

Review

New achievements on C-C bond formation in water catalyzed by metal complexes

Franco Scalambra^a, Pablo Lorenzo-Luis^b, Isaac de los Rios^c, Antonio Romerosa^{a,*}^aÁrea de Química Inorgánica- Laboratorio de Química Sostenible (CIESOL), Universidad de Almería, Almería, Spain^bInorganic Chemistry Area, Section of Chemistry Faculty of Science, Instituto Universitario de Bio-Organica "Antonio González", University of La Laguna, Tenerife, Spain^cDepartamento de Ciencia de los Materiales e Ingeniería Metalúrgica y Química Inorgánica, Facultad de Ciencias, Universidad de Cádiz, 11510 Puerto Real (Cádiz), Spain

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ABSTRACT

The C-C coupling is the best strategy to obtain new organic molecules and building blocks from economical and abundant small molecules. Traditionally these reactions are accomplished in organic solvents, which are often dried before use as water molecules can react quickly with both the catalyst or the intermediate of the reactions, blocking the catalytic cycle. Nevertheless, the efforts of the researchers are providing new synthetic procedures in water that can substitute some of those, previously developed, "dry reactions". In the last years, really useful processes to obtain C-C bonds in water were proposed. These reactions usually are catalysed with 4d-metals but also examples with metals of the first transition row were proposed. This review aims to summarize and order by types the C-C coupling catalytic reactions in water published during the last five years. The abundance of reactions and the significance of the published results shows that a long way is needed to achieve a good knowledge of catalytic C-C coupling reactions in water. Nevertheless, accomplish this objective can provide significant and valuable synthetic processes, more economical, cleaner, more selective, therefore friendlier and more respectful with nature.

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1. Introduction

This review highlights the importance of the synthetic processes in water catalysed by metal complexes, which are useful to develop industrially important molecules through new catalytic

* Corresponding author.

E-mail addresses: romerosa@ual.es (F. Scalambra), plorenzo@ull.es (P. Lorenzo-Luis), isaac.delosrios@uca.es (A. Romerosa).

methods. Giving details about the significance of the coordination compounds in mediating synthetic reactions is not the topic of this review. However, recalling why coordination compounds are useful to mediate catalytic organic synthesis and why it is important to use water as an environmentally friendly solvent, deserves few words.

The synthesis of a variety of organic compounds is only achievable by catalytic processes in which the catalyst is a metal complex, making it less energetically demanding, more selective and faster. Ideally, the catalytic cycle in which the metal is involved should be repeated an infinite number of times. Nowadays a large number of both useful commodities and fine chemicals are obtained by catalytic synthetic processes [1].

Nevertheless, nothing is perfect, and this kind of synthetic reactions suffer frequently of serious drawbacks. The most important inconvenience found in non-aqueous catalytic synthesis deals with the fact that the catalyst remains in the reaction medium during the whole catalytic process. For this reason, the catalyst cannot be easily reused and the products are usually contaminated with metal. This also means that the catalyst is lost, as an unavoidable consequence, leading irremediably to a negative environmental impact and an increase of the cost of the whole catalysed synthesis. Additionally, the organic solvents that are commonly used, are expensive, harmful to the environment and not easily recyclable. In contrast, water is cheap, non-toxic, non-inflammable and can be reused in a relatively easy manner.

The synthesis of organic compounds in water, particularly if they are catalysed by Lewis acids, is very imperative and has deserved considerable attention in organic synthesis [1–6]. Despite the interest of the researchers in these reactions, their development and study are quite complicate as water is not an innocent solvent: it can interact with reactants, products and also with reaction intermediates. Furthermore, most of the organic compounds are insoluble in water. Nevertheless, it is evident that some reactions proceed faster and with higher yields when carried out on the water, being also more selective [7–9] and easier to process [10,11]. Another interesting advantage of using water as reaction medium is that the catalyst remains dissolved in the aqueous phase and therefore, after filtering or extracting the product, it can be reused in a new catalytic reaction [12–15].

Chemical processes in water are referred to by many different designations, “in water” being the most frequent, followed by some synonyms as “aqueous”, “on water”, “concentrated organic phases”, “in the presence of water” and “at water” [16]. For non-catalysed reactions, Sharpless et al. showed that, in stirred aqueous suspensions, the rates of some reactions are boosted concerning the corresponding homogeneous counterpart in an organic solvent, defining this kind of processes as “on water” [17,18]. Nevertheless, this definition, does not include homogeneously catalysed systems [19–22], for which the term “in water” should be more appropriate [23].

The catalytic synthesis of organic compounds in water employs, most of the times, hydrosoluble metal complexes as catalysts, which present similar behaviour regarding their lipophilic analogues, but with all the indicated advantages of using water or a biphasic system as reaction medium. In theory, the aqueous phase containing the catalyst can be reused in multiple reaction runs, making the process cheaper, cutting the metal consumption and also reducing the contamination of the products to negligible levels. All these features make the synthetic processes in water catalysed by hydrosoluble metal complexes useful also for drug synthesis [24–26]. The advantages of performing reactions in water are so numerous that they are still interesting to be developed also when the reaction conditions could not be considered such as mild conditions, for example with temperatures higher than 100 °C or over atmospheric pressure.

If there are so many and so important advantages, why catalytic processes based on water-soluble catalysts are not being used extensively? The simplest reason for the lack of wide application of water in catalysis is since most of the known catalytically active coordination compounds are not water-soluble or decompose quickly by reaction with water. Therefore, it is mandatory to design new water-soluble complexes stable enough in the water and capable of being active in catalysis. To solve this problem, the ligands not only need to be hydrophilic but also must confer to the active catalyst enough stability to avoid decomposition during the passage through the multitude of catalytic cycles for what it was designed. The synthesis of water-soluble ligands and their metal complexes are therefore the first steps of this whole story but unfortunately accomplishing this goal is a very complicated matter. Also, it is important to pick out adequate ancillary ligands, which are necessary to complete the metal coordination sphere. One should also take into account that these co-ligands are not innocent as they can influence both steric and electronic properties of the complex and therefore its chemical reactivity.

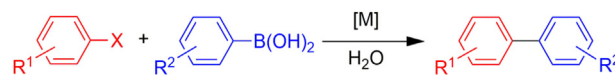
Despite the difficulties, the synthetic processes mediated by water-soluble metal complexes are continuously increasing as is shown in this review. Among the metal catalysed reactions in water, the catalytic formation of C–C bonds is of particular scientific and industrial interest as it provides a convenient and eco-friendly procedure to obtain fine organic moieties upon direct functionalization of the C-skeleton [27–34]. This review aims to provide a general view about the most significant catalytic approaches presented during the last five years concerning C–C bond formation in water, classified and grouped by classical established reaction classes.

2. Suzuki-Miyaura C–C coupling

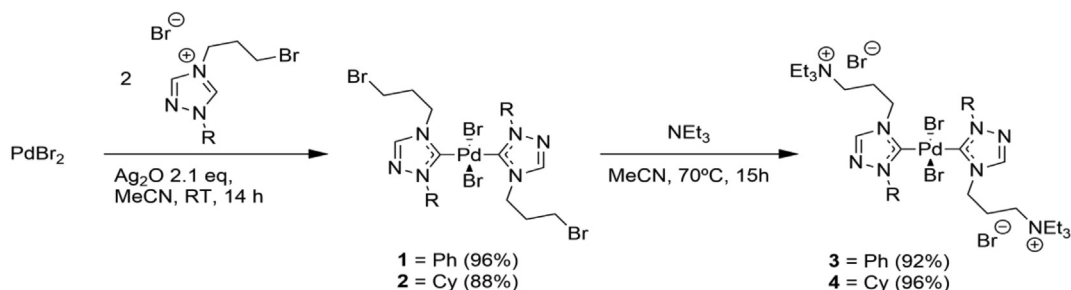
The Suzuki – Miyaura is a very important procedure to obtain new molecules by C–C coupling of boronic acids and organohalides, providing products that are not easily obtained by other more classical procedures (Scheme 1) [35–37], being very important and flexible for synthesizing organic molecules. This reaction is catalysed by a metallic compound: usually a Pd(0) complex. Therefore, extending the scope of Suzuki – Miyaura coupling to aqueous media and under mild conditions is a very important task for synthetic chemists as it can provide largely demanded organic compounds by a cheap and ecobenign procedure.

In 2018 Huynh et al. showed that a post-modification approach allowed the convenient synthesis of bis(1,2,4-triazolin-5-ylidene) palladium(II) complexes containing ammonium-functionalized groups. This achievement was significant as the synthesis of azolium salts is elusive [38]. The synthetic procedure requires the metalation of a bromo-functionalized 1,2,4-triazolium salt that affords the respective bromo-bis(NHC) (NHC = N-heterocyclic carbene) derivatives *trans*-[PdBr₂(R-tazy-Br)₂] (tazy = 4-benzyl-1-methyl-1,2,4-triazolin-5-ylidene) (R = Ph (1), Cy (2)) (Scheme 2).

This complex is transformed into the hydrophilic *trans*-[PdBr₂(R-tazy-NEt₃)₂]Br₂ (R = Ph (3), Cy (4)) by nucleophilic substitution of the bromo group by an amine (NEt₃ in the example), generating the respective ammonium salt. These square-planar palladium complexes were characterized by spectroscopic techniques and fully determined by single-crystal X-ray diffraction (Fig. 1 shows the crystal structure of 3).



Scheme 1. Suzuki-Miyaura coupling of boronic acids and aryl halides in water.



Scheme 2. Synthesis of 1–4 [38].

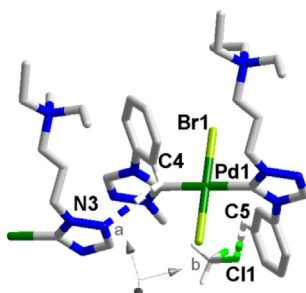


Fig. 1. Crystal structure of **3**: monoclinic (C2/c); Pd1-Br1 2.440(8) Å; C4-H4...N3 3.007(6) Å; C5-H5...C11 2.952(3) Å. Adapted from Ref. [38].

All the synthesized complexes were found to be active catalysts for the Suzuki–Miyaura C–C coupling in water of a large variety of substrates (Table 1 shows a selection) with a very low amount of catalyst. The complexes bearing the more electron-donating and less bulky ligands revealed to be more active, leading to the satisfactory conversion of the substrates with a very low catalyst loading (0.001 mol %). Experimental and theoretical calculations suggest that the synthesized complexes are pre-catalysts, being

transformed into the active catalytic species when dissolved in the reaction media.

