1.50-1.40 (m, 5H, CyH), 1.35-1.20 (m, 5H, CyH), 0.89 (s, 3H, CCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 120.9, 37.6, 37.3, 32.7, 26.3, 24.2, 21.9, 11.9 ppm; IR (ATR) ν = 2923, 2857, 2244, 1454, 848 cm^{-1}; MS (EI) *m*/*z* (%): 151 (M^+, 0.1%), 97 (100), 96 (14), 55 (44).



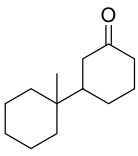
((2-(1-methylcyclohexyl)ethyl)sulfonyl)benzene (31e):[276] Colorless oil; t_r = 15.82 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 7.1 Hz, 2H, ArH), 7.67 (t, *J* = 7.4 Hz, 1H, ArH), 7.58 (t, *J* = 7.4 Hz, 2H, ArH), 3.15-2.95 (m, 2H, SO_2CH_2), 1.70-1.60 (m, 2H, $SO_2CH_2CH_2$), 1.45-1.30 (m, 5H, CyH), 1.30-1.15 (m, 5H, CyH), 0.81 (s, 3H, CCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.4, 133.7, 129.4, 128.2, 52.1, 37.5, 33.8, 32.5, 26.3, 24.6, 21.9 ppm; IR (ATR) ν = 2923, 2857, 1450, 1303, 1145, 1083, 748 cm^{-1}; MS (EI) *m*/*z* (%): 266 (M^+, 27%), 252 (20), 251 (100), 90 (13).



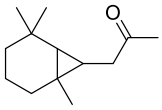
Dimethyl 2-(1-methylcyclohexyl)succinate (31f):[276] Colorless oil; t_r = 12.60 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.69 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2CH_3), 2.85-2.70 (m, 2H, C*H*$_2$$CO_2CH_3$), 2.55-2.40 (m, 1H, C*H*(CH_2)CO_2CH_3), 1.65-1.55 (m, 1H, CyH), 1.55-1.35 (m, 6H, CyH), 1.30-1.20 (m, 3H, CyH), 0.92 (s, 3H, CCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.9, 173.5, 51.9, 51.4, 36.4 (2C), 35.3, 31.8, 26.1, 21.9, 21.8 ppm; IR (ATR) ν = 2927, 2857, 1735, 1438, 1160 cm^{-1}; MS (EI) *m*/*z* (%): 211 (M^+-OCH_3, 9%), 146 (83), 114 (100), 97 (34), 81 (11), 55 (43).



3-(1-methylcyclohexyl)cyclopentan-1-one (31g):[276] Colorless oil; t_r = 11.79 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.35-2.30 (m, 1H, COC*H*$_2$), 2.25-2.05 (m, 3H, C*H*$_2$COC*H*$_2$), 2.00-1.90 (m, 2H, Alkyl-H), 1.70-1.30 (m, 8H, Alkyl-H), 1.30-1.20 (m, 3H, Alkyl-H), 0.87 (s, 3H, CCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 220.1, 39.7, 39.4, 36.6, 36.0, 34.2, 26.6, 23.3, 21.9 (2C) ppm; IR (ATR) ν = 2923, 2857, 1739, 1457, 1153, 755 cm^{-1}; MS (EI) *m*/*z* (%): 180 (M^+, 5%), 97 (100), 55 (42).

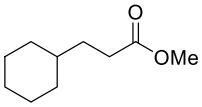


1'-Methyl-[1,1'-bi(cyclohexan)]-3-one (31h):[163b] Colorless oil; t_r = 12.74 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.45-2.30 (m, 2H, $COCH_2$), 2.30-2.05 (m, 2H, $COCH_2$), 2.00-1.90 (m, 1H, CyH), 1.70-1.25 (m, 14H, CyH), 0.84 (s, 3H, CCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 213.5, 42.8, 41.7, 36.2, 35.8, 35.1, 26.5, 25.9, 25.2, 22.0, 21.9, 19.9 ppm; IR (ATR) ν = 2923, 2857, 1708, 1454, 1049 cm^{-1}; MS (EI) *m*/*z* (%): 194 (M^+, 1%), 98 (87), 97 (100), 96 (14), 83 (11), 81 (11), 69 (11), 67 (11), 55 (65).

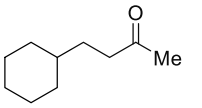


1-(1,5,5-trimethylbicyclo[4.1.0]heptan-7-yl)propan-2-one (31i):[163b] Yellowish oil; t_r = 10.10 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.40-2.30 (m, 2H, C*H*$_2$$COCH_3$), 2.16 (s, 3H, $COCH_3$), 1.70-1.50 (m, 4H, CyH), 1.40-1.30 (m, 1H, C*H*CH_2COCH_3), 1.30-1.10 (m, 1H, C*H*$CHCH_2COCH_3$), 1.04 (s, 3H, $C(CH_3)_2$), 1.03 (s, 3H, $C(CH_3)_2$), 0.91 (s, 3H, CCH_3), 0.67 (td, *J* = 7.0, 5.6 Hz, 1H, CyH), 0.15 (d, *J* = 5.6 Hz, 1H, CyH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.6, 44.8, 38.3, 36.0, 32.3, 31.4, 29.9, 29.8, 28.5, 22.5, 21.8, 20.2, 18.5 ppm; IR (ATR) ν = 2927, 2865, 1712, 1457, 1357, 1160 cm^{-1}; MS (EI) *m*/*z* (%): 194 (M^+, 14%), 179 (19), 176 (10), 161 (28), 151 (38), 137 (25), 136 (72), 125 (18), 124 (20), 123 (34), 122 (25), 121 (57), 119 (11), 109 (71), 108 (11), 107 (33),

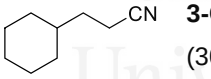
96 (17), 95 (100), 94 (13), 93 (48), 91 (24), 83 (16), 82 (68), 81 (97), 80 (13), 79 (40), 77 (23), 69 (96), 67 (43), 55 (44), 53 (19).



Methyl 3-cyclohexylpropanoate (31j):[277] Colorless oil; t_r = 9.27 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.70-3.65 (s, 3H, CO_2CH_3), 2.40-2.30 (m, 2H, C$H_2CO_2CH_3$), 1.80-1.60 (m, 5H, CyH), 1.60-1.45 (m, 2H, , C$H_2CH_2CO_2CH_3$), 1.25-1.10 (m, 4H, CyH), 0.95-0.85 (m, 2H, CyH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.8, 51.6, 37.4, 33.1, 32.5, 31.8, 26.7, 26.4 ppm; IR (ATR) ν = 1594, 1491, 1294, 1247, 1144, 1089, 1029, 773, 694 cm^{-1}; MS (EI) *m*/*z* (%): 170 (M^+, 0.7%), 141 (18), 139 (14), 121 (13), 97 (100), 96 (26), 95 (10), 87 (93), 83 (11), 81 (14), 75 (18), 74 (76), 67 (18), 56 (60).

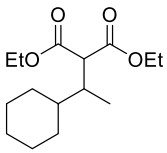


4-Cyclohexylbutan-2-one (31k):[278] Colorless oil; t_r = 8.96 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.50-2.40 (m, 2H, $COCH_2$), 2.14 (s, 3H, $COCH_3$), 1.75-1.60 (m, 5H, CyH), 1.50-1.40 (m, 2H, $COCH_2CH_2$), 1.30-1.10 (m, 4H, CyH), 0.90-0.80 (m, 2H, CyH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.9, 41.5, 37.4, 33.2, 31.4, 30.0, 26.7, 26.4 ppm; IR (ATR) ν = 2923, 2854, 1712, 1261, 887, 844, 767 cm^{-1}; MS (EI) *m*/*z* (%): 154 (M^+, 7%), 136 (13), 121 (31), 97 (72), 96 (100), 83 (13), 81 (74), 79 (14), 71 (67), 69 (22), 68 (18), 67 (39), 59 (27), 58 (53), 55 (75), 54 (15), 53 (10).

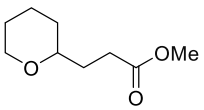


3-Cyclohexylpropanenitrile (31l):[279] Colorless oil; t_r = 8.85 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.35 (t, J = 7.4 Hz, 2H, CH_2CN), 1.75-1.65 (m, 5H, CyH), 1.60-1.50 (m, 2H, CH_2CH_2CN), 1.40-1.30 (m, 1H, CyH), 1.30-1.15 (m, 3H, CyH), 0.95-0.85 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 120.2, 36.8, 32.7 (2C), 26.5, 26.1, 14.8 ppm; IR (ATR) ν = 2923, 2854, 2167, 1450, 844 cm^{-1}; MS (EI) *m*/*z* (%): 137 (M^+, 2%), 136 (16), 108 (27), 95 (17), 94 (11), 83 (55), 82 (100), 67 (12), 55 (74), 54 (15).

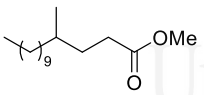
[277] Yasu, Y.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2012**, *354*, 3414-3420.
[278] Wang, D.-W.; Lu, S.-M.; Zhou, Y.-G. *Tetrahedron Lett.* **2009**, *50*, 1282-1285.
[279] Zhou, F.; Hu, X.; Zhang, W.; Li, C.-J. *Org. Chem. Front.* **2018**, *5*, 3579-3584.



Diethyl 2-(1-cyclohexylethyl)malonate (31m):[280] Colorless oil; t_r = 13.26 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.25-4.15 (m, 4H, OC*H*$_2$CH$_3$), 3.39 (d, *J* = 9.2 Hz, 1H, CH(CO$_2$Et)$_2$), 2.25-2.10 (m, 1H, CyC*H*CH$_3$), 1.80-1.70 (m, 2H, CyH), 1.70-1.55 (m, 4H, CyH), 1.27 (t, *J* = 7.1 Hz, 6H (OCH$_2$C*H*$_3$), 1.25-1.20 (m, 1H, CyH), 1.20-1.05 (m, 3H, CyH), 1.00-0.95 (m, 1H, CyH), 0.90 (d, *J* = 7.0 Hz, 3H, CyCHC*H*$_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.5, 169.2, 61.3, 61.2, 56.0, 40.4, 38.7, 31.7, 27.5, 26.9, 26.7, 26.6, 14.3, 13.0 ppm; IR (ATR) ν = 2977, 2927, 2854, 1731, 1149, 1033 cm^{-1}; MS (EI) *m*/*z* (%): 225 (M$^+$-OEt, 11%), 187 (45), 161 (94), 160 (100), 141 (28), 133 (42), 132 (11), 115 (47), 114 (11), 110 (12), 109 (26), 88 (12), 87 (23), 86 (12), 81 (22), 69 (34), 67 (16), 55 (24).



Methyl 3-(tetrahydro-2*H*-pyran-2-yl)propanoate (31n):[281] Colorless oil; t_r = 9.21 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.05-3.90 (m, 1H, OC*H*CH$_2$), 3.67 (s, 3H, CO$_2$CH$_3$), 3.39 (td, *J* = 11.2, 3.2 Hz, 1H, OCHC*H*$_2$), 3.30-3.20 (m, 1H, OCHC*H*$_2$), 2.55-2.30 (m, 2H, C*H*$_2$CO$_2$CH$_3$), 1.80-1.70 (m, 3H, CyH), 1.60-1.40 (m, 4H, CyH), 1.35-1.15 (m, 1H, CyH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.4, 76.9, 68.6, 51.6, 32.0, 31.6, 30.3, 26.2, 23.6 ppm; IR (ATR) ν = 2931, 2846, 1739, 1442, 1168, 1087, 755 cm^{-1}; MS (EI) *m*/*z* (%): 172 (M$^+$, 0.7%), 143 (13), 141 (26), 140 (12), 130 (28), 111 (24), 99 (33), 98 (50), 85 (100), 67 (16), 57 (23), 56 (12), 55 (25).



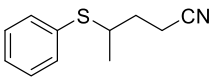
Methyl 4-methyltetradecanoate (31o):[282] Colorless oil; t_r = 13.48 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.67 (s, 3H, CO$_2$CH$_3$), 2.45-2.20 (m, 2H, C*H*$_2$CO$_2$CH$_3$), 1.70-1.60 (m, 1H, CH$_2$C*H*(CH$_3$)CH$_2$), 1.50-1.30 (m, 2H, AlkylH), 1.30-1.20 (m, 18H, AlkylH), 0.95-0.80 (m, 6H, 2CH$_3$) ppm (a mixture of isomers was observed); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.8, 51.6, 36.8, 34.3, 32.5, 32.1, 32.0, 30.1, 29.8 (2C), 29.6, 29.5, 29.4, 29.3, 27.1, 25.1, 22.8, 19.4, 14.3 ppm (a mixture of isomers was observed); IR (ATR) ν = 2923, 2854, 1743, 1457, 1168 cm^{-1}; MS (EI) *m*/*z* (%): 256 (M$^+$, 3%),

[280] Xue, F.; Wang, F.; Liu, J.; Di, J.; Liao, Q.; Lu, H.; Zhu, M.; He, L.; He, H.; Zhang, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 6667-6671.

[281] Pak, C. S.; Lee, E.; Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523-1530.

[282] Cahiez, G.; Chaboche, C.; Duplais, C.; Giulliani, A.; Moyeux, A. *Adv. Synth. Catal.* **2008**, *350*, 1484-1488.

199 (38), 183 (17), 88 (12), 87 (100), 85 (12), 83 (11), 74 (50), 71 (16), 69 (13), 57 (24), 55 (24).

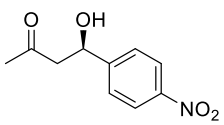


4-(phenylthio)pentanenitrile (31p):[283] Colorless oil; t_r = 12.55 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45-7.40 (m, 2H, ArH), 7.35.7.30 (m, 3H, ArH), 3.35-3.20 (m, 1H, SC*H*(CH_3)), 2.65-2.50 (m, 2H, CH_2CN), 1.95-1.80 (m, 2H, C*H*$_2$$CH_2CN$), 1.33 (d, J = 6.8 Hz, 3H, SCH(C*H*$_3$)) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 133.4, 133.1, 129.2, 127.8, 119.5, 42.6, 32.0, 21.1, 15.0 ppm; IR (ATR) ν = 3062, 2962, 2923, 2865, 2244, 2163, 1473, 1442, 1083, 1025, 744, 694 cm^{-1}; MS (EI) *m*/*z* (%): 191 (M^+, 52%), 137 (24), 110 (100), 109 (20), 65 (10).

6. ENANTIOSELECTIVE ORGANOCATALYZED REACTIONS IN EUTECTOGELS

General procedure for the enantioselective aldol reaction in eutectogels: Ketone **32** and aldehyde **33** were placed on the top of the eutectogel at 20 ºC (water bath) for 24 h. Once the reaction was completed, the organic compounds were extracted with EtOAc (3 x 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Products were purified by chromatography on silica gel (hexane/ethyl acetate).

General procedure for recycling experiments: Once the reaction was finished, the organic compounds were extracted with 2-MeTHF (3 x 1 mL) and the remaining organic solvent into the eutectogel was evaporated under vacuum. Finally, fresh reagents were added, repeating the process.

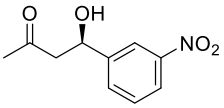


4-Hydroxy-4-(4-nitrophenyl)butan-2-one (34a):[284] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.21 (d, J = 8.8 Hz, 2H, ArH), 7.54 (d, J = 8.8 Hz, 2H, ArH), 5.30-5.25 (m, 1H, CH_2C*H*OH), 3.62 (brs, 1H, OH), 2.90-

[283] Lo, J. C.; Kim, D.; Pan, C.-M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutiérrez, S.; Giacoboni, J.; Smith, M. W. *J. Am. Chem. Soc.* **2017**, *139*, 2484-2503.
[284] Martínez, R.; Berbegal, L.; Guillena, G.; Ramón, D. J. *Green Chem.* **2016**, *18*, 1724-1730.

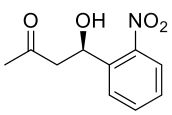
2.85 (m, 2H, COC*H*$_2$CH), 2.23 (s, 3H, COCH$_3$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ = 208.6, 150.1, 147.5, 126.6, 123.9, 69.1, 51.6, 30.8 ppm.

The enantiomeric excess was determined by HPLC with a Chiracel AS column at 254 nm (*n*-hexane/iPrOH: 85/15, 1.0 mL/min), t_r = 17.99 (major), t_r = 26.79 (minor).



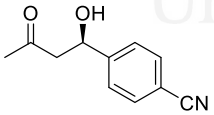
4-Hydroxy-4-(3-nitrophenyl)butan-2-one (34b):[284] ^{1}H NMR (300 MHz, CDCl$_3$) δ = 8.25-8.20 (m, 1H, ArH), 8.15-8.10 (m, 1H, ArH), 7.75-7.70 (m, 1H, ArH), 7.54 (t, *J* = 7.9 Hz, 1H), 5.30-5.25 (m, 1H, CH$_2$C*H*OH), 3.64 (d, *J* = 3.1 Hz, 1H, OH), 2.90-2.85 (m, 2H, COC*H*$_2$CH), 2.24 (s, 3H, COCH$_3$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ = 208.8, 148.5, 144.9, 131.9, 129.6, 122.7, 120.9, 68.9, 51.6, 30.9 ppm.

The enantiomeric excess was determined by HPLC with a Chiracel ADH column at 254 nm (*n*- hexane/iPrOH: 95/5, 1.0 mL/min), t_r = 26.78 (major), t_r = 29.02 (minor).



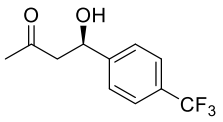
4-Hydroxy-4-(2-nitrophenyl)butan-2-one (34c):[284] ^{1}H NMR (300 MHz, CDCl$_3$) δ = 8.00-7.90 (m, 2H, ArH), 7.70-7.65 (m, 1H, ArH), 7.50-7.40 (m, 1H, ArH), 5.69 (dd, *J* = 9.4, 2.0 Hz, 1H, CH$_2$C*H*OH), 3.15 (dd, *J* = 17.8, 2.0 Hz, 1H, COC*H*$_2$CH), 2.80-2.70 (m, 1H, COC*H*$_2$CH), 2.24 (s, 3H, COCH$_3$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ = 208.8, 147.2, 138.3, 133.8, 128.3, 128.2, 124.5, 65.7, 51.0, 30.5 ppm.

The enantiomeric excess was determined by HPLC with a Chiracel ADH column at 254 nm (*n*- hexane/iPrOH: 98/2, 1.0 mL/min), t_r = 42.34 (major), t_r = 45.77 (minor).



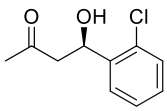
4-(1-Hydroxy-3-oxobutyl)benzonitrile (34d):[284] ^{1}H NMR (300 MHz, CDCl$_3$) δ = 7.70-7.60 (m, 2H, ArH), 7.50-7.45 (m, 2H, ArH), 5.25-5.20 (m, 1H, CH$_2$C*H*OH), 3.56 (d, *J* = 3.2 Hz, 1H, OH), 2.90-2.80 (m, 2H, COC*H*$_2$CH), 2.22 (s, 3H, COCH$_3$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ = 208.7, 148.1, 132.5, 126.4, 118.9, 111.5, 69.2, 51.6, 30.9 ppm.

The enantiomeric excess was determined by HPLC with a Chiracel ODH column at 230 nm (*n*- hexane/iPrOH: 95/5, 1.0 mL/min), t_r = 34.30 (major), t_r = 40.06 (minor).



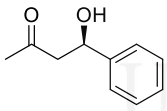
4-Hydroxy-4-(4-(trifluoromethyl)phenyl)butan-2-one (34e):[284] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.61 (d, J = 8.2 Hz, 2H, ArH), 7.48 (d, J = 8.2 Hz, 2H, ArH), 5.22 (t, J = 6.1 Hz, 1H, CH_2CHOH), 2.85 (d, J = 6.1 Hz, 2H, $COCH_2CH$), 2.21 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 208.9, 146.7, 129.8, 128.5, 126.1, 125.6 (q, J = 3.8 Hz), 122.9, 69.4, 51.8, 30.9 ppm.

The enantiomeric excess was determined by HPLC with a Chiracel AS column at 210 nm (*n*- hexane/iPrOH: 92/8, 1.0 mL/min), t_r = 8.97 (major), t_r = 11.35 (minor).



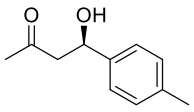
4-(2-chlorophenyl)-4-hydroxybutan-2-one (34f):[284] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.60 (m, 1H, ArH), 7.35-7.30 (m, 2H), 7.25-7.20 (m, 1H, ArH), 5.51 (dt, J = 9.7, 2.2 Hz, 1H, CH_2CHOH), 3.55 (d, J = 3.3 Hz, 1H, OH), 3.00 (dd, J = 17.7, 2.2 Hz, 1H, $COCH_2CH$), 2.68 (dd, J = 17.7, 9.7 Hz, 1H, $COCH_2CH$), 2.22 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.4, 140.1, 131.2, 129.4, 128.7, 127.4, 127.2, 66.7, 50.1, 30.8 ppm.

The enantiomeric excess was determined by HPLC with a Chiracel AS column at 210 nm (*n*- hexane/iPrOH: 98/2, 1.0 mL/min), t_r = 16.96 (minor), t_r = 18.89 (major).



4-Hydroxy-4-phenylbutan-2-one (34g):[284] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40-7.35 (m, 4H, ArH), 7.35-7.30 (m, 1H, ArH), 5.20-5.15 (m, 1H, CH_2CHOH), 3.28 (d, J = 2.8 Hz, 1H, OH), 2.95-2.80 (m, 2H, $COCH_2CH$), 2.21 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.3, 142.8, 128.7, 127.9, 125.8, 70.0, 52.1, 30.9 ppm.

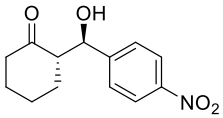
The enantiomeric excess was determined by HPLC with a Chiracel AS column at 210 nm (*n*- hexane/iPrOH: 90/10, 1.0 mL/min), t_r = 9.95 (major), t_r = 12.34 (minor).



4-Hydroxy-4-(*p*-tolyl)butan-2-one (34h):[285] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25-7.20 (m, 2H, ArH), 7.20-7.15 (m, 2H, ArH), 5.13 (dd, J = 9.2, 3.2 Hz, 1H, CH_2CHOH), 2.95-2.80 (m, 2H, $COCH_2CH$), 2.34 (s, 3H, $ArCH^3$), 2.20 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.4, 139.8, 137.6, 129.4, 125.7, 69.9, 52.1, 31.0, 21.3 ppm.

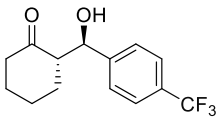
[285] Yu, N.; Han, S.; Yu, H. *Tetrahedron* **2015**, *71*, 4665-4669.

The enantiomeric excess was determined by HPLC with a Chiracel ASH column at 210 nm (*n*- hexane/iPrOH: 90/10, 1.0 mL/min), t_r = 9.09 (major), t_r = 11.28 (minor).



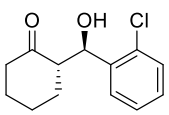
2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (34i) *syn:anti* (1:4):[284] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25-8.20 (m, 2H, ArH), 7.55-7.50 (m, 2H, ArH), 5.49 (d, *J* = 2.2 Hz, 1H *syn*, C*H*OH), 4.90 (d, *J* = 8.4 Hz, 1H *anti*, C*H*OH), 2.65-2.60 (m, 1H), 2.55-2.50 (m, 1H), 2.40-2.30 (m, 1H), 2.15-2.10 (m, 1H), 1.90-1.80 (m, 1H), 1.70-1.50 (m, 3H), 1.45-1.35 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 214.9 (*anti*), 214.2 (*syn*), 149.2, 148.5, 147.7, 147.2, 128.0 (*anti*), 126.7 (*syn*), 123.7 (*anti*), 123.6 (*syn*), 74.2 (*anti*), 70.3 (*syn*), 57.3 (*anti*), 56.9 (*syn*), 42.8 (2C, *anti, syn*), 30.9 (*anti*), 28.0 (*syn*), 27.8 (anti), 26.1 (*syn*), 24.9 (*syn*), 24.8 (*anti*) ppm.

The enantiomeric excess was determined by HPLC with a Chiracel ADH column at 254 nm (*n*- hexane/iPrOH: 90/10, 1.0 mL/min), *syn*: t_r = 18.72 (major), t_r = 20.66 (minor), *anti*: t_r = 24.06 (minor), t_r = 27.25 (major).



2-(hydroxy(4-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one *syn:anti* (1:2) (34j):[284] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.60 (m, 2H, ArH), 7.50-7.40 (m, 2H, ArH), 5.45 (d, *J* = 1.0 Hz, 1H *syn*, C*H*OH), 4.85 (d, *J* = 8.6 Hz, 1H *anti*, C*H*OH), 2.65-2.60 (m, 1H), 2.50-2.45 (m, 1H), 2.40-2.30 (m, 1H), 2.15-2.00 (m, 1H), 1.90-1.75 (m, 1H), 1.70-1.65 (m, 1H), 1.60-1.50 (m, 2H), 1.40-1.30 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.3 (*anti*), 214.6 (*syn*), 145.6 (*syn*), 145.1 (*anti*), 130.4 (*anti*), 127.5 (*anti*), 126.2 (*anti*), 125.5 (q, *J* = 3.5 Hz, *anti*), 125.3 (q, *J* = 3.5 Hz, *syn*), 74.4 (*anti*), 70.4 (*syn*), 57.4 (*anti*), 57.1 (*syn*), 42.8 (2C, *anti, syn*), 30.9 (*anti*), 28.1 (*syn*), 27.9 (*anti*), 26.0 (*syn*), 25.0 (*syn*), 24.9 (*anti*) ppm.

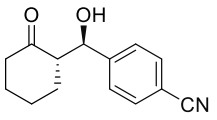
The enantiomeric excess was determined by HPLC with a Chiracel AD column at 210 nm (*n*- hexane/iPrOH: 90/10, 1.0 mL/min), *syn*: t_r = 7.21 (major), t_r = 8.38 (minor), *anti*: t_r = 10.70 (minor), t_r = 13.55 (major).



2-((2-chlorophenyl)(hydroxy)methyl)cyclohexan-1-one *syn:anti* (1:3.3) (34k):[284] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.60-7.55 (m, 1H, ArH), 7.35-7.30 (m, 2H, ArH), 7.25-7.20 (m, 1H, ArH), 5.71 (d, *J* = 1.8 Hz, 1H *syn*, C*H*OH), 5.35 (d, *J* = 8.1 Hz, 1H *anti*, C*H*OH), 2.85-2.80 (m, 1H *syn*), 2.70-2.65 (m 1H),

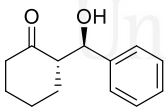
2.50-2.40 (m, 1H), 2.40-2.30 (m, 1H), 2.15-2.05 (m, 1H), 1.85-1.80 (m, 1H), 1.70-1.50 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$: δ = 215.4 (*anti*), 215.0 (*syn*), 139.2 (*anti*), 138.7 (*syn*), 133.1 (*anti*), 129.4 (*anti*), 128.9 (*anti*), 128.7 (*syn*), 128.4 (*anti*), 128.3 (*syn*), 70.4 (*syn*), 127.4 (*anti*), 126.8 (*syn*), 70.6 (*anti*), 67.9 (*syn*), 57.7 (*anti*), 53.7 (*syn*), 42.9 (*anti*), 30.6 (*anti*), 28.1 (*syn*), 28.0 (*anti*), 26.1 (*syn*), 25.1 (*anti*), 25.0 (*syn*) ppm.

The enantiomeric excess was determined by HPLC with a Chiracel ODH column at 210 nm (*n*- hexane/iPrOH: 95/5, 1.0 mL/min), *syn*: t_r = 7.22 (major), t_r = 8.38 (minor), *anti*: t_r = 9.35 (major), t_r = 11.87 (minor).



4-(hydroxy(2-oxocyclohexyl)methyl)benzonitrile (34l) *syn:anti* (1:2.5):[286] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.60 (m, 2H, ArH), 7.45-7.40 (m, 2H, ArH), 5.43 (d, *J* = 2.0 Hz, 1H *syn*, C*H*OH), 4.84 (d, *J* = 8.5 Hz, 1H *anti*, C*H*OH), 2.60-2.50 (m, 2H), 2.45-2.30 (m, 1H), 2.15-2.10 (m, 1H), 1.90-1.75 (m, 3H), 1.40-1.30 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.0 (*anti*), 214.3 (*syn*), 147.1 (*syn*), 146.5 (*anti*), 132.3 (*anti*), 133.2 (*syn*), 127.9 (*anti*), 126.7 (*syn*), 119.0 (*syn*), 118.9 (*anti*), 111.9 (*anti*), 111.0 (*syn*), 74.4 (*anti*), 70.3 (*syn*), 57.3 (*anti*), 56.9 (*syn*), 42.8 (2C, *anti*, *syn*), 30.9 (*anti*), 28.0 (*syn*), 27.8 (*anti*), 26.0 (*syn*), 24.9 (*syn*), 24.8 (*anti*) ppm.

The enantiomeric excess was determined by HPLC with a Chiracel ADH column at 240 nm (*n*- hexane/iPrOH: 95/5, 1.0 mL/min), *syn*: t_r = 31.58 (major), t_r = 39.68 (minor), *anti*: t_r = 46.53 (minor), t_r = 59.58 (major).

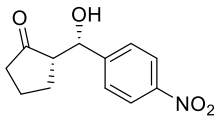


2-(hydroxy(phenyl)methyl)cyclohexan-1-one (34m) *syn:anti* (1:2.5):[287] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40-7.30 (m, 5H), 5.40 (d, *J* = 2.1 Hz, 1H *syn*, C*H*OH), 4.79 (d, *J* = 8.8 Hz, 1H *anti*, C*H*OH), 2.90-2.80 (m, 1H *syn*), 2.65-2.50 (m, 1H), 2.50-2.30 (m, 2H), 2.15-2.10 (m, 1H), 2.00-1.50 (m, 4H), 1.35-1.30 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.7 (*anti*), 202.0, 141.1, 135.7, 130.4, 128.5, 128.3, 128.1, 127.2, 125.9, 74.9 (*anti*), 70.8 (*syn*), 57.6 (*anti*), 57.3 (*syn*), 42.9 (*anti*), 40.5 (*syn*), 31.0 (*anti*), 28.1 (*syn*), 28.0 (*anti*), 26.2 (*syn*), 25.0 (*syn*), 24.9 (*anti*) ppm.

[286] Bañón-Caballero, A.; Guillena, G.; Nájera, C. *Green Chem.* **2010**, *12*, 1599-1606.

[287] Guillena, G.; Hita, M. d. C.; Nájera, C.; Viózquez, S. F. *J. Org. Chem.* **2008**, *73*, 5933-5943.

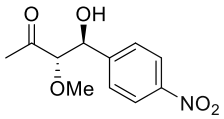
The enantiomeric excess was determined by HPLC with a Chiracel ODH column at 210 nm (*n*- hexane/iPrOH: 95/5, 0.5 mL/min), *syn*: t_r = 18.79 (major), t_r = 21.48 (minor), *anti*: t_r = 25.58 (major), t_r = 37.91 (minor).



2-(hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (34n)

***syn:anti* (1.8:1):**[284] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25-8.20 (m, 2H, ArH), 7.55-7.50 (m, 2H), 5.43 (d, *J* = 2.9 Hz, 1H *syn*, C*H*OH), 4.85 (d, *J* = 9.2 Hz, 1H *anti*, C*H*OH), 2.50-2.10 (m, 3H), 2.10-1.90 (m, 2H), 1.85-1.45 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 222.4 (*anti*), 219.5 (*syn*), 150.2, 148.8, 147.8, 147.3, 127.5 (*anti*), 126.5 (*syn*), 123.9 (*anti*), 123.8 (*syn*), 74.6 (*anti*), 70.7 (*syn*), 56.2 (*syn*), 55.2 (*anti*), 39.1 (*syn*), 38.7 (*anti*), 27.0 (*anti*), 22.6 (*syn*), 20.5 (2C, *anti, syn*) ppm.

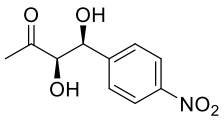
The enantiomeric excess was determined by HPLC with a Chiracel AD column at 280 nm (*n*- hexane/iPrOH: 96/4, 1.0 mL/min), *syn*: t_r = 32.64 (major), t_r = 48.06 (minor), *anti*: t_r = 56.63 (minor), t_r = 61.25 (major).