Another recently published Pd-NHC complex useful for the Suzuki–Miyaura coupling reaction in water is the Pd(II)-tetracarbene **5** (Fig. 2) [39]. This complex was obtained by a solvothermal method. The crystal structure determined by single-crystal X-ray diffraction is constituted by a square-planar Pd atom coordinated by the C-4 and C-5 atoms of the imidazolyli-dene rings (Fig. 2). The solutions of complex **5** in water are stable also under air. Its structure, together with its stability could lead to the erroneous consideration that it is not suitable as a catalyst.

Nevertheless, **5** showed to be highly active in the homogeneous Suzuki–Miyaura C–C cross-coupling. The reaction was useful for coupling a large variety of aryl halides and aryl-boronic acids (Table 2 displays a selection) in the water at 100 °C but requires the presence of a base such as K_2CO_3 . Another advantage of using complex **5** is its easy recovering from the reaction medium by precipitation simply adjusting the pH, which allows to recycle the catalyst and also to reduce the metal contamination of the products.

During the same year, the allyl palladium complexes **6–8** containing the popular aqueous-soluble phosphine TPPMS (3,3',3''-phosphinetriyltribenzenesulfonate) were also published (Scheme 3).

Table 1

Examples of Suzuki–Miyaura reaction catalyzed by **3**. Conditions: aryl halide (0.1 mmol), phenylboronic acid (0.12 mmol), K_2CO_3 (1.5 mmol), H_2O (1 mL). Yields determined by NMR [38].

Substrate 1	Substrate 2	Product	mol%	T (K)	Yield (%)	TON	t (h)
			0.001	373	100	100,000	10
			0.001	373	50	50,000	10
			0.002	373	83	41,500	24
			0.01	373	80	8000	24
			0.1	373	100	100	24
			0.5	373	trace		

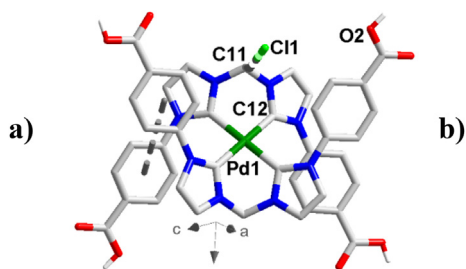


Fig. 2. a) Crystal structure of **5**: triclinic (P-1); Pd1-Cl2 2.037(4) Å; C11-H11...Cl1 2.715(5) Å; $\pi\cdots\pi$ interactions at 4.695 Å (*face-to-face geometry*). b) Chemical Structure of **5**. Adapted from Ref. [39].

The metal completes its coordination geometry with carbenes obtained from alkylated natural xanthenes [40]. Between these complexes, only **8** showed to be very active, also in coupling phenylboronic acid with heterocyclic halides. Table 3 includes a selection of substrates used and products obtained.

An interesting step ahead in C–C Suzuki–Miyaura reactions in water was accomplished by using to build DNA-encoded chemical library (DEL) [41–45]. Boronic acids and esters, including also heteroaryl boronates, were efficiently coupled with aryl halides linked to DNA. These reactions were achieved in water at temperatures from 60 to 80 °C by using as precatalyst the complex sSPhos-G2-Pd (**9**) (Scheme 4) in so short times as 20 min (Table 4 includes a representative selection) [46]. This new method was found to be

very flexible and convenient as it respects the original structure and activity of the DNA oligomers used as substrates. The compatibility of this new synthetic strategy with the features required to be considered a DEL synthesis were assessed by reacting eight different 58-base pair double-stranded DNA (dsDNA), bearing different terminal aryl halides, with eight diversely substituted arylboronic acids. Only nine product were not obtained from the 64 possible by combinations of differently functionalized DNA fragments. The DNA-compatibility was evaluated by enzymatic ligation of a 4'-methyl-[1,1'-biphenyl]-4-carboxamide functionalized DNA with a 12-base pair sequence. These both results support that the synthetic method is flexible and feasible and could be used on a broad range of substrates, making it a valuable tool to develop new DELs.

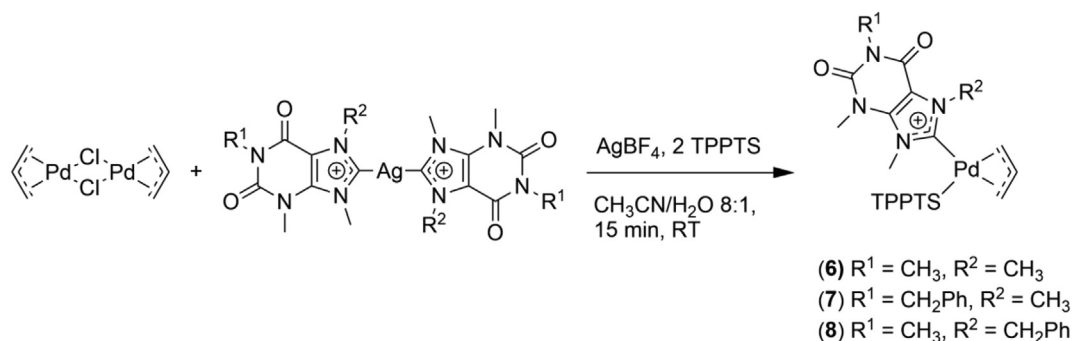
Another interesting Suzuki–Miyaura cross-coupling reaction in water catalysed by the palladium complex $\text{Na}_2[\text{Pd}(\text{BuHSS})]$ (BuHSS = N,N'-bis(2-hydroxy-5-sulfonatobenzyl)-1,4-diaminobutane) (**10**) was published in 2018 (Fig. 3). This complex was found to be an active catalyst of the reaction in a reasonable loading (0.1 mol%), under air and in presence of Cs_2CO_3 [47].

Catalyst **10** displays an adequate activity and robustness for the C–C coupling of a large variety of substrates (Table 5 shows some significant examples). The obtained products, which are insoluble in water, were isolated by simple filtration (up to 91%) and washing with 0.01 M aqueous HCl, without requiring any additional purification. It is interesting to point out that the products only contain less than 5 ppm of metal contamination, which is acceptable for the pharmaceutical industry.

Table 2

Examples of products obtained by the Suzuki–Miyaura reaction catalyzed by **5**. Conditions: aryl halide (1.0 mmol), phenylboronic acid (1.1 mmol), K_2CO_3 (2.0 mmol), TBAB (1.0 mmol), H_2O (2 mL), under air. Isolated yields are reported [39].

Substrate 1	Substrate 2	Product	mol%	T (K)	Yield (%)	TON	t (h)
			1	373	99	100	0.5
			1	373	99	100	0.5
			1	373	95	100	0.5
			1	373	95	100	0.5
			1	373	90	90	0.5
			1	373	97	100	1

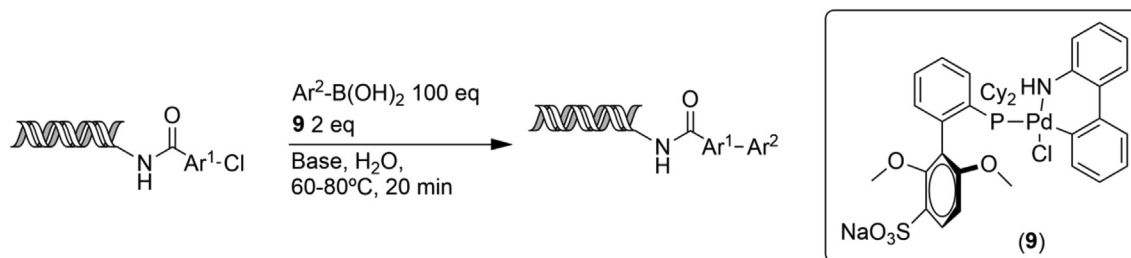


Scheme 3. Synthesis of complexes **6–8**. (TPPTS: 3,3',3''-phosphinetriyltribenzenesulfonate) [40].

Table 3

Examples of Suzuki-Miyaura reaction catalysed by **8**. Conditions: aryl halide (0.5 mmol), phenylboronic acid (0.6 mmol), K_2CO_3 (0.75 mmol), Bu_4NBr (0.75 mmol), H_2O (10 mL). Isolated yields are reported.

Substrate 1	Substrate 2	Product	mol%	T (K)	Yield (%)	TON	t (h)
			0.001	333	98	980	2
			0.001	353	95	950	2
			0.001	353	95	950	2



Scheme 4. On-DNA Suzuki – Miyaura cross-coupling catalysed by **9** [46].

Moreover, besides the tetradentate ligands as the BuHSS in **10**, the SNS-type pincers were found to be useful to formulate palladium complexes active for catalysing the Suzuki-Miyaura reaction in water. Complexes **11–14** (Fig. 4a), containing the SNS ligand pyridine-2,6-dimethanethioether, showed to be good catalysts at temperatures from 80 to 140 °C [48]. The crystal structure of complex **12** was consistent with previously published structures of similar complexes and supported the characterization proposed for the other metal compounds included in the paper (Fig. 4b).

All these complexes were catalytically active under the checked reaction conditions, being the complex **13** the most versatile. Representative reacted substrates and their corresponding products are displayed in Table 6. Nevertheless, all catalysts were active against the scope substrates, including aryl chlorides and aryl bromides containing electron-donating and electron-withdrawing substituents. When Bu_4NBr is present the reaction may be fine-tuned to either proceed via steric or electronic control. It was also

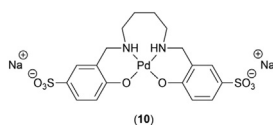
determined that the catalytic activity of **13** is dependent on the presence of Bu_4NBr in the reaction, suggesting that sterically less demanding planar phenyl group facilitates the access to the metal than bulkier side groups of the others checked pincer complexes. The SNS-ligand in these complexes displays both electron-donating and electron-withdrawing substituents. Therefore, catalytic activity is favoured by steric less bulky groups and opposed to electronic effects. In presence of this additive, the reaction mixture turned black, suggesting that Pd nanoparticles were responsible for the catalysis. Nevertheless, mercury drop experiments showed that the reaction is homogeneously catalysed. The complexes were able to be recycled up to three times without significant loss of activity.

The mechanism of the reactions was experimentally and theoretically investigated. The authors conclude that it proceeds via an electronic exchange between Pd(II) and Pd(IV) species, in contrast with previously proposed mechanisms involving the

Table 4

Examples of DNA compatible Suzuki – Miyaura cross-coupling in water catalyzed by **9**. Conditions: **9** (1 equiv.; 1 mM in H₂O), boronate (50–100 equiv.; 200 mM in 1,4-dioxane/H₂O (1/1)), sSPhos-Pd-G2 (2 equiv.; 10 mM in DMA), CsOH (600 mM in H₂O), borate buffer (pH 8.2, 125 equiv.) [46].

Substrate 1	Substrate 2	Product	T (K)	Yield (%)	TON	t (min)
			RT	99	50	15
			RT	99	50	15
			RT	96	48	15
			RT	83	42	15
			RT	73	37	15
			RT	61	36	15

**Fig. 3.** Structure of **10** [47].

reduction of Pd(II) to Pd(0) [49]. This proposal justifies the observed effect of the linker-chain length as well as the backbone nature of the SNS ligand on the catalytic activity of Pd complexes.