4-Hydroxy-3-methoxy-4-(4-nitrophenyl)butan-2-one (34o)

***syn:anti* (1:3.3):**[284] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25-8.20 (m, 2H, ArH), 7.60-7.55 (m, 2H, ArH), 5.05 (d, *J* = 4.0 Hz, 1H *syn*, C*H*OH), 5.03 (d, *J* = 6.3 Hz, 1H *anti*, C*H*OH), 3.77 (d, *J* = 4.0 Hz, 1H *syn*, C*H*OCH_3), 3.70 (d, *J* = 6.3 Hz, 1H *anti*, C*H*OCH_3), 3.38 (s, 3H *syn*, $COCH_3$), 3.32 (s, 3H *anti*, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 210.0 (*anti*), 147.9, 147.5, 146.9, 127.8 (*anti*), 127.3 (*syn*), 123.7 (*syn*), 123.6 (*anti*), 90.1 (*syn*), 89.7 (*anti*), 73.5 (*anti*), 73.4 (*syn*), 59.8 (2C, *anti*, *syn*), 27.7 (*syn*), 27.6 (*anti*) ppm.

The enantiomeric excess was determined by HPLC with a Chiracel ODH column at 280 nm (*n*- hexane/iPrOH: 90/10, 0.8 mL/min), *anti*: t_r = 15.34 (major), t_r = 18.14 (minor), *syn*: t_r = 19.05 (minor), t_r = 24.24 (major).

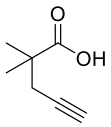


3,4-Dihydroxy-4-(4-nitrophenyl)butan-2-one (34p) *syn:anti* (1.6:1):[288] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.30-8.25 (m, 2H, ArH), 7.65-7.60 (m, 2H, ArH), 5.23 (d, *J* = 2.5 Hz, 1H *syn*, CC*H*OH), 5.11 (d, *J* = 4.7 Hz, 1H *anti*, CC*H*OH), 4.49 (d, *J* = 4.7 Hz, 1H *anti*, COC*H*OH), 4.42 (d, *J* = 2.5 Hz, 1H *syn*, COC*H*OH), 2.38 (s, 3H *syn*), 2.02 (s, 3H *anti*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 206.7, 206.6, 147.4, 127.4, 127.3, 123.9, 80.7, 80.1, 74.6, 73.1, 26.1 ppm.
The enantiomeric excess was determined by HPLC with a Chiracel ADH column at 254 nm (*n*- hexane/iPrOH: 80/20, 0.8 mL/min), *anti*: t_r = 10.62 (minor), t_r = 11.93 (major), *syn*: t_r = 13.77 (minor), t_r = 17.35 (major).

7. CYCLOISOMERIZATION OF ALKYNOIC ACID DERIVATIVES

General procedure for the preparation of PdO-Fe_3O_4 catalyst: To a stirred solution of $PdCl_2$ (345 mg, 2 mmol), KCl (2 g, 26 mmol, to increase the palladium solubility) in deionized water (240 mL) micro-Fe_3O_4 (8 g, 34 mmol) was added. After 10 min at room temperature, the mixture was slowly basified with NaOH (1 M) to pH around 13. The mixture was stirred for 24 h at room temperature in air. After that, the catalyst was filtered and washed with deionized water (3 x 10 mL). The solid was dried at 100 ºC for 24 h in a standard glassware oven, obtaining the expected catalyst: incorporation of palladium of 2.74 % according to XRF.

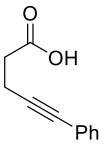
General procedure for the preparation of starting material: 2,2-dimethylpent-4-ynoic acid (**40b**), 5-phenylpent-4-ynoic acid (**40e**) and *N*-tosylpent-4-ynamide (**40f**) were prepared according to reported procedures.[197a, 197c]



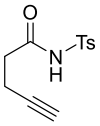
2,2-Dimethylpent-4-ynoic acid (40b):[289] Orange oil; t_r = 7.50 min; R_f = 0.33 (hexane/ethyl acetate 3/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.40 (d, *J* = 2.7 Hz, 2H, H_2CC≡CH), 1.97 (t, *J* = 2.7 Hz, 1H, C≡CH), 1.25 (s, 6H, CH_3) ppm; ^{13}C NMR

[288] Gerasimchuk, V. V.; Romanov, R. R.; Woo, G. H.-T.; Dmitriev, I. A.; Kucherenko, A. S.; Zlotin, S. G. *ARKIVOC* **2017**, 241-249.
[289] Welsch, T.; Tran, H.-A.; Witulski, B. *Org. Lett.* **2010**, *12*, 5644-5647.

(75 MHz, $CDCl_3$) δ = 182.8, 89.5, 70.8, 41.0, 29.4, 24.8, 24.4 ppm; IR (ATR) ν = 2971, 2875, 1699, 1387, 1366, 1224, 1082, 969, 751 cm^{-1}; MS (EI) *m*/*z* (%): 125 (M^+-1, 13%), 111 (100), 79 (27), 59 (30).



5-Phenylpent-4-ynoic acid (40e):[290] Brown solid; t_r = 12.10 min; R_f = 0.30 (hexane/ethyl acetate 1/1); m.p. 84-86 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35–7.30 (m, 2H, ArH), 7.25–7.20 (m, 3H, ArH), 2.70–2.60 (m, 4H, CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.8, 131.6, 128.2, 127.8, 123.4, 87.6, 81.3, 33.4, 15.1 ppm; IR (ATR) ν = 2923, 1693, 1434, 1301, 1211, 1097, 917, 754, 690 cm^{-1}; MS (EI) *m*/*z* (%): 174 (M^+, 47%), 173 (12), 147, (10), 146 (93), 131 (30), 129 (41), 128 (100), 127 (46), 117 (19), 116 (16), 114 (89), 89 (19), 78 (10), 77 (19), 51 (13).



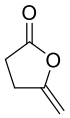
***N*-tosylpent-4-ynamide (40f):**[197b] White solid; t_r = 15.63 min; R_f = 0.36 (hexane/ethyl acetate 2/1); m.p. 119-123 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.75 (s, 1H, NH), 7.95 (d, *J* = 8.4 Hz, 2H, ArH), 7.35 (d, *J* = 8.4 Hz, 2H, ArH), 2.60–2.35 (m, 7H, $2CH_2$ and CH_3), 1.99 (t, *J* = 2.5 Hz, 1H, C≡CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.1, 145.5, 135.5, 129.8, 128.6, 81.9, 70.2, 35.2, 21.9, 13.8 ppm; IR (ATR) ν = 3272, 2360, 1727, 1434, 1413, 1330, 1160, 1120, 1079, 856, 817, 686, 665 cm^{-1}; MS (EI) *m*/*z* (%): 251 (M^+, 7%), 187 (37), 186 (13), 155 (27), 92 (10), 91 (100), 65 (18).

General procedure of cycloisomerization reactions: In a 10 mL glass tube, the catalyst PdO-Fe_3O_4 (0.5 mg), the corresponding substrate **40** (0.1 mmol) and the solvent (0.2 mL), were added. Subsequently, the tube was sealed with a septum and heated to the corresponding temperature for the time necessary for each starting reagent. After the reaction was completed, the tube was cooled. Then, the mixture was quenched with water and extracted with AcOEt (3 x 1 mL). The organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent and purified by column chromatography.

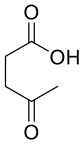
[290] Suzuka, T.; Okada, Y.; Ooshiro, K.; Uozumi, Y. *Tetrahedron* **2010**, *66*, 1064-1069.

Procedure for recycling the catalytic system: The reaction was performed according to the general procedure. After 10 minutes, the mixture was extracted with ethyl acetate, dissolving all organic compounds, in such a way that water and catalyst remained in the reaction tube. To the remaining mixture, compound **40a** was added, carrying out the reaction again under the same reaction conditions.

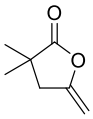
On the other hand, in order to recycle only the catalyst, we extracted the product with water and AcOEt (3 x 1 mL) and then, decanting the solution with the aid of a magnet, the catalyst remained in the reaction tube. Then, fresh water and compound **40a** were added to the tube, carrying out the new reaction under standard conditions.



5-Methylenedihydrofuran-2(3*H*)-one (41a):[291] Colorless oil; t_r = 5.25 min; R_f = 0.43 (hexane/ethyl acetate 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.75 (dd, *J* = 4.6, 2.1 Hz, 1H, C=C*H*$_2$), 4.32 (dt, *J* = 2.1, 1.8 Hz, 1H, C=C*H*$_2$), 2.95–2.85 (m, 2H, C*H*$_2$CO$_2$H), 2.70–2.65 (m, 2H, C*H*$_2$CH$_2$CO$_2$H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.0, 155.7, 88.9, 28.2, 25.2 ppm; IR (ATR) ν = 1702, 1398, 1366, 1162, 608 cm^{-1}; MS (EI) *m*/*z* (%): 98 (M^+, 100%), 70 (30), 56 (47), 55 (22).



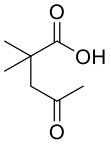
4-Oxopentanoic acid (42a):[198a] Colorless oil; t_r = 7.77 min; R_f = 0.36 (hexane/ethyl acetate 3/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.25 (s, 1H, COOH), 2.77 (t, *J* = 6.4 Hz, 2H, C*H*$_2$CO$_2$H), 2.64 (t, *J* = 6.4 Hz, 2H, C*H*$_2$CH$_2$CO$_2$H), 2.21 (s, 3H, COC*H*$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 206.8, 178.4, 37.8, 29.9, 27.9 ppm; IR (ATR) ν = 2927, 1702, 1631, 1399, 1353, 1206, 1164 cm^{-1}; MS (EI) *m*/*z* (%): 116 (M^+, 46%), 101 (18), 99 (15), 73 (32), 56 (100), 55 (44).



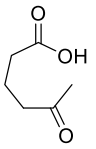
3,3-Dimethyl-5-methylenedihydrofuran-2(3*H*)-one (41b):[188b] Orange oil; t_r = 5.03 min R_f = 0.56 (hexane/ethyl acetate 3/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.76 (s, 1H, C=C*H*$_2$), 4.33 (s, 1H, C=C*H*$_2$), 2.70 (s, 2H, C*H*$_2$C(CH$_3$)$_2$), 1.31 (s, 6H, C*H*$_3$C*H*$_3$CCO$_2$H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 180.3, 153.4, 89.4, 41.0, 40.4, 24.7

[291] Alemán, J.; del Solar, V.; Cubo, L.; Quiroga, A. G.; Navarro Ranninger, C. *Dalton Trans.* **2010**, *39*, 10601-10607.

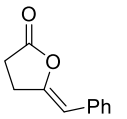
ppm; IR (ATR) ν = 2969, 2932, 1797, 1705, 1703, 1672, 1080, 969 cm^{-1}; MS (EI) *m*/*z* (%): 126 (M^+, 37%), 83 (37), 70 (16), 56 (100), 55 (16).



2,2-Dimethyl-4-oxopentanoic acid (42b):[292] Orange oil; R_f = 0.3 (hexane/ethyl acetate 4/1); ^{1}H NMR (300 MHz, acetone-d_6) δ = 2.78 (s, 2H, CH_2CO), 1.34 (s, 3H, $COCH_3$), 1.21 (s, 6H, $CH_3CH_3CCO_2H$) ppm; ^{13}C NMR (75 MHz, acetone-d_6) δ = 210.1, 178.9, 53.1, 49.4, 40.2, 25.9 ppm; IR (ATR) ν = 2975, 2875, 1784, 1705, 1475, 1361, 1135, 1055, 906 cm^{-1}; MS (EI) *m*/*z* (%): 126 (M^+- H_2O, 10%), 87 (12), 85 (24), 59 (24), 58 (15), 56 (29), 55 (11), 43 (100), 41 (16).



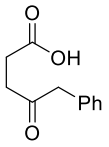
5-Oxohexanoic acid (42c):[291] Orange oil; t_r = 8.52 min; R_f = 0.27 (hexane/ethyl acetate 3/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.82 (s, 1H, CO_2H), 2.55 (t, *J* = 7.2 Hz, 2H, CH_2CO), 2.40 (t, *J* = 7.2 Hz, 2H, CH_2CO_2H), 2.16 (s, 3H, $COCH_3$), 1.90 (q, *J* = 7.2 Hz, 2H, $CH_2CH_2CO_2H$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 208.4, 179.3, 42.4, 33.0, 30.0, 18.6 ppm; IR (ATR) ν = 3160, 2962, 1703, 1409, 1363, 1155 cm^{-1}; MS (EI) *m*/*z* (%): 130 (M^+, 2%), 115 (10), 113 (10), 112 (100), 87 (32), 84 (29), 71 (18), 70 (55), 60 (29), 58 (21), 55 (27).



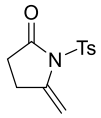
(*Z*)-5-Benzylidenedihydrofuran-2(3*H*)-one (41e):[293] Pale yellow oil; t_r = 12.65 min; R_f = 0.60 (hexane/ethyl acetate 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55 (d, *J* = 7.4 Hz, 2H, ArH), 7.32 (t, *J* = 7.4 Hz, 2H, ArH), 7.20 (t, *J* = 7.4 Hz, 1H, ArH), 5.55 (br s, 1H, C=CH), 3.10–2.95 (m, 2H, CH_2CO), 2.75–2.65 (m, 2H, CH_2CH_2CO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.1, 148.3, 134.1, 128.7, 128.5, 127.0, 105.2, 27.2, 26.6 ppm; IR (ATR) ν = 2925, 1798, 1681, 1493, 1448, 1225, 1776, 1097, 939, 693 cm^{-1}; MS (EI) *m*/*z* (%): 174 (M^+, 100%), 146 (22), 145 (32), 131 (12), 118 (43), 117 (12), 91 (25), 90 (53), 89 (30), 63 (11).

[292] Jaouhari, R.; Maillard, B.; Filliatre, C.; Villenave, J.-J. *Synthesis* **1982**, 760-763.

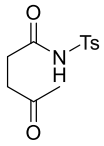
[293] Harkat, H.; Dembelé, A. Y.; Weibel, J.-M.; Blanc, A.; Pale, P. *Tetrahedron* **2009**, *65*, 1871-1879.



4-Oxo-5-phenylpentanoic acid (42e):[294] Orange oil; t_r = 12.84 min; R_f = 0.33 (hexane/ethyl acetate 3/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40–7.20 (m, 5H, ArH), 3.74 (s, 2H, CH_2Ph), 2.75 (t, *J* = 6.2 Hz, 2H, H_2CCO), 2.61 (t, *J* = 6.2 Hz, 2H, H_2CCOOH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 206.5, 178.1, 134.0, 129.6, 128.9, 127.3, 50.2, 36.3, 27.9 ppm; IR (ATR) ν = 3029, 2920, 1703, 1596, 1399, 1158, 741, 698 cm^{-1}; MS (EI) *m*/*z* (%): 192 (M^+, 9%), 101 (98), 92 (92), 91 (100), 89 (12), 73 (30), 65 (32), 63 (10), 55 (31).



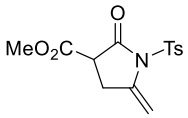
5-Methylene-1-tosylpyrrolidin-2-one (41f):[295] White solid; t_r = 16.04 min R_f = 0.40 (hexane/ethyl acetate 3/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.4 Hz, 2H, ArH), 7.32 (d, *J* = 8.4 Hz, 2H, ArH), 5.27 (s, 1H, C=CH), 5.13 (s, 1H, C=CH), 2.55–2.45 (t, *J* = 7.0 Hz, 2H, H_2CCO), 2.43 (s, 3H), 2.38 (t, *J* = 7.0 Hz, 2H, H_2CC).ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.8, 145.0, 139.0, 136.6, 129.5, 128.6, 111.3, 33.8, 30.6, 21.8 ppm; IR (ATR) ν = 2918, 2850, 1708, 1646, 1353, 1160, 1132, 1085 cm^{-1}; MS (EI) *m*/*z* (%): 236 (M^+-CH_3, 2%), 201 (25), 200 (31), 172 (19), 155 (11), 92 (10), 91 (100), 89 (10), 65 (37), 55 (18).



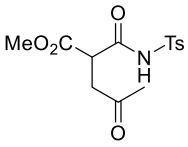
4-Oxo-*N*-tosylpentanamide (42f): Orange solid; t_r = 16.29 min; R_f = 0.20 (hexane/ethyl acetate 1/1); m.p. 148-151 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.87 (s, 1H, CONH), 7.92 (d, *J* = 8.2 Hz, 2H, ArH), 7.33 (d, *J* = 8.2 Hz, 2H, ArH), 2.75 (t, *J* = 6.1 Hz, 2H, CH_2CO), 2.51 (t, *J* = 6.1 Hz, 2H, CH_2CONH), 2.43 (s, 3H, $ArCH_3$), 2.15 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 207.7, 170.4, 145.2, 135.8, 129.8, 128.5, 37.6, 30.2, 30.0, 21.9 ppm; IR (ATR) ν = 3129, 2917, 1699, 1599, 1452, 1380, 1336, 1166, 1130, 1087, 862, 813, 659 cm^{-1}; MS (EI) *m*/*z* (%): 155 (M^+-$C_5H_8O_2N$, 20%), 108 (100), 107 (14), 91 (54), 65 (15), 43 (29). HRMS calcd. (%) for $C_{12}H_{15}NO_4S$-$C_5H_6O_2$: 171.0354; found: 171.0352.