In 2019 the complexes Ni-Sanp **15** and Co-Sanp **16** (Sanp = N,O, O,N-salicyldiene thiadiazole) were shown to be the first transition row metal compounds capable of catalysing satisfactorily the Suzuki-Miyaura coupling, showing that are possible valuable alternatives to the common use of Pd complexes in this reaction. These complexes showed also a catalytic activity for promoting the Buchwald-Hartwig C-N coupling reaction of aryl amines with aryl halides. The complexes **15** and **16** were easily obtained by the reaction of the pro-ligand H₂Sanp with Ni(AcO)₂ or CoCl₂ in water (Scheme 5) [50].

The catalytic activities of complexes **15** and **16** for the C–C coupling of phenylboronic acids with aryl halides were generally lower than those found for known Pd-complexes for similar reactions. However, both complexes, gave moderate to high yields, being the complex **15** the most active (Table 7 includes some representative examples). The different observed activity was justified by the unlike steric hindrance of the coordination geometry: octahedral for Co-Sanp and square planar for Ni-Sanp. The reaction proceeds in water but also in a mixture of ethanol/water and only in ethanol. An additional result indicated that ligand and complexes inhibit the corrosion of C-steel in acidic solution, which was studied by electrochemical measurements (PDP and EIS) and surface analysis (SEM/EDX).

Recently, the cationic ligand 1-butyl-3-methyl-2-(diphenylphosphino)imidazolium (**17**) (Fig. 5) was used to obtain *in situ*

hydrosoluble Pd species by reaction with PdCl₂ in water. The resulting dissolution catalyzes the C–C coupling of aryl iodides with arylboronic acids (Table 8 displays some significant results) [51]. It is important to point out that it was showed that this solution can be reused for the coupling reaction of 4-bromobenzonitrile with phenylboronic acid for up to six times without significant loss of activity.

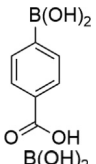
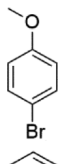
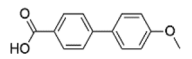
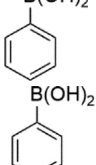
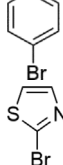
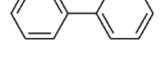
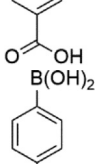
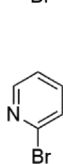

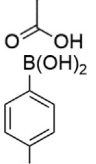
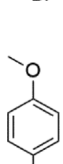

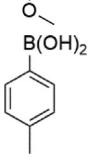
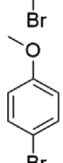
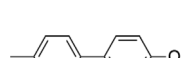


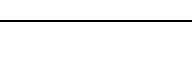
The most recent work about Suzuki-Miyaura reaction in water was published in 2020 and presented the new water-soluble Pd complexes **18–21** containing the NHC ligands piperidoimidazoline-2-ylidene functionalized with sulfonate, ester and carboxylic acid (Scheme 6) [52]. Complexes were obtained by heating the corresponding piperidoimidazolium salts with Pd(OAc)₂ and NaBr in pyridine. Complexes containing sulfonate (**18**) and carboxylate (**20**) groups display solubility in water up to 20 mg/mL and remain in water phase when the reaction products are extracted with organic solvents, while the other two complexes, which show a water solubility of ca. 10 mg/mL, pass to organic phase.

These complexes show catalytic activity for the Suzuki-Miyaura reaction of aryl halides with phenylboronic acid. The catalytic activity of the complexes was found to be strongly dependent on their functional groups, being enhanced by the carboxylate and sulfonate, being the complex **18** the most active for the C–C coupling of a large variety of arylbromides and chlorides with phenylboronic acid. A selection of the preformed reactions is summarized in Table 9.

Several bases were checked (KOH, Cs₂CO₃, etc.) to increase the reaction efficiency being K₂CO₃ the one that provided the best results. Also, the influence of pH and temperature were evaluated, being 90 °C the optimal for reactions catalysed by complex **18**. Addition of tetra-n-butylammonium bromide (TBAB) increased the reaction conversion from 48% to 98%. Mercury poisoning test, the suppression of catalysis by Hg(0) (98% to 19%), together with the influence of the TBAB in the reaction supported that **18** acts as a heterogeneous catalyst by formation of Pd(0) nanoparticle.

Table 5

Examples of Suzuki-Miyaura reaction catalysed by **10**. Conditions: Aryl halide (0.5 mmol), phenylboronic acid (0.75 mmol), Cs₂CO₃ (0.5 mmol), water (3 mL). Catalyst loading: 0.1 mol% [47].

Substrate 1	Substrate 2	Product	T (K)	Yield (%)	TON	t (h)
			353	90	900	2
			353	82	820	2
			353	80	800	2
			353	78	780	2
			353	74	740	2
			353	59	590	2

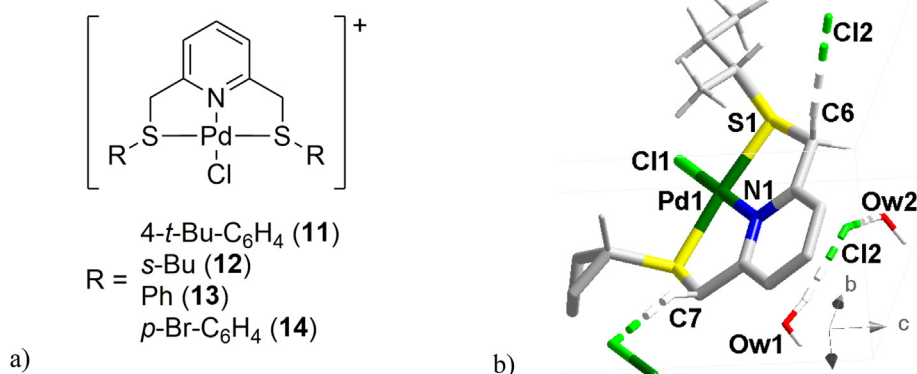


Fig. 4. a) Structure of complexes **11–14**. b) Crystal structure of the complex unit of **12**: triclinic (P-1); Pd1-Cl1 2.305(6) Å; Pd1-N1 2.002(3) Å; Pd1-S1 2.290(1) Å; C6-H6B...Cl2 3.121(1) Å; C7-H7B...Cl1 2.785(2) Å; Ow1-H1B...Cl2 2.325(1) Å; Ow2-H2A...Cl2 2.353(1) Å. Adapted from Ref. [48].

3. Heck reaction

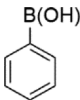
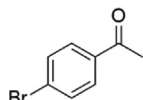
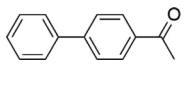
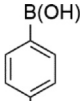
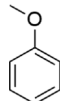
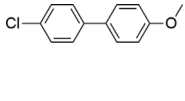
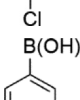
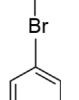
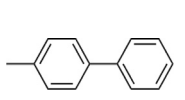
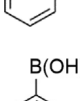
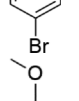
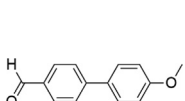
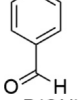
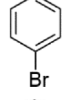

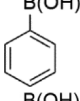
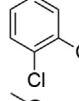
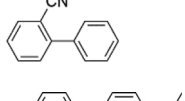
The synthesis of substituted alkenes by the reaction of an unsaturated organohalide (or triflate) with an alkene is one of the most versatile and, for this reason, one of the most used procedures for the synthesis of substituted alkenes in both basic and industrial synthesis. Usually, this reaction requires the presence of a base and is commonly catalysed by Pd(0) complexes [53–58]. Though this reaction is mainly known as *Heck reaction*, it was reported almost simultaneously by Mizoroki [59] and Heck, [60] constituting the first example of a C–C coupling reaction (Scheme 7)

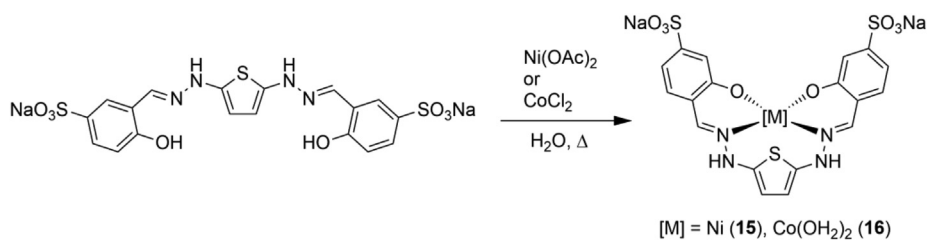
[61,62]. An idea of how important this reaction is for the industrial production of drugs and chemicals, could be provided by the fact that it is used in the industrial production of Singularir [63], naproxen [64], 2- and 4-vinyltoluene co-monomers for polystyrene [65] and the herbicide Proflurofen on ton scale [66]. The Heck reaction is combined with other synthetic processes to provide new versatile variants: heteroatomic-Heck [67,68], oxidative/dehydrogenative-Heck [69,70], reductive-Heck and decarboxylative-Heck reactions [71–73].

All the known variants of the Heck reaction usually provide functionalized olefins in good yield and under mild conditions











Table 6

Examples of Suzuki-Miyaura reaction catalysed by **13**. Conditions: aryl halide (1.63 mmol), phenylboronic acid (2.61 mmol), KOH (3.26 mmol), Bu₄NBr (0.82 mmol), H₂O (2 mL). Catalyst loading: 0.5 mol%. Yields determined by GC [48].

Substrate 1	Substrate 2	Product	T (K)	Yield (%)	TON	t (h)
			393	98	196	2
			393	96	192	2
			393	96	192	2
			393	92	184	2
			393	89	178	2
			393	87	174	2

**Scheme 5.** Synthesis of **15** and **16** [50].**Table 7**

Examples of Suzuki-Miyaura reaction catalysed by **15** and **16**. Conditions: aryl halide (1.1 mmol), phenylboronic acid (1.0 mmol), K₂CO₃ (2.0 mmol), H₂O (10 mL). Catalyst loading: 20 mol% [50].

Catalyst	Substrate 1	Substrate 2	Product	T (K)	Yield (%)	TON	t (h)
15				373	64	3.2	10
				373	55	2.8	12
16				373	60	3	11
				373	57	2.9	14

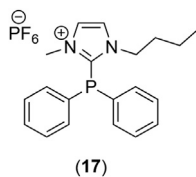


Fig. 5. Structure of the ligand **17** [51].