[294] Masatoshi, K.; Toshio, S.; Tamotsu, F. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3255-3264.

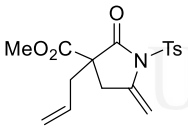
[295] Lorion, M. M.; Duarte, F. J. S.; Calhorda, M. J.; Oble, J.; Poli, G. *Org. Lett.* **2016**, *18*, 1020-1023.



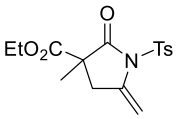
Methyl 5-methylene-2-oxo-1-tosylpyrrolidine-3-carboxylate (41g):[197b] Yellow oil; t_r = 15.45 min; R_f = 0.33 (hexane/ethyl acetate 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 8.4 Hz, 2H, ArH), 7.36 (d, *J* = 8.4 Hz, 2H, ArH), 5.55 (dd, *J* = 3.8, 2.0 Hz, 1H, C=CH_2), 4.65 (dd, *J* = 3.8, 2.0 Hz, 1H, C=CH_2), 3.73 (s, 3H, OCH_3), 3.53 (dd, *J* = 9.9, 7.6 Hz, 1H, HCCON), 3.15–2.85 (m, 2H, *H*$_2$*C*-C=CH_2), 2.46 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.5, 167.8, 145.8, 138.5, 134.8, 129.7, 128.2, 95.2, 53.1, 47.2, 30.0, 21.7 ppm; IR (ATR) ν = 3252, 2957, 2922, 2854, 1734, 1715, 1437, 1348, 1274, 1265, 1168, 1085, 813, 662 cm^{-1}; MS (EI) *m*/*z* (%): 251 (M^++1-$C_2H_3O_2$, 5%), 187 (33), 186 (13), 155 (25), 92 (10), 91 (100), 65 (17).



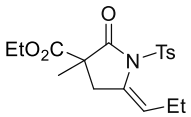
Methyl 4-oxo-2-(tosylcarbamoyl)pentanoate (42g): Orange oil; t_r = 12.58 min; R_f = 0.20 (hexane/ethyl acetate 3/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.98 (s, 1H, NH), 7.92 (d, *J* = 8.3 Hz, 2H, ArH), 7.32 (d, *J* = 8.3 Hz, 2H, ArH), 3.74 (t, *J* = 6.1 Hz, 1H, COCHCO), 3.68 (s, 3H, H_3CO), 3.10–3.05 (m, 2H, H_2CCO), 2.43 (s, 3H, $ArCH_3$), 2.14 (s, 3H, $COCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 205.8, 169.3, 165.8, 145.2, 135.5, 129.7, 128.6, 53.4, 47.5, 41.1, 29.7, 21.8 ppm; IR (ATR) ν = 3248, 1743, 1713, 1596, 1436, 1347, 1166, 1084, 813, 660 cm^{-1}; MS (EI) *m*/*z* (%): 155 (M^+-$C_7H_{10}O_4N$, 30%), 125 (10), 108 (100), 91 (61), 87 (15), 65 (14). HRMS calcd. (%) for $C_{14}H_{17}NO_6S$-$C_7H_8O_2$: 171.0354; found: 171.0353.



Methyl 3-allyl-5-methylene-2-oxo-1-tosylpyrrolidine-3-carboxylate (41h):[197b] Yellow oil ; t_r = 17.38 min; R_f = 0.53 (hexane/ethyl acetate 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.4 Hz, 2H, ArH), 7.34 (d, *J* = 8.4 Hz, 2H, ArH), 5.55–5.40 (m, 2H, *H*$_2$C=CH), 5.05–5.00 (m, 2H, H_2C=C), 4.60 (d, *J* = 1.7 Hz, 1H, H_2C=C*H*), 3.60 (s, 3H, OCH_3), 3.04 (dt, *J* = 15.9, 1.5 Hz, 1H, *H*$_2$*C*-C=CH_2), 2.71 (dt, *J* = 15.9, 1.5 Hz, 1H, *H*$_2$*C*-C=CH_2), 2.65–2.50 (m, 2H, *H*$_2$C-CH=CH_2), 2.45 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.2, 169.8, 145.8, 138.3, 131.0, 129.6, 128.2, 126.5, 120.8, 94.9, 54.9, 53.1, 37.9, 21.8, 16.9 ppm; IR (ATR) ν = 2958, 1759, 1736, 1655, 1435, 1368, 1258, 1172, 1087, 813, 669 cm^{-1}; MS (EI) *m*/*z* (%): 349 (M^+, 4%), 308 (46), 155 (64), 139 (10), 108 (25), 95 (18), 91 (100), 67 (10), 65 (21), 43 (18).



Ethyl 3-methyl-5-methylene-2-oxo-1-tosylpyrrolidine-3-carboxylate (41i):[197b] Yellow oil ; t_r = 16.64 min; R_f = 0.46 (hexane/ethyl acetate 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 8.4 Hz, 2H, ArH), 7.34 (d, *J* = 8.4 Hz, 2H, ArH), 5.54 (dd, *J* = 3.6, 1.9 Hz, 1H, C=CH_2), 4.60 (dd, *J* = 3.6, 1.9 Hz, 1H, C=CH_2), 4.10–3.90 (m, 2H,OC$H_2$$CH_3$), 3.07 (d, *J* = 15.5 Hz, 1H, H_2C-C=CH_2), 2.56 (d, *J* = 15.5 Hz, 1H, H_2C-C=CH_2), 2.44 (s, 3H, ArCH_3), 1.38 (s, 3H, CCH_3), 1.05 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.5, 170.2, 145.8, 138.3, 135.0, 129.7, 128.3, 95.0, 62.2, 51.4, 39.4, 21.9, 19.8, 13.9 ppm; IR (ATR) ν = 2983, 2930, 2850, 1757, 1733, 1655, 1369, 1173, 1085, 1041, 813, 665 cm^{-1}; MS (EI) *m*/*z* (%): 337 (M^+, 4%), 264 (100), 200 (41), 155 (49), 91 (97), 65 (17).



Ethyl (*Z*)-3-methyl-2-oxo-5-propylidene-1-tosylpyrrolidine-3-carboxylate (41j):[198b] Pale yellow oil ; t_r = 17.36 min; R_f = 0.5 (hexane/ethyl acetate 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 8.2 Hz, 2H, ArH), 7.32 (d, *J* = 8.2 Hz, 2H, ArH), 5.19 (t, *J* = 7.2 Hz, 1H, C=CHEt), 4.05–3.95 (m, 2H, COC$H_2$$CH_3$), 3.06 (dd, *J* = 13.2, 1.1 Hz, 1H, H_2CC=CHEt), 2.50–2.25 (m, 6H, ArCH_3 and H_2CC=CHEt), 1.31 (s, 3H, CCH_3), 1.07 (m, 6H, $COCH_2CH_3$ and $CHCH_2CH_3$).ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.4, 170.4, 145.4, 135.9, 129.9, 128.8, 121.9, 62.1, 53.5, 43.7, 23.3, 21.9, 19.2, 14.3, 14.0 ppm; IR (ATR) ν = 2977, 2935, 1754, 1734, 1691, 1363, 1165, 812, 664, 539 cm^{-1}; MS (EI) *m*/*z* (%): 365 (M^+, 2%), 292 (51), 210 (13), 155 (32), 136 (39), 92 (12), 91 (100), 65 (26).

8. SULFONE SYNTHESIS AND RELATED DERIVATIVES

General synthesis of Ar_3Bi: For commercially available organomagnesium reagents, a solution of $BiCl_3$ in dry THF (2 mmol, 1 M) was added dropwise over a solution of ArMgBr in THF or Et_2O (1 M) under an argon atmosphere with magnetic stirring. Once the addition was complete, the solution was heated to reflux for 12 h. Then, the reaction was allowed to reach room temperature and poured slowly over a cold saturated aqueous solution of NH_4Cl. The

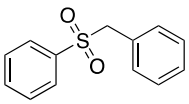
product was extracted 3 times with Et_2O. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure.[296]

For non-commercially available organomagnesium reagents, the corresponding aryl iodide/bromide (6.2 mmol) was dissolved in dry THF and cooled to -78 °C in an acetone bath. A *n*-BuLi solution (2.5 M, 6.2 mmol) was added dropwise and the mixture was stirred at that temperature for 1 h. Then, a suspension of $BiCl_3$ (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. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and reduced under reduced pressure. Ar_3Bi was usually purified by recrystallization from hot EtOH or by flash chromatography using a mixture of EtOAc and hexanes.[297]

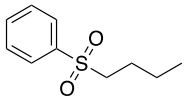
General procedure for the synthesis of sulfones: A solution of Ar_3Bi (0.2 mmol), sodium metabisulfite (1.32 mmol) and the corresponding electrophile (1.2 mmol) in 1.5 mL of DES was stirred for 5 h at 80 ^oC. Once the reaction was completed, water was added to dissolve the DES phase. That aqueous suspension was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate).

General procedure for recycling experiments: The reaction was performed according to the general procedure. Once the reaction was completed, the reaction mixture was cooled to room temperature, and 2-MeTHF (3 x 3 mL) was added to the reaction vessel. The biphasic mixture was stirred for 5 min, and the upper phase (VOC-phase, mainly unreacted organic reagents and products) was separated by decantation and analyzed by GC using tridecane as the internal standard. The eutectic mixture was dried under vacuum and was charged again with fresh reagents, repeating the process.

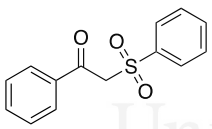
[296] Ghaoui, H.; Raihane, M.; Rhouta, B.; Bitinis, N.; Carlmark, A.; Arroyo, M.; Verdejo, R.; Lopez-Manchado, M. A.; Lahcini, M. *Polym. Int.* **2014**, *63*, 709-717.
[297] Luan, J.; Zhang, L.; Hu, Z. *Molecules* **2011**, *16*, 4191-4230; Liu, J.-Q.; Yang, J.-J.; Li, J.-F.; Li, K.; Xiao, X.-D.; Bai, Y.-L.; Wang, J.-W. *Mol. Catal.* **2017**, *443*, 125-130.



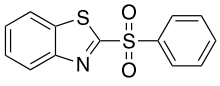
(Benzylsulfonyl)benzene (46a):[212b] White solid ; R_f = 0.27 (hexane/ethyl acetate 4/1); m.p. 144-146 ºC (ethanol); t_r =14.93 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.55 (m, 3H, ArH), 7.46 (t, J = 7.7 Hz, 2H, ArH), 7.35-7.20 (m, 3H, ArH), 7.08 (d, J = 7.0 Hz, 2H, ArH), 4.31 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.9, 133.8, 130.9, 129.0, 128.8, 128.7, 128.6, 128.2, 63.0 ppm; IR (ATR) ν = 1302, 1125, 755 cm^{-1}; MS (EI): *m*/*z* (%): 232 (M^+, 3%), 91 (100).



(Butylsulfonyl)benzene (46b):[298] Brown oil; R_f = 0.63 (hexane/ethyl acetate 1/1); t_r = 14.2 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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_2CH_2), 1.75-1.65 (m, 2H, $SO_2CH_2CH_2$), 1.50-1.30 (m, 2H, CH_2CH_3), 0.89 (t, J = 7.3 Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.3, 133.7, 129.4, 128.1, 56.2, 24.7, 21.6, 13.6 ppm; IR (ATR) ν = 2961, 1304, 1142 cm^{-1}; MS (EI) *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-Phenyl-2-(phenylsulfonyl)ethanone (46c):[299] White solid; m.p. 83-85 ºC; R_f = 0.5 (hexane/ethyl acetate 1/1); t_r = 16.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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) ppm;^{13}C NMR (75 MHz, $CDCl_3$) δ = 188.1, 138.8, 135.8, 134.5, 134.3, 129.4, 129.3, 129.0, 128.7, 63.5 ppm; IR (ATR) ν = 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).



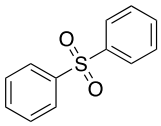
2-(phenylsulfonyl)benzo[*d*]thiazole (46d):[300] White solid; m.p. 153-156 ºC (ethanol); R_f = 0.30 (hexane/ethyl acetate 4/1); t_r = 17.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.20-8.10 (m, 3H, ArH), 8.00-7.90 (m, 1H, ArH), 7.70-7.60 (m, 1H, ArH), 7.60-7.50 (m, 4H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ

[298] Bonaparte, A. C.; Betush, M. P.; Panseri, B. M.; Mastarone, D. J.; Murphy, R. K.; Murphree, S. S. *Org. Lett.* **2011**, *13*, 1447-1449.

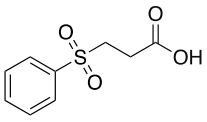
[299] Wei, W.; Liu, C.; Yang, D.; Wen, J.; You, J.; Suo, Y.; Wang, H. *Chem. Commun.* **2013**, *49*, 10239-10241.

[300] Liang, S.; Zhang, R.-Y.; Xi, L.-Y.; Chen, S.-Y.; Yu, X.-Q. *J. Org. Chem.* **2013**, *78*, 11874-11880.

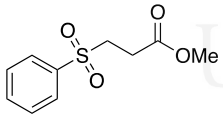
= 167.4, 153.0, 138.6, 137.1, 134.7, 129.6, 129.0, 128.0, 127.6, 125.6, 122.3 ppm; IR (ATR) ν = 1367, 1157, 719 cm^{-1}; MS (EI) *m*/*z* (%): 275 (M^+, 7%), 211 (36), 210 (100), 207 (12), 77 (38).



Sulfonyldibenzene (46e):[301] White solid; m.p. 117-118 ºC; R_f = 0.30 (hexane/ethyl acetate 4/1); t_r = 14.57 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.00-7.90 (m, 4H, ArH), 7.60-7.55 (m, 6H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.7, 133.3, 129.4, 127.8 ppm; IR (ATR) ν = 3066, 1307, 1152 cm^{-1}; MS (EI) *m*/*z* (%): 218 (M^+, 34%), 125 (100), 97 (14), 77 (32), 51 (17).

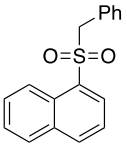


3-(phenylsulfonyl)propanoic acid (46f):[302] White solid; R_f = 0.43 (ethyl acetate/methanol: 2/1); m.p. 125-127 ºC (ethanol); t_r = 13.9 min; ^{1}H NMR (300 MHz, CD_3OD) δ = 8.00-7.90 (m, 2H, ArH), 7.80-7.70 (m, 1H, ArH), 7.65-7.55 (m, 2H, ArH), 3.50-3.40 (t, *J* = 7.4 Hz, 2H, SO_2CH_2), 2.70-2.60 (m, 2H, CH_2CO) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ = 172.2, 139.9, 135.3, 130.6, 129.3, 52.3, 28.6 ppm; IR (ATR) ν = 1701, 1320, 1156 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).

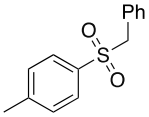


Methyl 3-(phenylsulfonyl)propanoate (46g):[303] Colorless oil; R_f = 0.47 (hexane/ethyl acetate 1/1); t_r = 14.0 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.95-7.85 (m, 2H, ArH), 7.75-7.65 (m, 1H, ArH), 7.65-7.55 (m, 2H, ArH), 3.64 (s, 3H, OCH_3), 3.50-3.40 (m, 2H, SO_2CH_2), 2.80-2.70 (m, 2H, CH_2CO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.5, 138.5, 134.1, 129.5, 128.2, 52.4, 51.5, 27.7 ppm; 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).

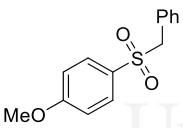
[301] Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X. Q.; Noyori, R. *Tetrahedron* **2001**, *57*, 2469-2476.
[302] Grove, C. I.; Di Maso, M. J.; Jaipuri, F. A.; Kim, M. B.; Shaw, J. T. *Org. Lett.* **2012**, *14*, 4338-4341.
[303] Lee, J. Y.; Hong, Y.-T.; Kim, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 6182-6186.