[74], but it is not extensively used for obtaining alkynes or allen-derivatives and it is even rarer if this reaction is performed in water. In 2018 the cationic alkynyl Heck reactions in water of aryl triflates and symmetrical, unsymmetrical and intramolecular alkynes were published (Scheme 8). In Table 10 are summarized some representative examples of the substrates used and the products obtained. The reaction requires the presence of the Pd(0)-catalyst **22** and an amine acting as a base to afford the final substituted allenes in mild conditions (65 °C) and times from 3 h to 17 h [75].

The Na₄-CO₂-dba (sodium salt of the bis(4-carboxylate)-dibenzyldeneacetone) ligand, simultaneously reduces Heck-derived byproducts and provides access to the reactive monoligated Pd(0)-complex (Scheme 9). It was proposed that the first step of the catalytic cycle starts with the dynamic equilibrium between **22** and a 12-electrons Pd(0)-intermediate compound, which forms

upon releasing of the dba ligand. Through the dba-carboxylate groups, the ligand might serve as a proton shuttle, facilitating the proton exchanges with the reaction media and leading to a neutral or anionic pathway. The next step of the reaction consists of an oxidative addition upon reaction with the aryl triflate forming a cationic aryl Pd(II)-intermediate, which evolves to a Pd(II)-species by carbopalladation with the alkyne. The authors propose that the cationic nature of the latter complex lowers relatively the barrier for the successive β-hydride elimination, facilitating the H-transfer from the substrate. This leads to the formation of the final allene and a Pd(II)-H complex that undergoes reductive elimination upon reaction with the amine present in the reaction medium, restoring the catalytically active Pd(0) species.

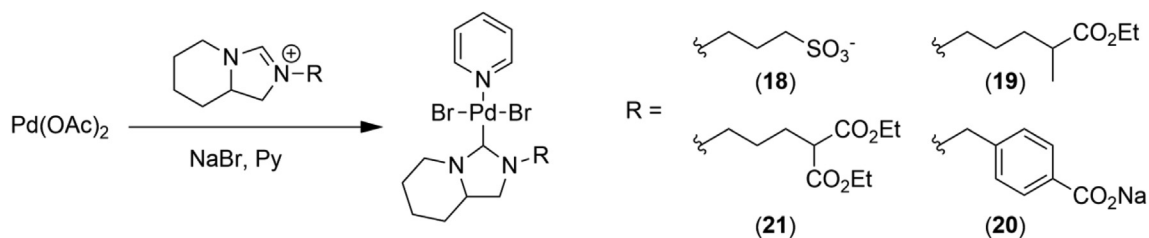
4. C-Arylation

Among the arylation reactions, the arylation of indoles represents a convenient path to the regioselective and direct C–H functionalization [76–79], avoiding the pre-functionalization of indole derivatives. Its atom economy and usual selectivity make this reaction a good choice for building arylated indoles [80–82]. These organic molecules are suitable as a scaffold for the synthesis of drugs and additives [83–88], and also in materials science [89,90]. For these reasons new synthetic methods, more practical and efficient to be implemented in the industry, are sought.

Table 8

Examples of Suzuki-Miyaura reaction catalysed by PdCl₂ in the presence of **17**. Conditions: aryl halide (0.5 mmol), arylboronic acid (0.75 mmol), **17** (0.4 mmol), H₂O (1 mL), PdCl₂ loading: 0.5 mol%. Yields determined by GC [51].

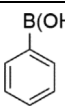
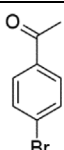
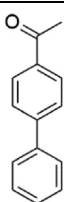
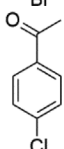

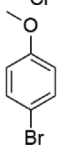

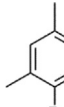

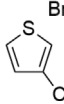

Substrate 1	Substrate 2	Product	T (K)	Yield (%)	TON	t (h)
			333	>99 ^a	500	24
			333	98 ^a	490	24
			333	93 ^b	465	24
			333	90 ^a	450	24
			353	82 ^b	410	24

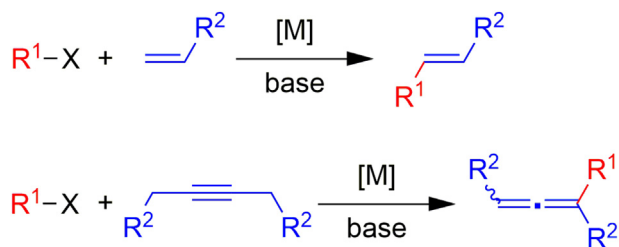


Scheme 6. Synthesis of **18–21**.

Table 9

Examples of Suzuki-Miyaura reaction catalysed by **18**. Conditions: aryl halide (1.0 mmol), phenylboronic acid (1.5 mmol), K₂CO₃ (1.5 mmol), Bu₄NBr (1.5 mmol), H₂O (1 mL). Catalyst loading: 0.5 mol%. Yields determined by GC [52].

Substrate 1	Substrate 2	Product	T (K)	Yield (%)	TON	t (h)
			333	99	198	0.5
			333	98	196	6
			333	92	184	0.5
			333	79	158	0.5
			333	64	128	8

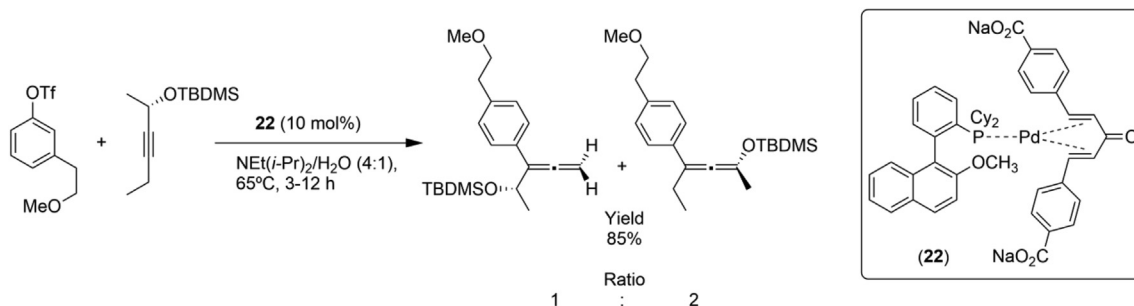


Scheme 7. General schemes of metal catalyzed Heck reaction between an organohalide (or triflate) and an alkene or an alkyne.

Pincer complexes have been shown to be excellent catalysts for a large number of high-value synthetic reactions and, for this reason, water-soluble metal complexes containing hydrophilic pincers were studied as catalysts for C-Aryl coupling processes in water. In 2017 N. Dharmaraj et al. [91] published the synthesis and characterization of complex **23**, which was fully characterized by single-crystal X-ray diffraction (Fig. 6). The crystal structure shows how the complex is constituted by a Pd(II) coordinates to an ONO pincer ligands and one PPh₃.

This compound is soluble in water and displayed good catalytic activity for the selective arylation (Scheme 10) with arylboronic acids on the N-methyl-2-oxindole-C3 carbon atom, giving rise to a large variety of diversely functionalized 3-aryl-N-methyl-2-oxindoles in good yield, up to gram scale, in water, under air and at room temperature [91]. Table 11 displays representative examples of the studied substrates, obtained products and reaction conditions. It is important to point out that the required amount of catalyst for accomplishing the reaction was as low as 0.01 mol% and it was not necessary to purify the products by column chromatography. Additionally, it was possible to recycle the catalyst for up to five runs.

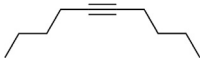
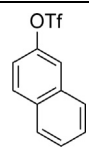
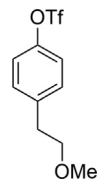
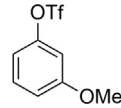
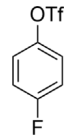
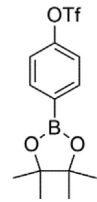

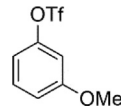
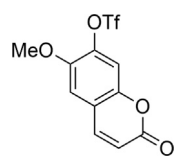
A mechanism for this reaction was proposed based on experimental results and previous studies (Scheme 11) [92–97]. The active specie, [Pd⁽⁰⁾L], which is the real catalyst of the reaction, forms from the starting Pd(II) complex by reduction with the aryl boronic acid [98]. The next step involves the oxidative addition of a molecule of deprotonated N-methyl-2-oxindole to the enol. The reaction of this intermediate with the phenylboronic acid leads to a Pd(II) complex containing both moieties, that are assembled by reductive elimination, affording the catalytical active specie and releasing the final product (3-phenyl-2-oxindole) [99]. The starting



Scheme 8. Asymmetrical alkyne Heck reaction catalysed by **22** [75].

Table 10

Examples of Alkynyl Heck reaction catalysed by **22**. Conditions: aryl triflate (1.0 equiv), alkyne (2.5 equiv), NEt(i-Pr)₂/H₂O (4:1). Catalyst loading: 0.5 mol%. Isolated yields are reported [75].

Substrates	Product	T (K)	t (h)	Yield	TON
		338	3–12	92%	9.2
		338	3–12	92%	9.2
		338	3–12	87%	8.7
		338	3–12	86%	8.6
		338	3–12	55%	5.5
		338	3–12	83%	8.3
		338	3–12	34%	3.4

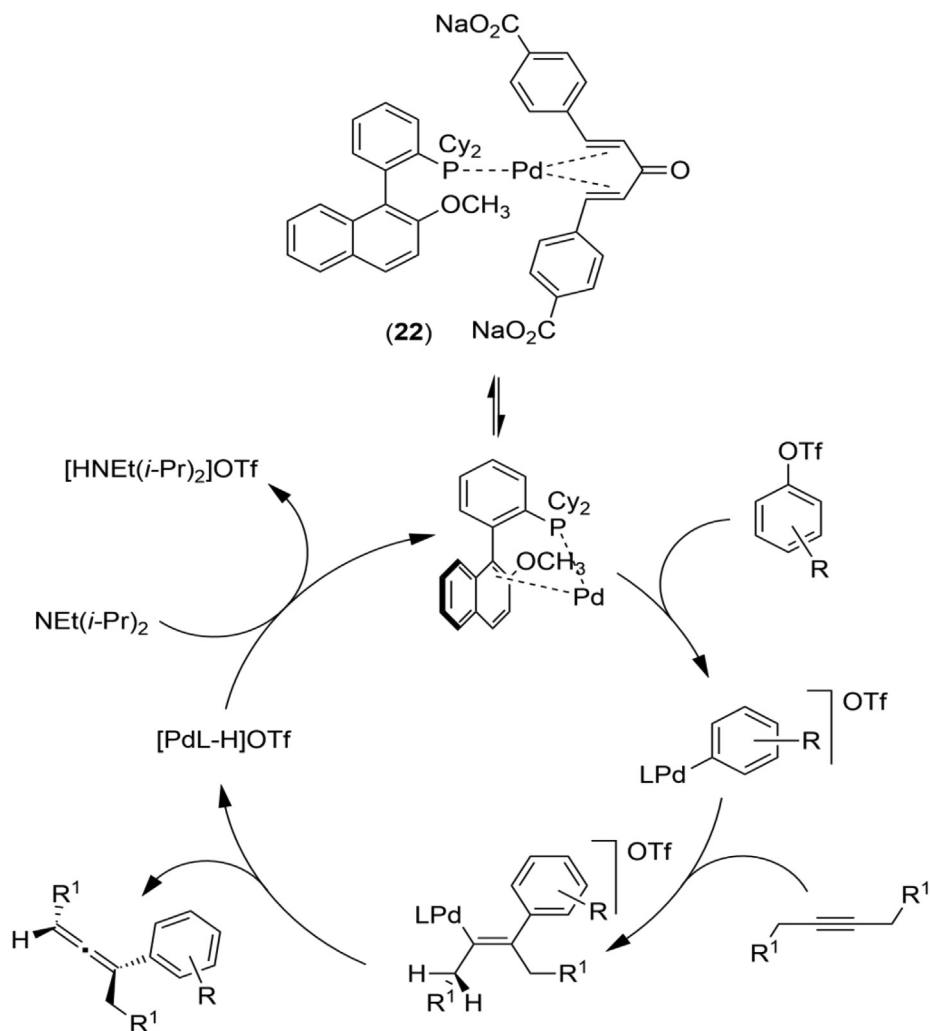
Pd(II) complex was recovered at the end of the reaction by introducing O₂ into the reaction media [100,101].