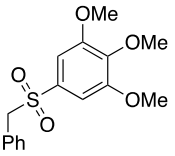
1-(benzylsulfonyl)naphthalene (46h):[304] White solid; R_f = 0.40 (hexane/ethyl acetate 7/3); m.p. 102-104 ºC; t_r = 20.38 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.67 (dd, J = 8.6, 0.8 Hz, 1H, ArH), 7.96 (d, J = 8.2 Hz, 1H, ArH), 7.90-7.80 (m, 2H, ArH), 7.60-7.45 (m, 2H, ArH), 7.35-7.30 (m, 1H, ArH), 7.15-7.10 (m, 1H, ArH), 7.10-7.00 (m, 2H, ArH), 6.90-6.80 (m, 2H, ArH), 4.40 (s, 2H, CH_2SO_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 135.3, 134.0, 133.0, 131.5, 130.7, 129.3, 129.2, 128.7 (2C), 128.5, 128.1, 127.0, 124.2, 124.1, 62.4 ppm; IR (ATR) ν = 3063, 2971, 1314, 1116 cm^{-1}; MS (EI) m/z (%): 282 (M^+, 18%), 127 (10), 91 (100).



1-(benzylsulfonyl)-4-methylbenzene (46i):[212b] White solid; R_f = 0.43 (hexane/ethyl acetate 7/3); m.p. 134-136 ºC; t_r = 17.09 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55-7.45 (m, 2H, ArH), 7.35-7.20 (m, 5H, ArH), 7.10-7.05 (m, 2H, ArH), 4.29 (s, 2H, ArH), 2.41 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.8, 135.1, 130.9, 129.6, 128.8, 128.7, 128.6, 128.4, 63.0, 21.8 ppm; IR (ATR) ν = 2920, 1456, 1310, 1131 cm^{-1}; MS (EI) m/z (%): 246 (M^+, 3%), 91 (100), 65 (10).



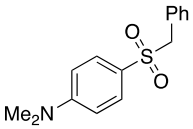
1-(benzylsulfonyl)-4-methoxybenzene (46j):[212b] White solid; R_f = 0.36 (hexane/ethyl acetate 6/4); m.p. 104-106 ºC; t_r = 18.17 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55-7.45 (m, 2H, ArH), 7.35-7.30 (m, 3H, ArH), 7.30-7.20 (m, 2H, ArH), 7.10-7.05 (m, 2H, ArH), 4.29 (s, 2H, ArH), 2.41 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.8, 131.0, 129.6, 128.8, 128.7 (2C), 114.2, 63.3, 55.8 ppm; IR (ATR) ν = 1594, 1491, 1294, 1247, 1144, 1089, 1029, 773, 694 cm^{-1}; MS (EI) m/z (%): 262 (M^+, 5%), 198 (14), 91 (100).



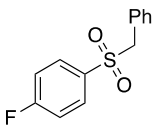
5-(benzylsulfonyl)-1,2,3-trimethoxybenzene (46k): White solid; R_f = 0.27 (hexane/ethyl acetate 7/3); m.p. 121-123 ºC; t_r = 20.3 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.25 (m, 3H, ArH), 7.15-7.05 (m, 2H, ArH), 6.76 (s, 2H, ArH), 4.29 (s, 2H, CH_2SO_2), 3.88 (s, 3H, OCH_3), 3.73 (s, 6H, 2xOCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.2, 142.4, 132.1, 131.0, 128.8, 128.7, 128.6, 106.0, 63.2, 61.1, 56.4 ppm; IR (ATR) ν = 2924, 2836, 1588, 1308, 1120 cm^{-1}; MS

[304] Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 1690-1693.

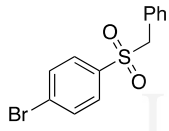
(EI) *m*/*z* (%): 322 (M^+, 39%), 243 (10), 227 (13), 91 (100); HRMS calcd. (%) for $C_{16}H_{18}O_5S$: 322.0875; found: 322.0882.



4-(benzylsulfonyl)-*N*,*N*-dimethylaniline (46l):[211b] White solid; R_f = 0.27 (hexane/ethyl acetate 7/3); m.p. 143-145 ºC; t_r = 21.19 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45-7.40 (m, 2H, ArH), 7.35-7.25 (m, 3H, ArH), 7.15-7.10 (m, 2H, ArH), 6.65-6.55 (m, 2H, ArH), 4.26 (s, 2H, CH_2SO_2), 3.04 (s, 6H, NMe_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.4, 131.0, 130.4, 129.2, 128.5, 123.5, 110.9, 63.4, 40.3 ppm; IR (ATR) ν = 2969, 1553, 1374, 1087 cm^{-1}; MS (EI) *m*/*z* (%): 275 (M^+, 100%), 211 (22), 210 (18), 168 (32), 136 (80), 120 (51), 91 (79), 77 (25), 65 (18).



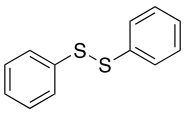
1-(benzylsulfonyl)-4-fluorobenzene (46m):[304] White solid; R_f = 0.43 (hexane/ethyl acetate 7/3); m.p. 150-152 ºC; t_r = 15.89 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65-7.55 (m, 2H, ArH), 7.35-7.25 (m, 3H, ArH), 7.15-7.05 (m, 4H, ArH), 4.31 (s, 2H, CH_2SO_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.8 (d, *J* = 256.4 Hz), 133.8 (d, *J* = 2.9 Hz), 131.5 (d, *J* = 9.6 Hz, 2C), 130.9, 129.0, 128.8, 128.2, 116.2 (d, *J* = 22.5 Hz), 63.2 ppm; IR (ATR) ν = 3063, 2988, 1456, 1314, 1147 cm^{-1}; MS (EI) *m*/*z* (%): 250 (M^+, 2%), 91 (100).



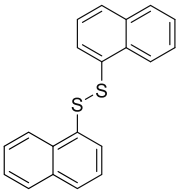
1-(benzylsulfonyl)-4-bromobenzene (46n):[305] White solid; R_f = 0.47 (hexane/ethyl acetate 7/3); m.p. 149-151 ºC; t_r = 17.92 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.60-7.55 (m, 2H, ArH), 7.50-7.40 (m, 2H, ArH), 7.40-7.20 (m, 3H, ArH), 7.10-7.05 (m, 2H, ArH), 4.30 (s, 2H, CH_2SO_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.9, 132.3, 130.9, 130.3, 129.3, 129.1, 128.8, 127.9, 63.0 ppm; IR (ATR) ν = 3064, 2944, 1576, 1312 cm^{-1}; MS (EI) *m*/*z* (%): 312 (M^+Br^{81}, 1), 310 (M^+Br^{79}, 1%), 91 (100).

[305] Schwertz, G.; Frei, M. S.; Witschel, M. C.; Rottmann, M.; Leartsakulpanich, U.; Chitnumsub, P.; Jaruwat, A.; Ittarat, W.; Schaefer, A.; Aponte, R. A.; Trapp, N.; Mark, K.; Chaiyen, P.; Diederich, F. *Chem. Eur. J.* **2017**, *23*, 14345-14357.

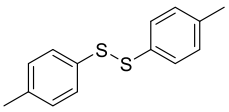
General procedure for the synthesis of disulfides: A solution of Ar_3Bi (0.2 mmol), sodium metabisulfite (1.32 mmol) in 1.5 mL of DES was stirred for 5 h at 80 ºC. Then, I_2 (1.2 mmol) was added and the reaction was stirred for 20 min. Once the reaction was completed, water was added to dissolve the DES phase. That aqueous suspension was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate).



1,2-Diphenyldisulfane (47a):[306] Yellowish solid; R_f = 0.53 (hexane); m.p. 57-59 ºC; t_r = 14.75 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55-7.45 (m, 4H, ArH), 7.35-7.15 (m, 6H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.2, 129.2, 127.7, 127.3 ppm; IR (ATR) ν = 3028, 2922, 686 cm^{-1}; MS (EI) *m*/*z* (%): 219 (M^++1, 15%), 218 (100), 185 (16), 154 (17), 109 (66), 65 (18).



1,2-Di(naphthalen-1-yl)disulfane (47b):[307] White solid; R_f = 0.3 (hexane); m.p. 133-134 ºC; t_r = 25.42 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.40-8.30 (m, 2H, ArH), 7.90-7.80 (m, 2H, ArH), 7.80-7.75 (m, 2H, ArH), 7.65-7.60 (m, 2H, ArH), 7.50-7.45 (m, 4H, ArH), 7.30-7.20 (m, 2H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.2, 133.6, 132.9, 130.4, 129.4, 128.7, 126.8, 126.5, 125.6, 125.2 ppm; IR (ATR) ν = 3051, 2923, 2848, 2362, 1580, 1495, 862, 813, 736 cm^{-1}; MS (EI) *m*/*z* (%): 318 (M^+, 65%), 281 (14), 255 (15), 254 (27), 207 (23), 160 (89), 159 (61), 158 (10), 128 (64), 116 (24), 115 (100), 79 (13).



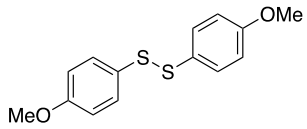
1,2-Di-*p*-tolyldisulfane (47c):[308] Yellowish oil; R_f = 0.43 (hexane); t_r = 15.76 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 8.0 Hz, 4H, ArH), 7.10 (d, *J* = 8.0 Hz, 4H, ArH), 2.32 (s, 6H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.6, 134.0, 129.9, 128.7, 21.2 ppm; IR (ATR) ν = 2920, 1487, 1077,

[306] Banfield, S. C.; Omori, A. T.; Leisch, H.; Hudlicky, T. *J. Org. Chem.* **2007**, *72*, 4989-4992.

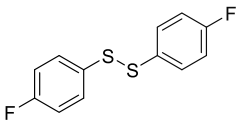
[307] Francisco, M. A.; Kurs, A.; Katritzky, A. R.; Rasala, D. *J. Org. Chem.* **1988**, *53*, 596-600.

[308] Loghmani-Khouzani, H.; Poorheravi, M. R.; Sadeghi, M. M. M.; Caggiano, L.; Jackson, R. F. W. *Tetrahedron* **2008**, *64*, 7419-7425.

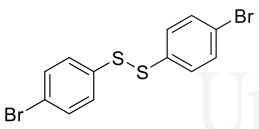
1038, 1015, 800 cm^{-1}; MS (EI) *m/z* (%): 248 (M^++2, 14), 247 (M^++1, 23), 246 (M^+, 100), 124 (12), 123 (84), 79 (14), 77 (15).



1,2-Bis(4-methoxyphenyl)disulfane (47d):[306] Brown oil; R_f = 0.46 (hexane/ethyl acetate 4/1); t_r = 17.2 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.45-7.35 (m, 4H, ArH), 6.85-6.80 (m, 4H, ArH), 3.79 (s, 6H, 2xOCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.0, 132.8, 128.6, 114.8, 55.5 ppm; IR (ATR) ν = 2833, 1241, 608 cm^{-1}; MS (EI) *m/z* (%): 278 (M^+, 64%), 139 (100), 125 (11), 96 (10).



1,2-Bis(4-fluorophenyl)disulfane (47e):[309] Yellow oil; R_f = 0.46 (hexane); t_r = 14.27 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44 (dd, *J* = 8.8, 5.1 Hz, 4H, ArH), 7.01 (t, *J* = 8.8 Hz, 4H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.7 (d, *J* = 248.2 Hz), 132.3 (d, *J* = 3.5 Hz), 131.4 (d, *J* = 8.2 Hz), 116.4 (d, *J* = 22.1 Hz) ppm; IR (ATR) ν = 1588, 1485, 1224, 1154, 821 cm^{-1}; MS (EI) *m/z* (%):255 (M^++1, 12), 254 (M^+, 78%), 128 (21), 127 (100), 83 (39).

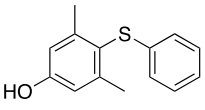


1,2-Bis(4-bromophenyl)disulfane (47f):[306] White solid; R_f = 0.63 (hexane); m.p. 89-90 ºC; t_r = 16.84 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.45-7.40 (m, 4H, ArH), 7.35-7.30 (m, 4H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 135.9, 132.4, 129.6, 121.7 ppm; IR (ATR) ν = 1465, 1382, 1078, 1065, 1004, 808 cm^{-1}; MS (EI) *m/z* (%):378 (M^++4, 54), 376 (M^++2, 100%), 374 (M^+, 48), 297 (12), 295 (11), 190 (21), 189 (68), 188 (21), 187 (64), 109 (30), 108 (85), 82 (11), 69 (14), 63 (11).

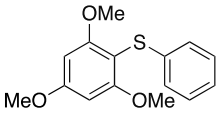
General procedure for the synthesis of sulfides: A solution of Ar_3Bi (0.2 mmol), sodium metabisulfite (1.32 mmol) in 1.5 mL of DES was stirred for 5 h at 80 ºC. Then, I_2 (1.2 mmol) was added and the reaction was stirred for 20 min, before the corresponding pro-nuclephile was added (1.2 mmol). Once the reaction was completed, water was added to dissolve the DES phase. That aqueous suspension was extracted with EtOAc (3 x 5 mL). The combined

[309] Yang, Z.; Shi, Y.; Zhan, Z.; Zhang, H.; Xing, H.; Lu, R.; Zhang, Y.; Guan, M.; Wu, Y. *ChemElectroChem* **2018**, *5*, 3619-3623.

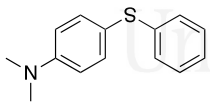
organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate).



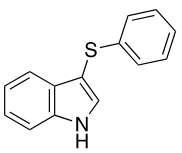
3,5-Dimethyl-4-(phenylthio)phenol (48a):[224a] White solid; R_f = 0.33 (hexane/ethyl acetate 4/1); m.p. 98-101 ºC; t_r = 15.4 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25-7.15 (m, 2H, ArH), 7.10-7.00 (m, 1H, ArH); 6.95-6.90 (m, 2H, ArH), 6.70 (s, 2H, ArH), 5.19 (s, 1H, OH), 2.39 (s, 6H, 2xCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.2, 146.1, 138.7, 129.0, 125.3, 124.6, 121.7, 115.5, 22.0 ppm; IR (ATR) ν = 3280, 2919, 690 cm^{-1}; MS (EI) *m*/*z* (%): 231 (M^++1, 17), 230 (M^+, 100%), 152 (23), 151 (10), 91 (15).



Phenyl(2,4,6-trimethoxyphenyl)sulfane (48b):[224a] White solid; R_f = 0.30 (hexane/ethyl acetate 4/1); m.p. 119-121 ºC; t_r = 16.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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, 2xOCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.0, 162.6, 138.8, 128.6, 125.7, 124.4, 98.8, 91.3, 56.4, 55.5 ppm; IR (ATR) ν = 3010, 1576, 1122 cm-1; MS (EI) m/z (%): 276 (M^+, 100%), 228 (12).



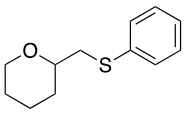
***N,N*-dimethyl-4-(phenylthio)aniline (48c):**[224a] White solid; R_f = 0.53 (hexane/ethyl acetate 4/1); m.p. 63-65 ºC; t_r = 15.54 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40-7.35 (m, 2H, ArH), 7.20-7.15 (m, 2H, ArH), 7.10-7.00 (m, 3H, ArH), 6.70-6.65 (m, 2H, ArH), 2.95 (s, 6H, 2xCH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.7, 140.4, 136.2, 128.8, 126.9, 125.0, 117.5, 113.1, 40.4 ppm; IR (ATR) ν = 2898, 1509, 1368, 739 cm^{-1}; MS (EI) *m*/*z* (%): 229 (M^+, 100%), 228 (18), 197 (23), 196 (24), 184 (14), 152 (21).



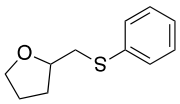
3-(phenylthio)-1*H*-indole (48d):[310] White solid; R_f = 0.20 (hexane/ethyl acetate 4/1); m.p. 147-149 ºC (ethanol); t_r = 16.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.34 (br s, 1H, NH), 7.61 (d, *J* = 7.49 Hz, 1H, ArH), 7.44 (d, *J* = 2.6 Hz, 1H, ArH), 7.41 (d, *J* = 8.2 Hz, 1H, ArH), 7.30-7.20 (m, 1H, ArH),

[310] Qi, H.; Zhang, T.; Wan, K.; Luo, M. *J. Org. Chem.* **2016**, *81*, 4262-4268.

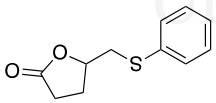
7.20-7.00 (m, 6H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.3, 136.6, 130.8, 129.2, 128.8, 126.0, 124.9, 123.2, 121.0, 119.8, 111.7, 102.9 ppm; IR (ATR) ν = 3406, 1338, 737 cm^{-1}; MS (EI) *m*/*z* (%): 225 (M^+, 100%), 224 (40), 223 (18), 193 (20), 148 (13), 77 (12).