In the same year, an efficient catalytic asymmetric 1,4-addition of aryl boronic acids to nitroalkenes in water was published. This reaction provides chiral nitro compounds convenient for being used as starting material for the synthesis of chiral drugs and natural products. The reaction (Scheme 12) is catalysed by the rhodium dimer [Rh(C₂H₄)₂Cl]₂ in the presence of the chiral diene ligand **24** [102].

This reaction is highly enantioselective (ee > 80%) and efficient (yields > 70%): significant examples are showed in Table 12. The products can be easily separated from the aqueous phase, washed and dried without further additional purification. Mechanistic studies of the catalytic process showed that a protonation stage is the rate-limiting step, which is accelerated by water addition leading to extremely high catalytic turnover (Scheme 13). It is interesting to point out that the rhodium complex is susceptible to be reduced into metal nanoparticles, which was observed for

the first time in this paper. The modifier used to stabilize the nanoparticles was the same chiral ligand constituting the complex but sustained over a polystyrene-type polymer. In this situation, the enantioselectivity of the process was found to be the same in a wide substrate scope and without additional additives. Under a general method rhodium nanoparticle (1 mol%) and a chiral diene (0.1 mol%) gave rise to very high enantioselectivities due to a strong ligand accelerating effect. The heterogeneous catalytic system can be recycled maintaining high enantioselectivity during all the checked runs. Despite similarities in enantioselectivity and yields between the homogenous and heterogeneous processes, there are also enough differences, also with other asymmetrical 1,4-addition homogenous catalytic methods previously published [103,104].

Another interesting arylation reaction in water was catalysed by the complexes [RuCl₂(η⁶,η¹-arene-CH₂-NHC)] (**25–29**) [105]. The structural determination by single-crystal X-ray diffraction of one of the members of the family, complex **26**, supported that they



Scheme 9. Proposed mechanism for alkynyl-Heck reaction catalysed by **22** [75].

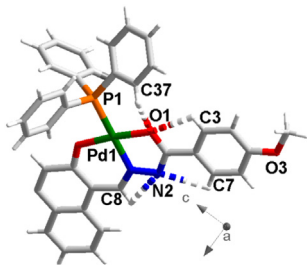
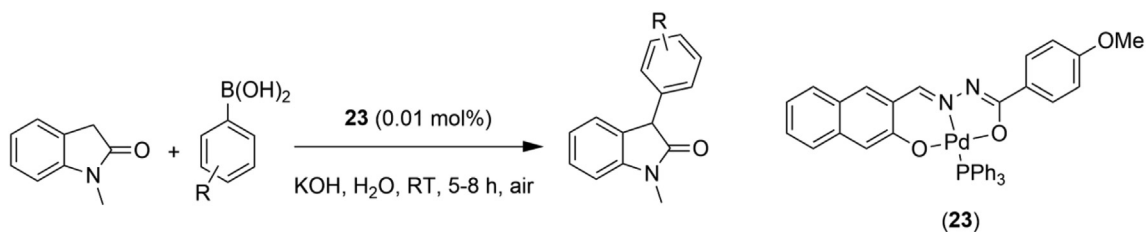


Fig. 6. Crystal structure of the complex **23**: monoclinic ($P2_1/n$); Pd1-O1 1.990(1) Å; Pd1-P1 2.296(6) Å; C3-H3...O1 2.436(1) Å; C7-H7...N2 2.520(2) Å; C8-H8...N2 2.413(2) Å; C37-H37...O1 2.471(2) Å. Adapted from Ref. [91].

are constituted by a distorted-octahedral Ru atom that is chelated by the arene-NHC ligand and coordinated by two chlorides, one of them interacting with the arene/NHC of a neighbour complex molecule (Fig. 7).

The catalytic activity of this family of complexes was assessed for the ortho arylation of 2-phenylpyridine with a variety of (hetero)arylchlorides (Fig. 8), which was performed at 100 °C with 2.5 mol% of catalyst.

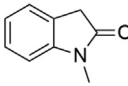

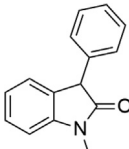
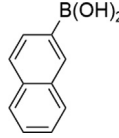
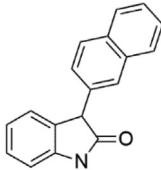
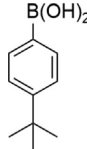
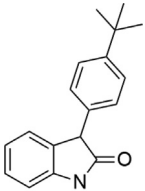
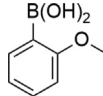
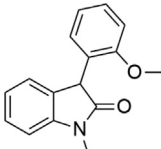
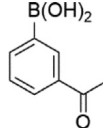
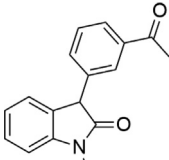
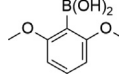
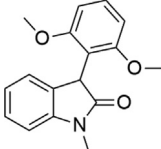
The experimental studies of the reaction showed that water additionally to its role as safe and recoverable solvent also is a positive catalyst partner, nevertheless the authors do not provided additional information to support this affirmation. Additives and bases such as KOAc improved the process catalytic activity. In Table 13 are included some noteworthy reaction examples.



Scheme 10. N-methyl-2-oxindole-C3-arylation catalyzed by **23** [91].

Table 11

Examples of α -Arylation of 1-methyl-indolin-2-one catalyzed by **23**. Conditions: 1-methyl-indolin-2-one (4 mmol), aryl boronic acid (4 mmol), KOH (5 mmol). Catalyst loading: 0.001 mol%. Isolated yields are reported [91].

Substrate 1	Substrate 2	Product	T (K)	Yield (%)	TON	t (h)
			RT	90	9000	5
			RT	70	7000	7
			RT	78	7800	5
			RT	87	8700	5
			RT	71	7100	5
			RT	61	6100	8

Related to these results, arene piano-stool ruthenium complexes, which were previously used as active catalysts in synthesizing organic molecules, were also evaluated as catalysts for arylation reactions [106–115]. The arene ruthenium complex **30**, which was synthesized by the procedure showed in Scheme 14, was characterized by spectroscopic techniques in solution and solid-state by single-crystal X-ray diffraction.

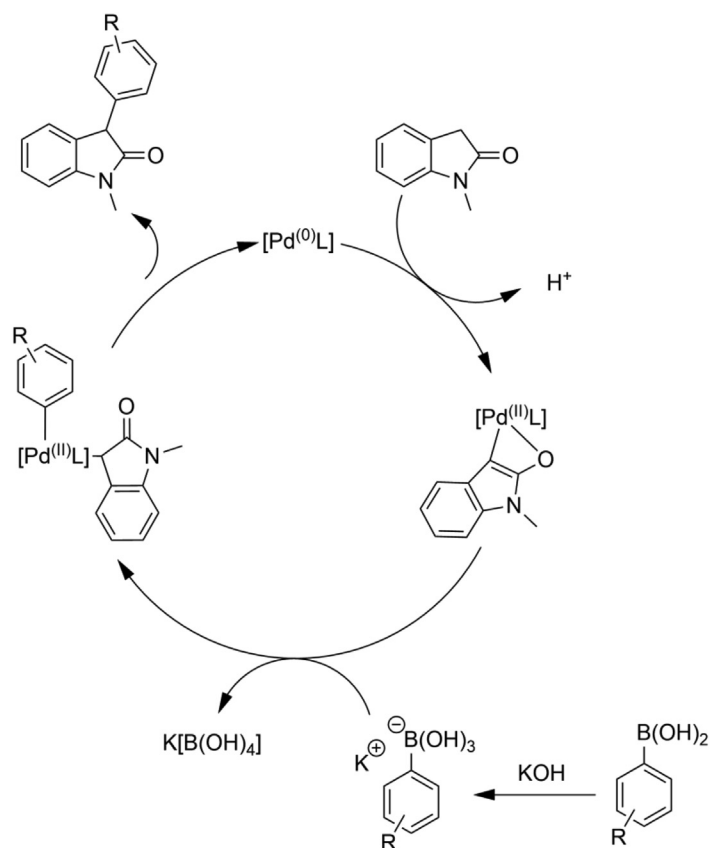
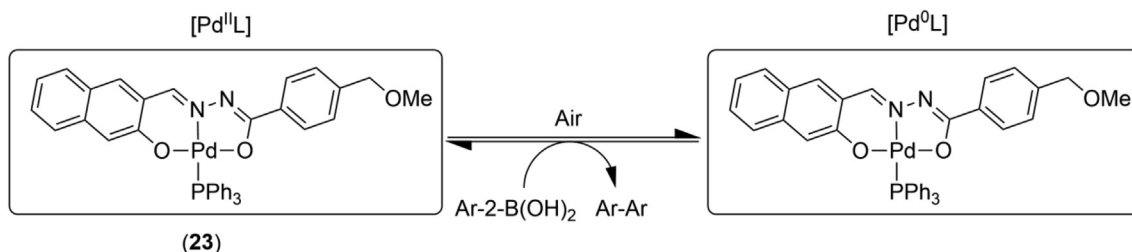
The crystal structure of **30** showed how the ruthenium is coordinated to a η^3 -*p*-cymene, two chlorides and the ligand 2,6-bis(diphenylmethyl)-4-methylaniline by the NH_2 group (Fig. 9) [116].

Complex **30** showed to be a good catalyst (yields > 60%) for the oxidative C–C-homocoupling in water of aryl boronic acids, which was accomplished at room temperature. Table 14 shows some representative examples, including used substrates, obtained products and reaction conditions. The bulky aniline ligands drive significantly the reaction selectivity to the formation of biaryls, opening the door to the exploration of new hydrosoluble catalysts active for the synthesis of these compounds. Under optimized reaction conditions a different selective activity was observed to the cross- and homocoupled-biaryls.

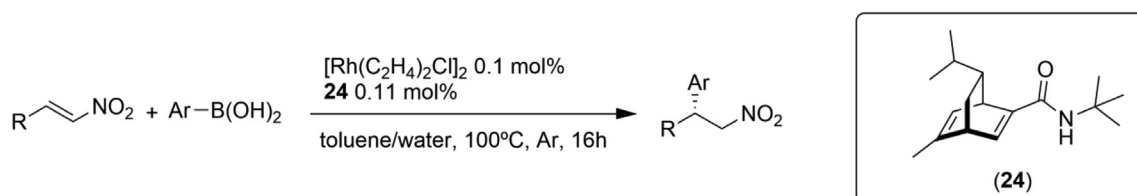
The proposed mechanism was based on experimental results and literature reports [117], which support that initially, the catalyst forms a σ -aryl-Ru(II) intermediate after reacting with aryl boronic acid (Scheme 15). The authors proposed that the bulky diphenylmethane substituents on the *ortho* positions of the phenyl ring of the ligand facilitate the elimination of the chloride, producing a vacancy on the metal that is occupied by the substrate. This intermediate reacts with a second molecule of arylboronic acid to form a di(σ -aryl)-Ru(II) intermediate, which evolves by reductive elimination releasing the biaryl derivative and a Ru(0) species, which is oxidized by the Cu(II)/aerial O_2 oxidative system to restore the active starting ruthenium complex, closing the catalytic cycle.

Another interesting reaction is the catalytic synthesis of bis-(indolyl)methanes (BIMs) by oxidative coupling of indoles with benzylamines, which is catalysed by the aqua-cobalt complex **31** under both inert and air atmosphere (Scheme 16) [118].

This reaction is so effective that aromatic amines are able to be transformed into the corresponding bis-(indolyl)methanes (BIMs) with yields usually up to 85% (Examples are displayed in Table 15).



Scheme 11. Proposed mechanism for the synthesis in the water of 3-phenyl-2-oxindole from N-methyl-2-oxindole catalysed by **23** [91].



Scheme 12. Arylation of nitroalkenes catalysed by $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ in the presence of ligand **24** [102].

This reaction can transform grams of reactant into products and is therefore useful for pharmaceutical industrial production.

5. C-Hydroarylation

Hydroarylation is an interesting reaction in which the C-arylation is combined with the hydration of the resulting product giving rise to substituted Z,E-alkenes. This reaction can be used

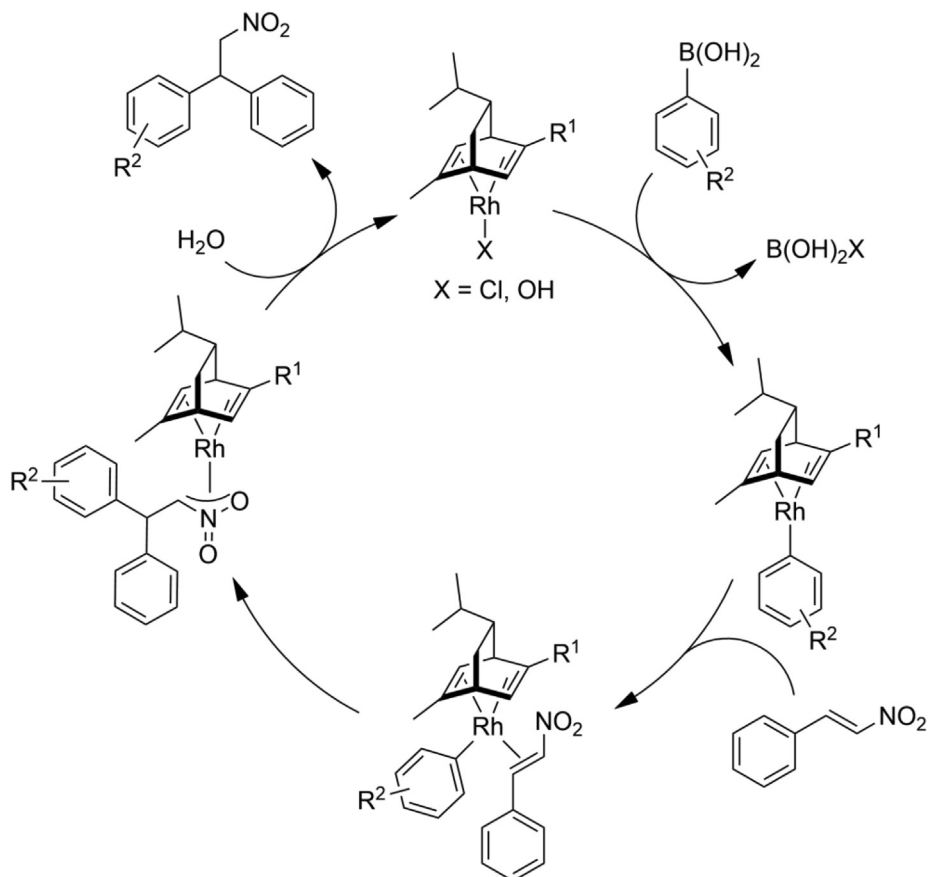
for the synthesis of valuable compounds for the industry, such as enamides, which are interesting building blocks for synthesizing more complex molecules [119–123]. In 2020 it was shown that it is possible the hydroarylation of ynamides in water catalysed by $\text{Pd}(\text{OAc})_2$ in presence of NaTPPTS (sodium 3,3',3''-phosphinetriyl tribenzenesulfonate) (Scheme 17).

The resulting catalytic system showed to be highly active for the reaction between aryl- and alkyl-ynamides with arylboronic acids. The reaction worked for substrates containing either

Table 12

Examples of arylation of nitroalkenes by the dimer $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ in the presence of **24**. Conditions: $[\text{Rh}]$ (0.1 mol%), **24** (0.11 mol%), $\text{H}_2\text{O}/\text{toluene}$ 1:1. Yields determined by HPLC [102].

Substrate 1	Substrate 2	Product	T (K)	Yield (%) (ee)	TON	t (h)
			373	99 (91% ee)	990	16
			373	97 (92% ee)	970	16
			373	92 (93% ee)	920	16
			373	92 (94% ee)	920	16
			373	78 (84% ee)	780	16

**Scheme 13.** Proposed mechanism for the 1,4-addition of aryl boronic acids and nitroalkenes in water catalysed by $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ in the presence of ligand **24**.

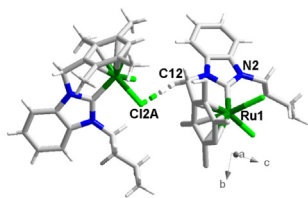


Fig. 7. Crystal structure of the complex unit of **26**: triclinic (P-1); Ru1A-Cl2A 2.414 (1) Å; C12-H12B...Cl2A 2.891(9) Å; Ru(η^6, η^1 -arene-CH₂-NHC)_{centroid} 1.682 Å. Adapted from Ref. [105].

electron-donating and electron-withdrawing groups [124]. As a result, the major compounds obtained from the reaction are (Z)- α, β -disubstituted enamides when aryl-ynamides were used as a substrate while the E/Z ratio lowers when the substrates were alkylynamides, such as are showed in Table 16.

6. α -Alkylation

The carbonyl compounds are among the most valuable chemical compounds and are frequently used as construction bricks to

design and build new organic molecules. The carbon-carbon coupling at α -carbonyl position is a valuable strategy to obtain very useful molecules. It is not necessary to stress that the α -substituted ketones display rich chemistry, being also common molecules in biological systems [125]. Frequently, the α -substitution of carbonyls gives rise to new molecules containing stereogenic centres [126–128]. Usually, these reactions are performed in the presence of a strong base with very toxic alkyl halides as alkylating reagents [129]. For this reason, great efforts have been done to obtain new procedures to accomplish α -alkylation reactions, particularly of ketones. In this line, a certain interest has been devoted to using alcohols as alkylating agents, which can be accomplished by (i) a hydrogen auto-transfer process or (ii) a hydrogen-borrowing catalytic reaction; both steps are catalysed by complexes containing metals such as Ru, Ir, Pd, etc. [130–133]. The process requires the initial alcohol dehydrogenation to lead to the corresponding aldehyde, furtherly a cross-aldol condensation occurs with the ketone, giving rise finally to the α, β -unsaturated ketone. The last step of the reaction implicates the metal hydride generated when the alcohol is dehydrogenated: this species finally transfers the needed hydride to afford an α -alkylated ketone.

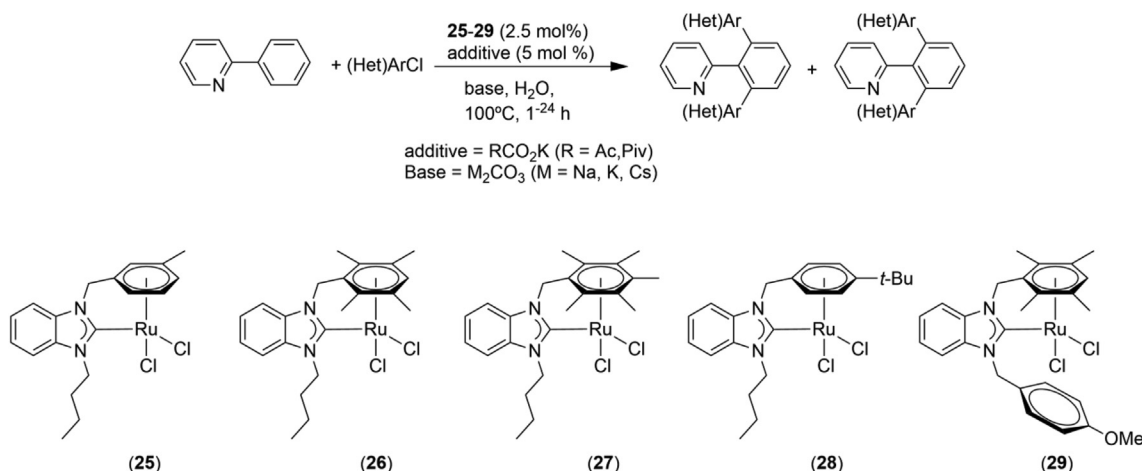
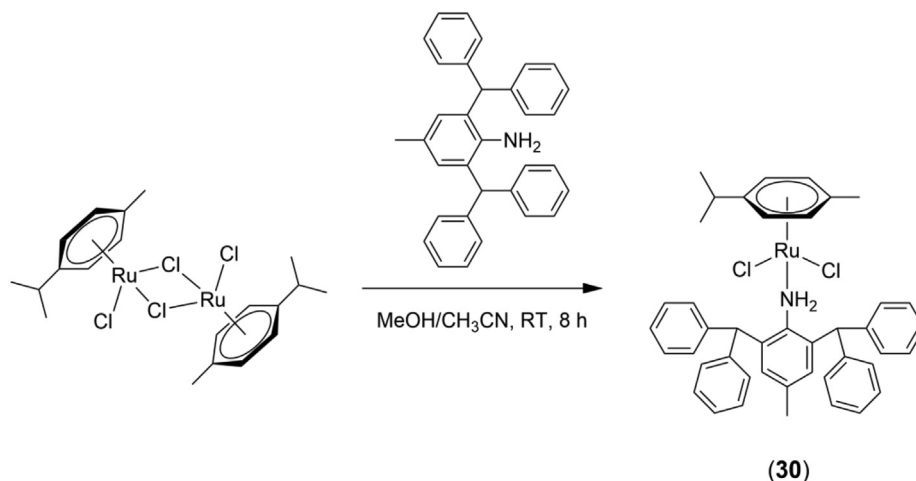
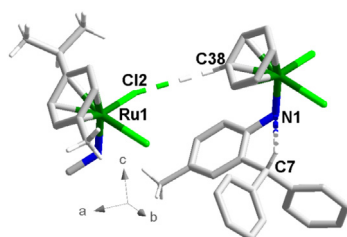


Fig. 8. Top: heteroarylation of 2-phenylpyridine catalysed by **25–29**. Bottom: structures of **25–29** [105].