2-((phenylthio)methyl)tetrahydro-2*H*-pyran (48e):[311] Yellow oil; R_f = 0.67 (hexane/ethyl acetate 4/1); t_r = 12.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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_2O), 3.09 (dd, *J* = 13.2, 6.6 Hz, 1H, *H*CHS), 2.93 (dd, *J* = 13.2, 5.8 Hz, 1H, HC*H*S), 1.90-1.70 (m, 2H, CH_2Cy), 1.65-1.45 (m, 3H, CH_2Cy), 1.45-1.25 (m, 1H, CH_2Cy) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.9, 129.0, 128.9, 125.9, 76.4, 68.8, 39.6, 31.3, 25.9, 23.3 ppm; IR (ATR) ν = 2933, 1088, 689 cm^{-1}; MS (EI) *m*/*z* (%): 208 (M^+, 40%), 124 (28), 85 (100), 67 (17), 57 (15).



2-((phenylthio)methyl)tetrahydrofuran (48f):[224b] Yellow oil; R_f = 0.50 (hexane/ethyl acetate 4/1); t_r = 12.3 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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, *H*CHO), 3.80-3.70 (m, 1H, HC*H*O), 3.15 (dd, *J* = 13.0, 5.8 Hz, 1H, *H*CHS), 2.97 (dd, *J* = 13.0, 6.8 Hz, 1H, HC*H*S), 2.10-2.00 (m, 1H, *H*CHCHO), 2.00-1.80 (m, 2H, C*H*$_2$CH$_2$O), 1.75-1.60 (m, 1H, HC*H*CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.5, 129.2, 129.0, 126.0, 77.7, 68.4, 39.0, 31.0, 25.9 ppm; IR (ATR) ν = 2865, 1053, 690 cm^{-1}; MS (EI) *m*/*z* (%): 194 (M^+, 39%), 124 (26), 123 (11), 71 (100).

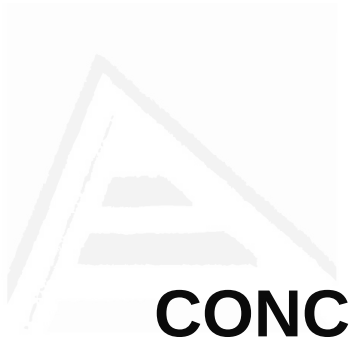


5-((phenylthio)methyl)dihydrofuran-2-(3*H*)-one (48g):[312] Yellow oil; R_f = 0.50 (hexane/ethyl acetate 1/1); t_r = 14.4 min ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.45-7.35 (m, 2H, ArH), 7.35-7.25 (m, 2H, ArH), 7.25-7.15 (m, 1H, ArH), 4.60 (ddd, *J* = 14.1, 7.2, 5.0 Hz, 1H, CHO), 3.32 (dd, *J* = 13.0, 5.0 Hz, 1H, *H*CHS), 3.04 (dd, *J* = 13.9, 7.4 Hz, 1H, HC*H*S), 2.65-2.45 (m, 2H, CH_2CO), 2.45-2.30 (m, 1H, *H*CHCH), 2.10-1.90 (m, 1H, HC*H*CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.5, 134.7,

[311] Tuladhar, S. M.; Fallis, A. G. *Can. J. Chem.* **1987**, *65*, 1833-1837.

[312] Vaskevich, A. I.; Tsizorik, N. M.; Rusanov, E. B.; Staninets, V. I.; Vovk, M. V. *Russ. J. Org. Chem.* **2012**, *48*, 193-201.

130.1, 129.1, 126.9, 78.5, 38.5, 28.4, 26.9 ppm; 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).



CONCLUSIONS

A truly alternative and sustainable reaction medium for traditional and hazardous solvents can be used in known and novel organic transformations, such as those appeared along this study, for instance:

The *in situ* generation of organoindium reagents and the subsequent addition to ketones was highly compatible with DES as reaction medium.

The rational design of DES-compatible palladium catalyst led to efficient catalytic systems for cross-coupling reactions, maintaining the previous results reported with traditional organic solvents.

Highly challenging C-H activation reaction could also be performed in DESs under mild reaction conditions.

The applicability of DESs for the radical conjugated addition of olefins proved to be beneficial, improving the sustainability and the results obtained in comparison to previous reported methodologies.

Deep Eutectic Solvent based materials, eutectogels, were efficiently applied for the enantioselective aldol reaction, obtaining similar results as standard protocols.

A heterogeneous and recyclable palladium catalyst proved to be compatible for the cycloisomerization of alkynoic acids and derivatives in neoteric media.

The fine tuning properties of DESs allowed the development of a multicomponent synthesis of sulfur containing compounds in an environmentally-friendly fashion.

Thus, DESs have the potential to provide notable advantages in organic synthesis methodologies due to their benign nature, highly tunable properties and the possibility in most of the cases to recycle the whole system.

BIOGRAPHY

I was born in Ibi (Alicante) on 14th August 1994.

I carried out my primary studies at school “San Juan y San Pablo” and secondary ones at “I.E.S Fray Ignacio Barrachina” in Ibi (Alicante).

From 2012 to 2016, I underwent the degree in Chemistry studies on the Sciences Faculty at the University of Alicante.

In September 2016, I joined the research group of Prof. Dr. Ramón at the Organic Chemistry Department of the University of Alicante, where I performed my Masters Degree in Medicinal Chemistry.

Since 2017 up until the present day, I have been working on my Doctoral Thesis. Part of the results are presented in this manuscript.

Since February 2018, I hold a predoctoral grant from Generalitat Valenciana (GVA).

From 11th September 2020 to 11th December 2020, I performed an intership at the prestigous research group of Prof. Dr. Nicolai Cramer, at the École Polytechnique Fédérale de Lausanne (EPFL), working in the iridium catalyzed asymmetric reductive amination.

ACKNOWLEDGMENTS

I would like to thank all the people and institutions which have helped and permitted me to reach the current situation, including Generalitat Valenciana (ACIF/2017/211).

I want to express my gratitude to all the people who kindly welcomed and helped me during my short stay at École Polytechnique Fédérale de Lausanne (EPFL). In particular, Prof. Dr. Cramer. I am also very thankful to Prof. Dr. García-Álvarez and Prof. Dr. D'Anna's research groups for their support on the cycloisomerization of alkynoic acids and the enantioselective aldol reaction in eutectogels projects, respectively.

I cannot thank the people who patently showed me how to work in the laboratory enough when I was starting, especially Dr. Juana M. Pérez, PhD and Dr. Xavier Marset, PhD. I would like to remark my gratitude to Xavi, who have supported me and taught me over these years. I am also grateful to Nere, it has been a pleasure to share this experience with you and thank you for being there through thick and thin.

Thanks to Alejandro, Diego Ros, Edu, Iris, Llorenç, María, Mario, Martín, Natalia, Sarah and all the rest of my lab mates for all the unforgettable moments that we have experienced together inside and outside the laboratory.

I would like to thank my friends, I am very lucky to have you. I am very grateful to have met you Patri, a hard-working chemist and even, a better friend.

I could not have finished writing this thesis without thanking my parents and sister for their unconditional support, patience, and for always believing in me. I would have never reached this point without you.

Finally, I should thank my PhD supervisor Prof. Dr. Ramón for all his support and dedication during this time and for giving me the opportunity to grow professionally by your side.

INDEX

ABBREVIATION LIST

AcChCl: acetylcholine chloride

aNHC: abnormal N-heterocylic carbene

Bipy: bipyridine ligand

Bn: Bencyl

ChCl: choline chloride

Cy: Cyclohexyl

DABCO: 1,4-Diazabicyclo[2.2.2]octane

DABSO: 1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct

DES: Deep Eutectic Solvent

DG: Directing Group

DMAP: 4-Dimethylaminopyridine

DMU: *N*,*N*'-dimethylurea

DSC: differential-scanning calorimetry

DTBB: 4,4′-di-*tert*-butylbiphenyl

EI: Electronic Impact

ET: Electron Transfer

EWG: Electron-withdrawing group

FG: Functional Group

GC: gas cromatography

HAT: Hydrogen-Atom Transfer

HBA: hydrogen-bond acceptor

HBD: hydrogen-bond donnor

HPLC: high-performance liquid cromatography

ICP: inductively coupled plasma

ICP-MS: Inductevely Coupled Plasma Mass Spectrometry

ICP-OES: Inductevely Coupled Plasma Optical Emission Spectrometry

IL: ionic liquid

IR: infrared

LMWG: Low Molecular Weight Gelator

MCR: multicomponent reaction

MD: Molecular Dynamics

2-MeTHF: 2-Methyltetrahydrofuran

MS: Mass Spectroscopy
NADES: Natural Deep Eutectic Solvent
NHC: N-Heterocyclic Carbene
NMR: Nuclear Magnetic Resonance
NP: Nanoparticle
PEG: Polyethylene glycol
PMHS: polymethylhydrosiloxane
PPG: Polypropylene glycol
PT: Proton Transfer
rt: room temperature
SCF: Super Critical Fluid
SDF: Spatial Density Functions
SET: Single Electron Transfer
TBAB: Tetrabutylammonium bromide
TEM: Transition Electron Microscopy
TEMPO: 2,2,6,6-Tetramethylpiperidine 1-oxyl
T_g: Glass transition temperature
TLC: Thin Layer Chromatography
TMS: Tetramethylsilane
UV/Vis: Ultraviolet/Visible Spectroscopy
VOC: Volatile Organic Compound
wt: weight
XDR: X-Ray Diffraction
XPS: X-Ray Photoelectron Microscopy
XRF: X-Ray Fluorescence

EPILOGUE

En los últimos años ha surgido un creciente interés y preocupación por el medio ambiente, debido a la concienciación social acerca del impacto negativo que provocan las actividades antropogénicas sin criterio medio ambiental, incluyendo la aparición de enfermedades zoonóticas. Es por ello, que la sostenibilidad es ahora una prioridad en nuestra sociedad y el desarrollo de procesos medioambientalmente sostenibles en la Química Industrial es totalmente necesario.

Consecuentemente, surge una nueva corriente llamada gráficamente Química Verde, o más correctamente Química Sostenible, que consiste en diseñar productos y procesos químicos alternativos que minimicen o eliminen el uso y la generación de sustancias tóxicas y dañinas para el medio ambiente. Dicha filosofía, se basa en 12 principios básicos enfocados como guía para los químicos hacia la búsqueda y desarrollo de procesos con un menor impacto medioambiental (Figura 1).

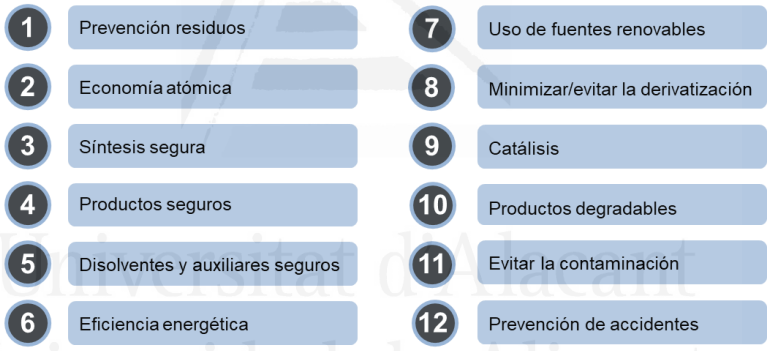


Figura 1.12 Principios de la Química Verde.

Otro de los retos para la Química Verde reside en la evaluación de la sostenibilidad de los procesos químicos. Para ello, se han determinado diferentes parámetros como la economía atómica y el factor *E*. La economía atómica se calcula dividiendo el peso molecular del producto por el sumatorio del peso molecular de los reactivos, expresado en porcentaje. Este parámetro asume el uso de cantidades estequiométricas para los reactivos de partida y rendimientos del 100% y, no tiene en cuenta las sustancias que no aparecen en la ecuación de la reacción tales como los disolventes. Por otro lado, el factor *E* se define como el cociente entre la masa de residuo y la masa del producto deseado. A diferencia de

la economía atómica, el factor *E* tiene en cuenta el rendimiento de la reacción y todas las sustancias auxiliares empleadas en el proceso y además, puede aplicarse a síntesis de varios pasos, lo que facilita una evaluación más global y completa de todo el proceso.

Actualmente, la mayoría de los procesos químicos siguen una economía lineal, que consiste en extraer-producir-usar-eliminar. La aparición de la Química Sostenible ha permitido en estos últimos años la optimización de ciertos procesos químicos, lo que ha conllevado a unas prácticas más concienciadas y menos perjudiciales para el medio ambiente, intentando potenciar factores como el reciclaje, el uso de materiales sostenibles y la disminución de la cantidad de residuos generados. No obstante, esto no es suficiente, por lo que se debe seguir avanzando hacia la sostenibilidad y una economía circular. Dicha vertiente pretende ofrecer procesos químicos que sean realmente circulares, de forma que los productos puedan ser reutilizados como material de partida casi indefinidamente e intentando hacer frente a las crisis ambientales con una gestión eficaz de los residuos y materias renovables, mediante el diseño de metodologías que permitan este enfoque.

Al aplicar los principios de la Química Sostenible a la síntesis orgánica, y más concretamente a la industria farmacéutica, se identifica rápidamente un problema en el uso de disolventes orgánicos volátiles, tóxicos y dañinos para el medio ambiente. Se estima que los disolventes constituyen entre el 80-90% de la masa no acuosa que se emplea en la industria farmacéutica. Por lo tanto, la búsqueda de disolventes alternativos y respetuosos con el medio ambiente y su aplicabilidad en síntesis orgánica es de gran interés.

La solución más evidente es la eliminación del disolvente. Sin embargo, la ausencia de disolvente no es aplicable en todas reacciones. En general, el uso de disolventes presenta varias ventajas como mejor transferencia de calor y de masa en las reacciones, evitar la formación de subproductos por dilución y estabilizar estados de transición de complejos organometálicos, entre otros.

Consecuentemente, han surgido varias alternativas a los disolventes convencionales, los llamados disolventes neotéricos. Entre ellos, cabe destacar el agua, los fluidos supercríticos, los disolventes perfluorados, los disolventes derivados de la biomasa (glicerol, 2-metiltetrahidrofurano, cireno, etc.), e incluso, polímeros inertes como el polietilenglicol (PEG). 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 e incompatibilidad de ciertos compuestos orgánicos en agua (hidrólisis), el elevado coste y consumo energético para generar los fluidos supercríticos, el alto precio y la persistencia de los disolventes perfluorados en el medio ambiente, la baja producción de disolventes derivados de la biomasa y la baja biodegradabilidad de los polímeros inertes.

Algo más sofisticados son los líquidos iónicos, formados por un catión orgánico y un anión orgánico/inorgánico con una coordinación débil entre ambos, por lo que generalmente son líquidos por debajo de los 100 ºC. Los líquidos iónicos presentan una volatilidad nula, no son inflamables, son estables a altas temperaturas y poseen un alto poder de solvatación. Sin embargo, se ha demostrado que algunos de los líquidos iónicos son tóxicos y persistentes en el medio ambiente. Además, su síntesis requiere un gran número de pasos sintéticos y el uso de disolventes derivados del petróleo.

Con el objetivo de evitar y eliminar todos estos inconvenientes, surgen las mezclas eutécticas (*Deep Eutectic Solvents*, DESs, en terminología inglesa), formadas por dos o más componentes, generalmente ácidos y bases de Brønsted y Lewis, los cuales pueden interaccionar entre ellos a través de enlaces de hidrógeno y fuerzas electrostáticas, generando una mezcla líquida con un punto de fusión muy inferior al de sus componentes por separado (Figura 2).

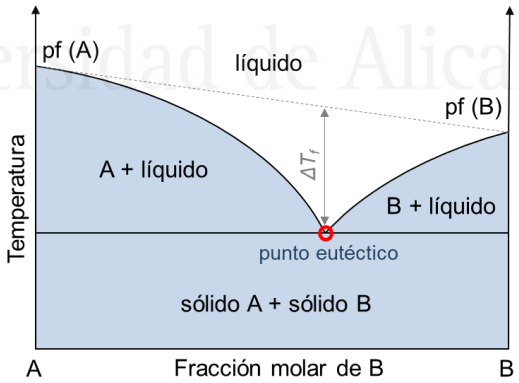


Figura 2. Diagrama de fases mezcla eutéctica.

Estos nuevos disolventes son una alternativa a los disolventes orgánicos volátiles, debido a sus propiedades tales como bajo coste, presión de vapor nula, alta reciclabilidad, no inflamables, síntesis sencilla y con economía atómica del 100% y, además, son seguros para el medio ambiente por su elevada biodegradabilidad.

Este tipo de disolventes ha ido creciendo en popularidad en los últimos años, debido a sus propiedades únicas y fácilmente ajustables. Más concretamente, las mezclas eutécticas se han empleado para la extracción de diversos compuestos (fenoles, polisacáridos, proteínas, etc.). La estructura de estos disolventes se ha utilizado como guía para la síntesis de diversos materiales, desde nanopartículas metálicas hasta carbones porosos. Además, también se han empleado en el campo de la electroquímica para el pulido de superficies metálicas.

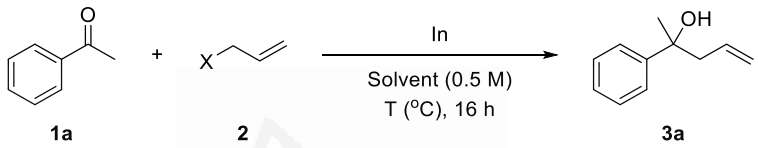
En el campo de la síntesis orgánica y la catálisis, las mezclas eutécticas han empezado a ganar protagonismo como medio de reacción en diferentes transformaciones orgánicas, reacciones metalocatalizadas, polimeraciones y biocatálisis. Sin embargo, todavía existen muy pocos ejemplos de reacciones orgánicas, típicas en la síntesis farmacéuticas, llevadas a cabo en DES como disolventes. Por lo tanto, el diseño de nuevos catalizadores/rutas sintéticas compatibles con estos disolventes brinda una oportunidad para el desarrollo de metodologías más sostenibles y respetuosas con el medio ambiente.

En este contexto, se decidió desarrollar diversas metodologías para la formación de enlaces C-C, C-O y C-S utilizando los DESs como medio de reacción.

Entre ellas, la alilación de compuestos carbonílicos mediada por indio metálico (reacción de Barbier). Los compuestos organometálicos derivados de los metales del primer grupo, tales como compuestos de organolitio, organomagnesio u organozinc, han demostrado tener una amplia aplicabilidad en síntesis orgánica durante muchos años. Sin embargo, estos compuestos son altamente sensibles al aire y a la humedad, lo que hace que su preparación y su manejo sea más difícil. En este aspecto, los compuestos de organoindio son una alternativa viable, ya que son estables al aire y a la humedad, poseen una reactividad moderada en comparación los compuestos organolíticos u organomagnesianos y ofrecen una amplia tolerancia de grupos funcionales.

Además, se ha descrito que los compuestos de organoindio son estables en medios próticos tales como el agua. En base a estos antecedentes, se decidió sintetizar diferentes compuestos de organoindio *in situ* utilizando las mezclas eutécticas como disolvente y, posteriormente, hacerlos reaccionar con diferentes electrófilos.

Para ello, inicialmente se optimizaron las condiciones de reacción utilizando la acetofenona, diferentes haluros de alilo e indio metálico como reacción modelo (Esquema 1).



Esquema 1. Optimización reacción de Barbier en DESs.

Una vez definidas las condiciones de reacción óptimas [NH_4Cl (28 mol%) como aditivo, cloruro de acetilcolina:acetamida (1:2) como disolvente, 25 ºC y 12 h de reacción], se estudió el alcance de la reacción con diferentes cetonas/aldehídos y cloruros de alilo, obteniendo en todos los casos resultados excelentes.

Además se encontró una relación entre la densidad y/o viscosidad del disolvente empleado y el rendimiento de la reacción (Figura 3). Dicha tendencia se postuló que podría deberse a la formación de huecos en el disolvente, en cuyo interior se encuentran los radicales generados durante la reacción.

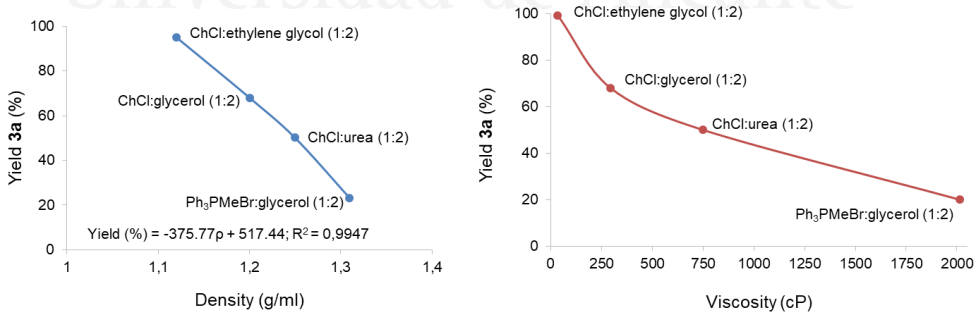


Figura 3. Relación entre la densidad/viscosidad y el rendimiento de la reacción.

Otro proyecto del presente trabajo se centró en el diseño de varios catalizadores de paladio compatibles con las mezclas eutécticas para llevar a cabo reacciones de acoplamiento C-C tales como Suzuki-Miyaura, Hiyama, Sonogashira y Heck.

En general, la actividad catalítica de los complejos metálicos en las reacciones de acoplamiento se puede mejorar utilizando ligandos dadores-σ. En este sentido, los carbenos N-heterocíclicos son ligandos dadores-σ y aceptores-π débiles, siendo los carbenos N-heterocíclicos anormales ligandos dadores-σ más fuertes, por lo que facilitan la adición oxidativa en las reacciones de acoplamiento. Es por ello que se decidió diseñar un catalizador de paladio con carbenos N-heterocíclicos anormales como ligandos, compatible con las mezclas eutécticas.

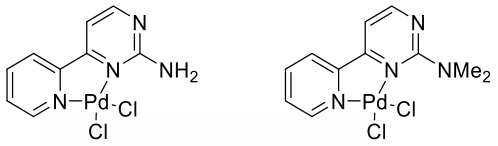
Una vez se sintetizó y caracterizó el complejo de paladio, se probó su actividad catalítica en varias reacciones de acoplamiento C-C, tales como Suzuki, Heck, Sonogashira e Hiyama. Hay que estacar que, en todos los casos se obtuvieron buenos resultados, lo que demuestra el importante papel del ligando en la actividad catalítica del complejo y su elevada compatibilidad en diversas mezclas eutécticas.

Para entender mejor el proceso catalítico, se realizó el test de mercurio. Por lo que, si las reacciones estaban catalizadas por nanopartículas de paladio (PdNPs) se debería observar una caída notable en el rendimiento de la reacción. Se observó una inhibición completa en las reacciones de Suzuki, Sonogashira y Heck. Sorprendentemente, la reacción de Hiyama no se vio afectada tras la adición de mercurio (2.5 equivalentes). Además, se analizaron todos los crudos de reacción para confirmar la formación *in situ* de nanopartículas de paladio y en todos los casos, se observó la formación de las mismas.

Normalmente, los catalizadores de paladio compatibles con DESs empleados en nuestro grupo de investigación, se pueden clasificar como aceptores de enlaces de hidrógeno atendiendo a la clasificación de los dos tipos componentes que puede formar un DES (aceptores o dadores de enlace de hidrógeno). Por lo tanto, nuestro siguiente objetivo fue el diseño de un nuevo catalizador de paladio tipo amino-bipiridina (ligando dador) con una elevada compatibilidad en mezclas eutécticas debido a su capacidad intrínseca de formar enlaces de hidrógeno (grupo amino -NH_2), para mejorar la actividad catalítica y ampliar la

aplicabilidad de estos catalizadores de paladio compatibles en DESs y también, mejorar la reciclabilidad del sistema catalítico anterior.

Tras realizar el diseño de los ligandos en función de los antecedentes bibliográficos y de las necesidades del sistema a emplear (compatibilidad con las mezclas eutécticas), se sintetizaron los complejos metálicos tipo bipiridina utilizando procedimientos sintéticos similares a los previamente descritos en la bibliografía (Figura 4).



Complejo A **Complejo B**

Figura 4. Complejos de paladio tipo amino-bipiridina.

Una vez sintetizados los complejos metálicos, se procedió al estudio de su actividad catalítica en reacciones de acoplamiento tales como Hiyama, Suzuki-Miyaura, Heck y Sonogashira, obteniendo muy buenos resultados en todos los casos. Además, se demostró la importancia de la presencia del grupo -NH_2 (complejo A) en el catalizador (capaz de formar enlaces de hidrógeno con la mezcla eutéctica y por tanto, aumentar su compatibilidad) con resultados mejores que con la ausencia de este grupo (complejo B).

Una vez comprobada la eficacia del sistema catalítico, se decidió aprovechar las propiedades únicas del medio de reacción para reciclar, no sólo el catalizador sino también el disolvente. Una vez terminada la reacción, se añadió 2-MeTHF (disolvente renovable) para extraer el producto y los reactivos de partida no reaccionados, quedando en el recipiente el disolvente eutéctico y el catalizador. De esta forma, agregando de nuevo los reactivos se puedo llevar a cabo el reciclado del sistema de la reacción hasta 3-5 veces sin pérdida notable de la actividad del catalizador (Figura 5).

Además, se comprobó la existencia de nanopartículas en el medio de reacción, por TEM y XPS, en todas las reacciones de acoplamiento. El test de mercurio confirmó que las nanopartículas de paladio generadas *in situ* en el medio de reacción eran realmente las

especies activas, ya que tras añadir 2.5 equivalentes de mercurio se observó un 2% de conversión del producto (inhibición de la reacción).

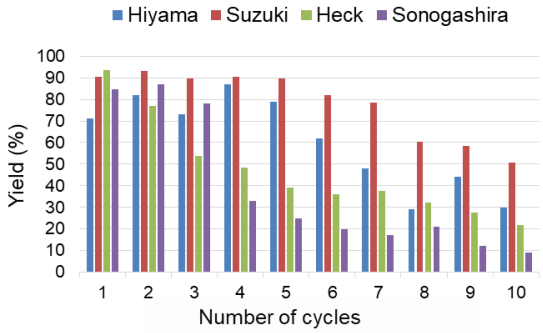


Figura 5. Reciclabilidad del sistema.

Por otro lado, se realizaron estudios cinéticos de las reacciones de acoplamiento, observando en todas ellas un periodo de inducción al inicio de la reacción compatible con la formación en primer lugar de las nanopartículas de paladio como catalizador real. Se comprobó por TEM que durante este periodo no se habían formado nanopartículas de paladio en ningún caso. Por lo tanto, esto parece indicar que el complejo A (catalizador de paladio tipo amino-bipiridina) juega un papel de pre-catalizador y las especies activas de la reacción son las nanopartículas de paladio formadas *in situ* en las reacciones de acoplamiento.

Por otra parte, se estudió la coordinación del ligando tipo bipiridina al centro metálico a través de estudios de UV-Vis. Tras el análisis de los resultados, se concluyó que el paladio posiblemente estuviera inicialmente coordinado al ligando tipo bipiridina a través de los grupos -NH_2 (Figura 6, coordinación A). Luego, este complejo inicial evolucionaría hacia el complejo termodinámico final (coordinación C) a través del intermedio B.

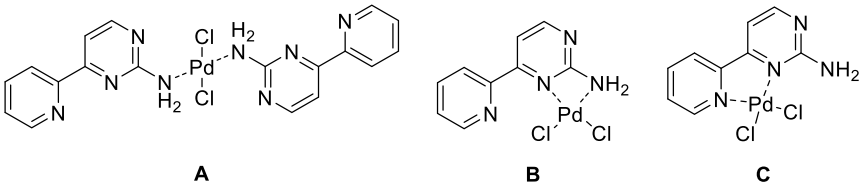
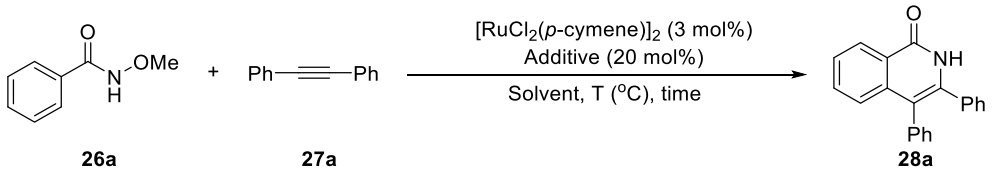


Figura 6. Diferentes coordinaciones del paladio con el ligando amino-bipiridina.

Otras de las transformaciones que se llevó a cabo en mezclas eutécticas fue la C-H activación catalizada por rutenio. Las condiciones de reacción se optimizaron utilizando *N*-metoxibenzamida y difenilacetileno como reacción modelo (Esquema 2).



26a **27a** **28a**

Esquema 2. Optimización C-H activación catalizada por rutenio.

Tras optimizar todos los parámetros, se determinó que un 3 mol% de $[RuCl_2(p\text{-cimeno})]_2$ y un 20 mol% de NaOAc como aditivo, era el mejor sistema catalítico; el cloruro de colina:etilienglicol (1:2) el mejor disolvente, y la temperatura y el tiempo de reacción se fijaron en 60 ^{o}C y 2 h.

Una vez optimizadas las condiciones de reacción, se estudió el alcance de la reacción. Para ello, se emplearon diferentes alquinos internos con sustituyentes aromáticos y alifáticos, observando mejores resultados en el caso de los aromáticos. Además, también se utilizaron olefinas con grupos electrón-atrayentes como sustratos con resultados excelentes.

Hasta la fecha, ninguna reacción radicalaria en síntesis orgánica se había realizado utilizando las mezclas eutécticas como disolventes. Por ello, se decidió desarrollar una ruta sintética radicalaria para la formación de enlaces C-C empleando los DESs como medio de reacción. El estudio se inició optimizando las condiciones de reacción para el acoplamiento radicalario entre 1-metilciclohexeno y acrilato de metilo. Se utilizaron varios silanos como agentes reductores, obteniendo el mejor resultado con el polimetilhidrosiloxano (PMHS), un silano no tóxico, barato y estable al aire y a la humedad. Se probaron varios catalizadores de hierro, obteniendo resultados excelentes con un catalizador de hierro comercial, económico y no tóxico $[Fe(acac)_3]$. Luego, se probaron diferentes mezclas eutécticas como disolventes, obteniendo el mejor resultado con el cloruro de colina:etilenglicol (1:2).

A continuación, se estudió el alcance de la reacción y para ello, se hicieron reaccionar diferentes olefinas pobres en electrones con un amplio abanico de grupos funcionales tales

como ésteres, cetonas, amidas, nitrilos y sulfonas, con el 1-metilciclohexeno, obteniendo rendimientos de buenos a excelentes. La ciclación intramolecular de la α-ionona dió un rendimiento del 95%. Además, se consiguió una buena reactividad al emplear el ciclohexeno como sustrato (generación de un radical más inestable) y en este caso, la reacción mostró una elevada compatibilidad con diversos grupos funcionales en los alquenos pobres en electrones (-CO_2Me, -COMe, -CN, entre otros) con rendimientos entre 80-98%.

La reacción se llevó a cabo a mayor escala con el objetivo de ampliar la aplicabilidad del proceso (Esquema 3). En este caso, se observó una ligera disminución del rendimiento de la reacción debido probablemente a los agregados de los silanos observados durante la reacción.

Esquema 3. Reacción a mayor escala (gramos).

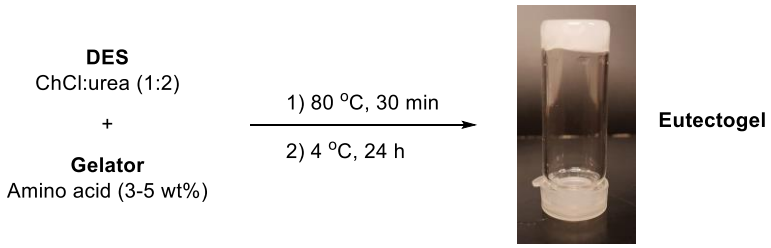
Con respecto al mecanismo de la reacción, se confirmó que el acoplamiento entre olefinas se trataba de un proceso radicalario, ya que tras llevar a cabo la reacción modelo bajo las condiciones de reacción óptimas en presencia de TEMPO, se observó una inhibición completa de la reacción. Además, se propuso un mecanismo para este acoplamiento radicalario. El uso de una mezcla eutéctica, en la cual uno de los componentes era el etilenglicol, pareció favorecer la formación de una especie de hierro catalíticamente activa ($X_2Fe^{III}OR$) y consecuentemente, se incrementó la reactividad con el silano presente en el medio de reacción. Las propiedades del disolvente parecieron ser cruciales, tras la formación del radical (transferencia de un átomo de hidrógeno-HAT), ya que según la bibliografía dicho radical está envuelto por moléculas de disolvente de manera que la “fuerza de solvatación” del disolvente empleado es crucial para que ese radical pueda escapar de

esa esfera de coordinación de las moléculas de disolvente y reaccionar con la olefina pobre en electrones para formar un nuevo enlace C-C.