Table 13

Examples of (hetero)arylation of 2-phenylpyridine catalyzed by **25–29**. Conditions: 2-phenylpyridine (0.5 mmol), (Het)ArCl (0.5 mmol), Cs₂CO₃ (1.5 mmol), KOAc (0.05 mmol). Catalyst loading: 2.5 mol%. Yields determined by GC or GC-MS [105].

Catalyst	Substrate 1	Substrate 2	Product A	Product B	T (K)	Yield % (A:B ratio)	TON	t (h)
25					373	100 (100:0)	50	1
26					373	100 (100:0)	50	1
27					373	80 (80:20)	40	1
28					373	90 (90:10)	45	1
29					373	85 (87:13)	42.5	1
25					373	90 (90:10)	45	20
26					373	88 (95:5)	44	20
27					373	95 (100:0)	47.5	20
28					373	89 (97:3)	44.5	20
29					373	83 (85:15)	41.5	20

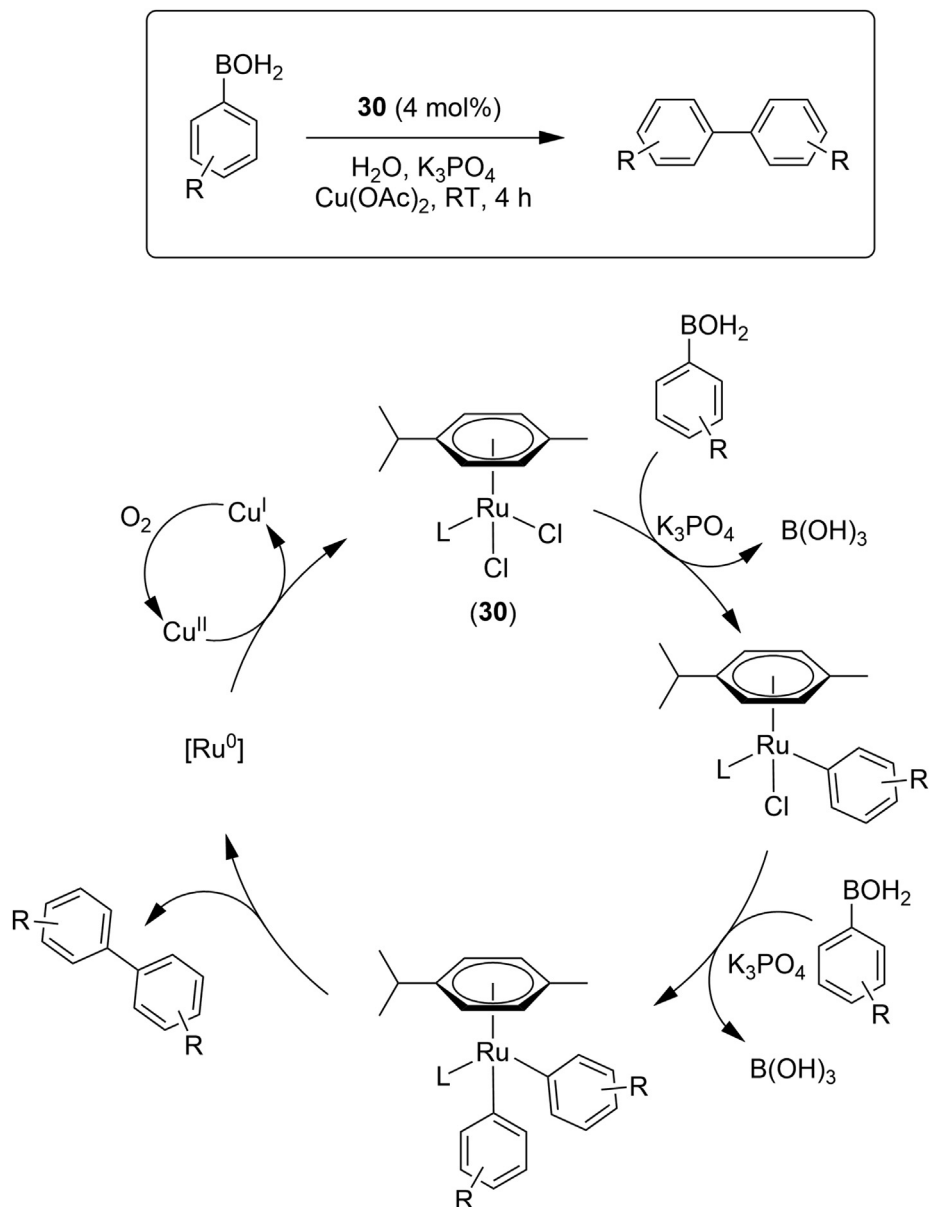
**Scheme 14.** Synthesis of **30** [116].**Fig. 9.** Crystal structure of the complex unit of **30**: triclinic (P-1); Ru1-Cl1 2.411(6) Å; Ru-(η^6 -p-cymene) centroid 1.668 Å; C38-H38...Cl2 3.541(3) Å; C7-H7...N1 2.559(3) Å. Adapted from Ref. [116].

The alcoholic- α -alkylation reaction is characterized by a high atom efficiency and by the production of water as the unique by-product. Usually, high-boiling organic solvents have been used for the α -alkylation of ketones with alcohols, such as toluene and p-xylene. In 2019 a new process to accomplish this reaction but in water was published (Scheme 18) [134], by using as catalyst a water-soluble dinuclear {Cp*Ir} complex containing the ligand 4,4',6,6'-tetrahydroxy-2,2'-bipyrimidine (**32**, Scheme 18). The process can promote the synthesis of a large variety of α -alkyl ketones under reasonable mild reaction conditions (100 °C, in air, c.a. 12 h.) in presence of KOH (Table 17 includes some representative examples).

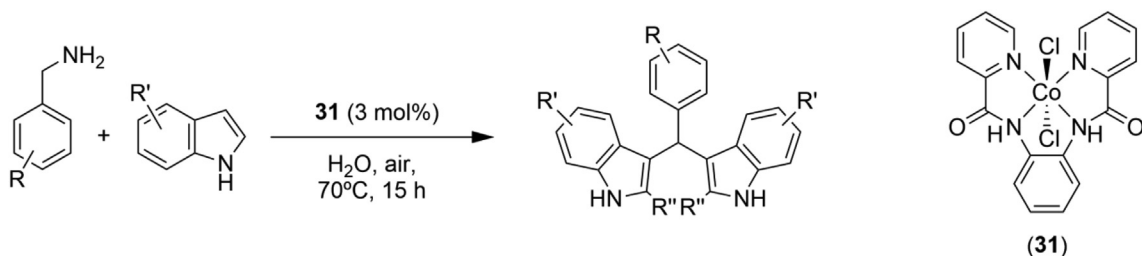
Table 14

Examples of Homocoupling of aryl boronic acids catalysed by **30**. Conditions: aryl boronic acid (1 mmol), Cu(OAc)₂ (1.5 mmol), K₃PO₄ (2 mmol), H₂O (5 mL). Catalyst loading: 4 mol%. Isolated yields are reported [116].

Substrate	Product	T (K)	Conv %	TON	T(h)
		RT	92	23	4
		RT	84	21	4
		RT	84	21	4
		RT	79	19.8	4
		RT	69	17.3	4
		RT	61	15.3	4



Scheme 15. Proposed mechanism for the coupling of arylboronic acids in water catalysed by **30** [116].



Scheme 16. Oxidative coupling of aromatic amines with indoles catalysed by **31** [118].


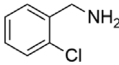
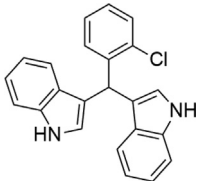
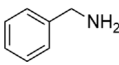
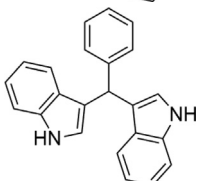
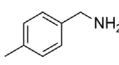
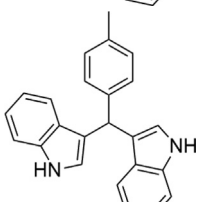
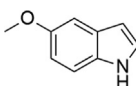
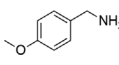
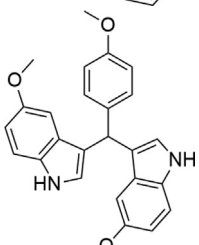
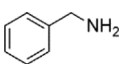
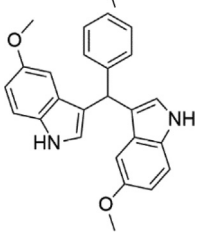
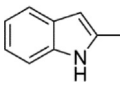
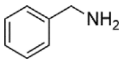
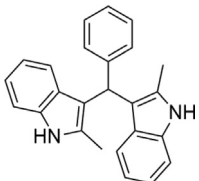
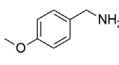
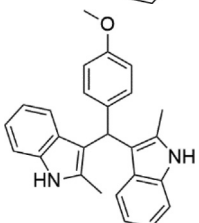
The synthesis of the biologically active molecule *donepezil* is a representative example of the variety of possible substrates that can be obtained by this procedure and how practical it can be (Scheme 19).