Otra aplicabilidad de las mezclas eutécticas es su uso para la formación de nuevos materiales tales como los geles supramoleculares. Los geles supramoleculares son materiales formados por un disolvente (componente mayoritario) y un gelante (componente minoritario), el cual genera un entramado tridimensional y confiere la apariencia sólida al material. El material se convierte en gel debido a la interacciones del gelante con el disolvente (enlaces de hidrógeno, fuerzas de van der Waals y/o interacciones π). Dependiendo del disolvente o el gelante empleado, existen diferentes tipos de geles. En base al disolvente empleado, los geles se pueden clasificar en hidrogeles u organogeles, si se ha utilizado agua o disolventes orgánicos, respectivamente. Recientemente, se han empleado otro tipo de disolventes para formar geles como por ejemplo líquidos iónicos (ionogeles) e incluso, mezclas eutécticas (eutectogeles).

Existen infinidad de moléculas gelantes capaces de formar este tipo de materiales, entre ellas los aminoácidos. Paralelamente, los aminoácidos se han utilizado ampliamente como organocatalizadores en síntesis orgánica en transformaciones como la reacción aldólica enantioselectiva.

Por lo tanto, en vista de estos antecedentes se decidió sintetizar diferentes geles utilizando las mezclas eutécticas como disolvente y varios aminoácidos como moléculas gelantes y la posterior aplicación de este material para llevar a cabo la reacción aldólica enantioselectiva. En primer lugar, se sintetizaron los diferentes eutectogeles (Esquema 4).



Esquema 4. Preparación de eutectogeles con diferentes aminoácidos como gelantes.

Para ello, se utilizó la mezcla eutéctica cloruro de colina:urea (1:2) y diferentes aminoácidos (L-serina, *trans*-4-hidroxi-L-prolina, L-prolinamida y L-prolina). La mezcla del DES y el aminoácido (3-5 % en masa) se agitó durante 30 minutos a 80 ºC, hasta obtener una disolución totalmente clara. Tras esto, se enfrió la mezcla a 4 ºC durante un día para finalmente obtener el eutectogel.

Una vez preparados varios eutectogeles, se probaron en la reacción aldólica entre acetona y *p*-nitrobenzaldehído en ausencia de disolvente. De los diferentes materiales utilizados, la combinación cloruro de colina:urea (1:2) + L-prolina (5% en masa) como gelante fue el que mejor resultados ofreció.

Luego, se estudió la aplicabilidad de la reacción. Se hicieron reaccionar diferentes aldehídos aromáticos con la acetona, observando que la naturaleza electrónica del anillo aromático era de gran importancia (se observaron peores rendimiento en presencia de sustituyentes electrón-dadores). Además, se emplearon diferentes cetonas junto con diversos aldehídos obteniendo en general buenos resultados.

Una de las ventajas del uso de este tipo de materiales reside en la posibilidad de reciclar el sistema catalítico. Tras la reacción aldólica, se añadió una pequeña cantidad de 2-MeTHF para extraer todos los compuestos orgánicos. Una vez extraídos dichos compuestos, y eliminado el disolvente orgánico a vacío, el eutectogel se pudo reciclar de nuevo hasta 5 veces consecutivas.

Por otro lado, para evaluar la versatilidad del eutectogel se decidió utilizar este material para la reacción Michael enantioselectiva entre el isobutiraldehído y el *trans*-β-nitroestireno/*N*-fenilmaleimida como electrófilos. Sin embargo, aunque se obtuvieron rendimientos excelentes, los excesos enantioméricos no superaron el 27% *ee* (resultados similares a los obtenidos anteriormente en la bibliografía con L-prolina como organocatalizador).

Además del desarrollo de diversas metodologías para la formación de enlaces C-C, diferentes disolventes neotéricos, incluidas las mezclas eutécticas, se utilizaron como medio de reacción para transformaciones basadas en la formación de enlaces C-O. Más concretamente, para la cicloisomerización de ácidos alquinoicos y derivados.

Con respecto a la sostenibilidad de los procesos, uno de los factores más importantes a tener en cuenta a la hora de diseñar el sistema catalítico o catalizador es su posible reciclabilidad. Es por ello, que los catalizadores heterogéneos son preferibles, en algunos casos, a los homogéneos.

Las nanopartículas metálicas aúnan las ventajas de los catalizadores homogéneos y heterogéneos, siendo una opción muy atractiva como sistema catalítico. Existe también la posibilidad de soportar dichas nanopartículas metálicas, lo que mejora y facilita la reciclabilidad del sistema. Entre los diferentes soportes que se pueden emplear, la magnetita (Fe_3O_4) destaca por sus propiedades magnéticas, lo que facilita la recuperación del catalizador, ya que con el uso de un simple imán se podría reciclar fácilmente el sistema catalítico (Figura 7).

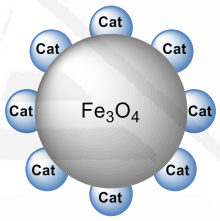
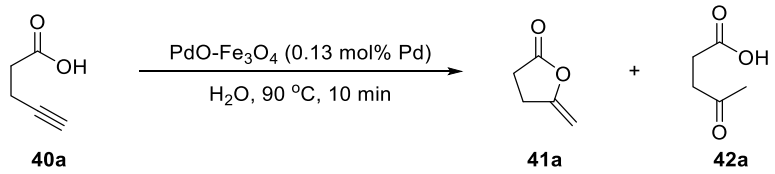


Figura 7. Representación general de los catalizadores metálicos soportados en magnetita.

Debido a la alta actividad catalítica observada con las nanopartículas de óxido de paladio(II) soportadas en magnetita (PdO-Fe_3O_4) en varias reacciones desarrolladas en nuestro grupo de investigación, se decidió utilizar este catalizador en la cicloisomerización de ácidos alquinoicos y sus derivados, para la síntesis de diferentes lactonas y lactamas en disolventes neotéricos.

En primer lugar, se optimizaron las condiciones de reacción, realizando un barrido con diferentes especies metálicas soportadas y ajustando disolvente, temperatura y tiempo de reacción, obteniendo los mejores resultados con las condiciones mostradas en el Esquema 5.



Esquema 5. Condiciones de reacción óptimas para la cicloisomerización de ácidos alquinoicos.

Destacar que durante la optimización de la reacción, se observó que la enol-lactona derivada de la reacción de cicloisomerización, se podía hidrolizar aumentando el tiempo de reacción para dar el correspondiente cetoácido en el caso de usar agua como disolvente en lugar de la mezcla eutéctica. Además, se realizó un estudio cinético de la reacción en el que se observó que la reacción de hidrólisis no tenía lugar hasta que el proceso de cicloisomerización hubiera terminado, mostrando así la elevada selectividad del catalizador de paladio.

Una vez determinadas las mejores condiciones de reacción y el sistema catalítico, se estudió el alcance de la reacción para el proceso de cicloisomerización/hidrólisis. La metodología mostró una elevada compatibilidad con diferentes grupos funcionales y ofreció muy buenos resultados con alquinos terminales e incluso, internos. Además, se probaron diferentes alquinilimidas como sustratos obteniendo excelentes resultados en todos los casos.

A continuación, se procedió a comprobar la reciclabilidad del sistema. Por un lado, se intentó reciclar juntos tanto del catalizador PdO-Fe_3O_4 como del disolvente y, además, se estudió el reciclado solamente del catalizador. En el primer caso, una vez completada la reacción, se añadió acetato de etilo para extraer los productos orgánicos, de tal forma que tanto el agua como el catalizador metálicos permanecieron en el tubo, listos para otra carga de reactivo. Para reciclar únicamente el catalizador se añadió tanto acetato de etilo como agua, dejando la mezcla reposar y decantando el líquido con ayuda de un imán, de tal forma que en el tubo de reacción únicamente permaneció el catalizador junto a la barra de agitación magnética. Destacar que en ambos casos, se pudo reciclar el sistema hasta 4 ciclos consecutivos sin pérdida de actividad catalítica.

Por otro lado, se llevó a cabo un estudio de la heterogeneidad del catalizador y su posible lixiviación en el medio. Los resultados parecieron indicar que una pequeña parte del paladio pasa a la disolución acuosa como diferentes intermedios de paladio (alrededor del 7% del paladio inicial).

La reacción también se hizo a mayor escala (gramos), obteniéndose el producto puro sin necesidad de otros pasos de purificación con un 92% de rendimiento (1.07 gramos).

Finalmente, las mezclas eutécticas también fueron empleadas con éxito en la formación de enlaces C-S para la síntesis de sulfonas, disulfuros y sulfuros de manera más sostenible.

Los compuestos de organoazufre como los sulfuros o las sulfonas, son compuestos de gran interés en síntesis orgánica debido a sus propiedades químicas, biológicas y farmacéuticas.

La síntesis de sulfonas, a través de rutas sintéticas más convencionales, se ha llevado a cabo mediante la oxidación de sulfuros. Sin embargo, existen varias desventajas asociadas a esta metodología como el uso de tioles (mal olor), condiciones de oxidación agresivas y limitaciones en presencia de grupos sensibles a ser oxidados en esas condiciones. Es por ello, que a lo largo de los años han ido surgiendo diferente alternativas para su síntesis.

Recientemente, la síntesis multicomponente utilizando SO_2 (g) se ha descrito como una metodología alternativa para la obtención de sulfonas, pero este protocolo implica ciertas limitaciones como el uso de SO_2 (g), por su difícil manejo y su toxicidad. Consecuentemente, se han desarollado alternativas más eficaces y seguras que utilizan compuestos sólidos que liberan SO_2 en el medio de reacción, como alternativa al uso de SO_2 (g).

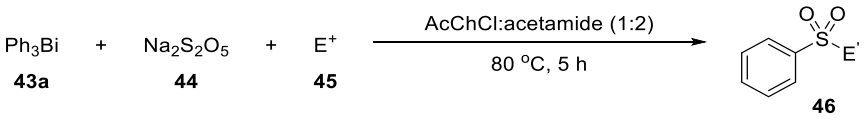
Un ejemplo de ello son las sales de metabisulfito ($M_2S_2O_5$), que al calentarlas en presencia de agua, liberan SO_2. Existen varias metodologías en la bibliografía que describen la síntesis de sulfonas empleando estas sales, sin embargo, en todas estas metodologías se utilizan catalizadores y ligandos muy específicos y caros, se necesitan aditivos, condiciones de reacción anhidras e inertes, así como el uso de disolventes orgánicos tóxicos y volátiles, en los que las sales de metabisulfito son muy poco solubles.

Por lo tanto, el desarrollo de una metodología más sostenible y que elimine las desventajas presentes en las anteriores rutas sintéticas, sería de gran interés para la síntesis orgánica.

En este sentido, se llevó a cabo la síntesis multicomponente de sulfonas a partir de compuestos de triarilbismuto (Ar_3Bi) y metabisulfito de sodio ($Na_2S_2O_5$) en mezclas eutécticas como medio de reacción. El alto poder de disolución de los DESs, favoreció la completa disolución de las sales inorgánicas y, por lo tanto, la efectividad del proceso. Además, tanto los compuestos de triarilbismuto como las sales de metabisulfito son reactivos no tóxicos y estables.

El estudio se inició optimizando las condiciones de reacción, empleando trifenilbismuto, $Na_2S_2O_5$ y bromuro de bencilo como reacción modelo. Se emplearon diferentes disolventes orgánicos convencionales (tolueno, cloroformo, acetonitrilo, DMSO, DMF, metanol y etanol), pero se obtuvieron rendimientos muy bajos en todos los casos. A continuación, se utilizó el agua y varias mezclas eutécticas, obteniendo un 99% de rendimiento con la mezcla cloruro de acetilcolina:acetamida (1:2). Estos resultados, muestran los beneficios y ventajas del uso y propiedades de las mezclas eutécticas como medios de reacción, como la elevada solubilidad tanto de las sales inorgánicas ($Na_2S_2O_5$) como del resto de compuestos orgánicos (Ar_3Bi y el SO_2 generado *in situ* en la reacción).

Una vez determinadas las condiciones óptimas de reacción, se emplearon diferentes electrófilos para estudiar la aplicabilidad de esta reacción para la síntesis de diferentes sulfonas (Esquema 6). Hay que destacar que se obtuvieron rendimientos de buenos a excelentes utilizando diferentes haluros de alquilo, acrilatos, entre otros.

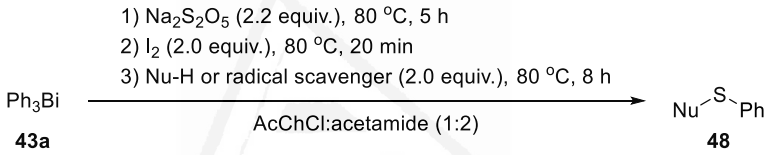


Esquema 6. Estudio del alcance de la reacción empleando diferentes electrófilos.

También se utilizaron diferentes compuestos de triarilbismuto (Ar_3Bi), obteniendo mejores resultados con los sistemas de Ar = Ph, 1-naftil, 4-$(Me_2N)C_6H_4$, 4-FC_6H_4, aunque con el resto de sustratos los rendimientos fueron entorno 60-80%.

Tras esto, se decidió añadir iodo molecular (I_2) al medio de reacción, ya que previamente se había descrito la reducción diferentes ácidos sulfónicos o sulfonatos de sodio con I_2 para la síntesis de disulfuros. La adición de iodo molecular resultó en la síntesis de varios disulfuros con rendimientos de buenos a moderados. En este caso, se observó que la naturaleza electrónica de los compuestos de triarilbismuto (Ar_3Bi) tenía un gran impacto en el rendimiento de la reacción, obteniendo peores resultados en presencia de sustituyentes electrón-dadores en los anillos aromáticos.

El iodo molecular también se empleó para la síntesis de varios sulfuros en una síntesis de tres pasos de manera directa (sin necesidad de aislar los productos en cada paso de reacción; Esquema 7).



Esquema 7. Síntesis de sulfuros en mezclas eutécticas.

En primer lugar, se forma la sal de sulfinato, luego tras la adición de iodo molecular el tiol correspondiente y finalmente, el tiol reacciona con el nucleófilo/compuesto aceptor de radicales para dar lugar al sulfuro deseado. Varios nucleófilos y/o compuestos aceptores de radicales, fueron evaluados obteniendo rendimientos de 55-80%.

Por otra parte, se estudió la reciclabilidad del sistema. Una vez finalizada la reacción para la síntesis de sulfonas, se añadió una pequeña cantidad de 2-MeTHF para extraer el producto y los reactivos de partida que no reaccionaron y, tras esto, la mezcla eutéctica se pudo reciclar siguiendo este procedimiento hasta 5 veces consecutivas con rendimientos excelentes.

Por lo tanto, de los resultados obtenidos se puede concluir que las mezclas eutécticas son una alternativa viable y sostenible a los disolventes orgánicos tradicionales (tóxicos y dañinos para el medio ambiente), y pueden ser empleadas como medio de reacción para llevar a cabo transformaciones orgánicas, tanto clásicas como novedosas, como por ejemplo aquellas que han aparecido en el presente trabajo:

La formación *in situ* de diferentes compuestos de organoindio y su consecuente, adición a cetonas en mezclas eutécticas como disolvente.

El diseño racional de distintos catalizadores de paladio compatibles con las mezclas eutécticas, para llevar a cabo reacciones de acoplamiento (Suzuki-Miyaura, Hiyama, Heck y Sonogashira), con una elevada eficacia y manteniendo los resultados publicados anteriormente para estas transformaciones en otros medios de reacción más convencionales.

La activación de enlaces C-H catalizada por rutenio llevada a cabo con muy buenos resultados bajo condiciones de reacción suaves y utilizando los DESs como disolvente.

La aplicabilidad de los DESs en reacciones radicalarias, como la adición de diferentes olefinas, mostrando un uso beneficioso de este medio de reacción y mejorando la sostenibilidad de procesos en comparación con las metodologías previas.

La formación de materiales novedosos como los eutectogeles y su aplicación en diferentes reacciones organocatalizadas tales como la reacción aldólica enantioselectiva.

El desarrollo de un catalizador de paladio heterogéneo, fácilmente reciclable y compatible con varios disolventes neotéricos, para la cicloisomerización de ácidos alquinoicos y sus derivados.

La síntesis multicomponente de sulfonas, disulfuros y sulfuros a través de una metodología sostenible y respetuosa con el medio ambiente, utilizando las propiedades únicas y fácilmente ajustables de las mezclas eutécticas.

Por lo tanto, se ha demostrado que las mezclas eutécticas ofrecen potencialmente notables ventajas como medio de reacción en síntesis orgánica debido a sus propiedades como su nula/baja toxicidad, propiedades fácilmente ajustables cambiando la composición de la mezcla y la posibilidad de reciclar el sistema catalítico en la mayoría de los casos.