Efforts were made to obtain a detailed mechanism of the reaction. An important finding was that the hydroxyl group of the

ligand is determinant to promote the catalytic hydrogen transfer. The proposed mechanism (Scheme 20), which was also supported by previously published data [135–139], consists of the initial formation of an unsaturated species by deprotonation of the catalyst by a base. Later, the ligand is doubly protonated by two molecules of alcohol affording a dialkoxy-iridium intermediate, which further

Table 15

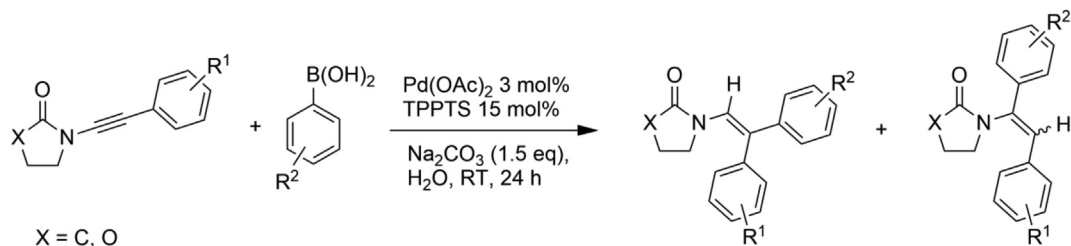
Examples of oxidative coupling of aromatic amines with indoles catalysed by **31**. Conditions: amine (1 mmol), indole (2 mmol), water (0.5 mL). Catalyst loading 3 mol%. Isolated yields are reported [118].

Substrate 1	Substrate 2	Product	T. (K)	Yield (%)	TON	T(h)
			343	80	26.6	15
			343	75	25	15
			343	53	17.6	15
			343	85	28.3	15
			343	65	21.6	15
			343	54	18	15
			343	40	13.3	15

experiences a β -hydrogen elimination. Finally, the dimeric iridium-hydride intermediate and two molecules of aldehyde undergo a cross-aldol condensation by simultaneous transfer of two hydrides from the iridium and two hydroxyl-protons from the ligand, affording two molecules of α,β -unsaturated ketone, the final product, and regenerating also the catalyst.

7. Michael addition

Michael addition or more generally Michael reaction was for the first time proposed by Arthur Michael [140–143], and involves the C-addition at the β -carbon of an unsaturated moiety containing an

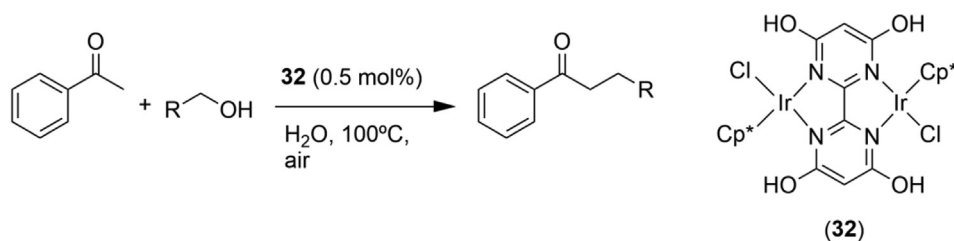


Scheme 17. Aqueous hydroarylation of ynamides catalysed by Pd(OAc)₂/NaTPPTS [124].

Table 16

Examples of hydroarylation of ynamides catalysed by dissolution in water of Pd(OAc)₂/NaTPPTS [124].

Catalyst	Substrate 1	Substrate 2	Product 1	Product 2	% Conv	T (K)	t (h)
					93	RT	24
			80:20 		72	RT	24
			85:15 		62	RT	24
			85:15 		38	RT	24
			2:1				



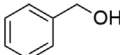
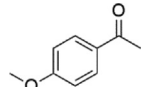
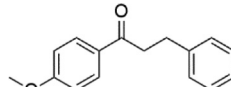
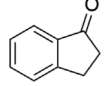
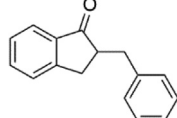
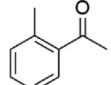
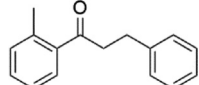
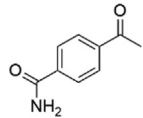
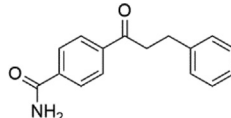
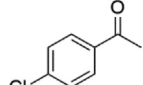
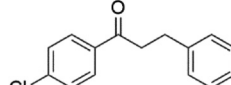
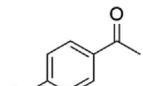
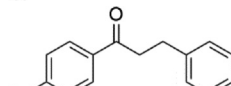
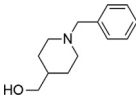
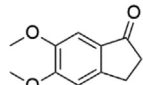
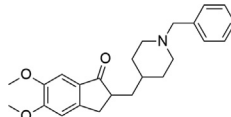
Scheme 18. α -alkylation of ketones with alcohols in water catalyzed by **32** [134].

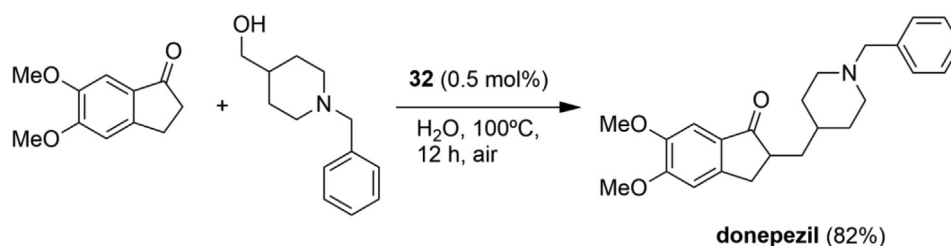
electron-withdrawing group. Typical Michael donors are enolates, while the most classical acceptors are α,β -unsaturated carbonyls, although many variants exist nowadays [144]. It is not very common to find Michael additions performed in water. The few existing examples lead to poor to moderate enantioselectivity [9], which is attributed by the authors to the plausible participation of water molecules in the different reaction steps [145].

Z. Wang et al, published in 2018 the enantioselective reaction between pyrroles and nitroalkenes in water to give nitroethylpyrrole derivatives in excellent yields and enantiomeric excesses (Table 18). The reaction (Scheme 21) proceeds using CuBr₂ in the presence of ligand **33** and a surfactant like Na-laurylsulfonate, and can be scaled up to prepare grams of product in water/CHCl₃ biphasic medium under mild conditions. Representative examples

Table 17

Examples of the α -alkylation of ketones catalyzed by **32**. Conditions: alcohol (0.5 mmol), ketone (0.65 mmol), KOH (1 equiv.), H₂O (1 mL), air. Catalyst loading: 0.5 mol%. Isolated yields are reported [134].

Substrate 1	Substrate 2	Product	T. (K)	Yield (%)	TON	T(h)
			373	85	170	12
			373	83	166	12
			373	80	160	12
			373	71	142	12
			373	67	134	12
			373	50	100	12
			373	82	164	12

**Scheme 19.** Synthesis of the AChE inhibitor donepezil in water catalyzed by **32** [134].

are summarized in Table 1 [146]. It was the first example of a Michael reaction in the presence of water [147].

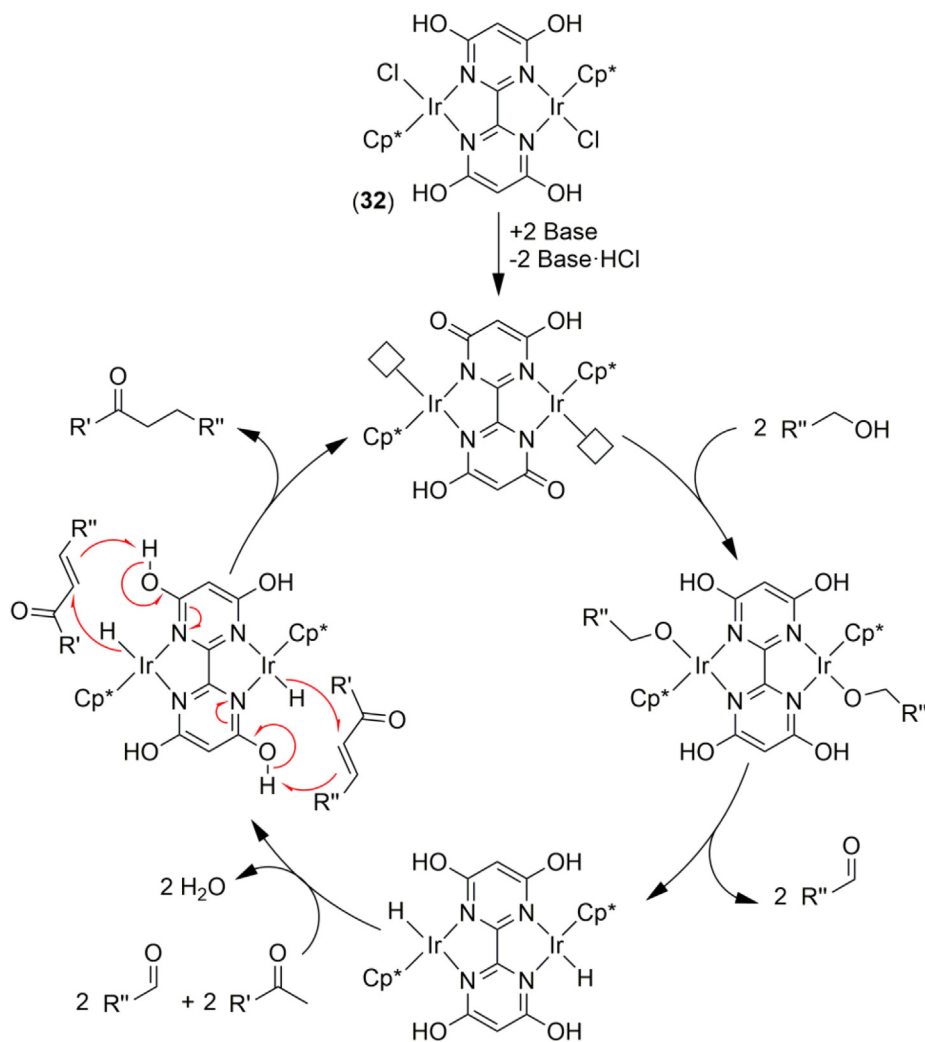
The authors propose that the active catalyst is constituted by a Cu atom coordinated to the tertiary amines-Schiff base **33** (Fig. 10). The importance of this reaction lays in the wide range of applications for which nitroethylpyrroles are used: they are precursors for many useful molecules, finding applications in electronic and photovoltaic devices, chemical/biological sensors [148], but also for the preparation of many pharmaceutical drugs [149].

8. Ring closing metathesis

The popular synthetic procedure named ring-closing metathesis (RCM) leads to the synthesis of molecules containing unsaturated rings by the metathesis of the carbon atoms of two terminal alkenes [150,151]. The reaction was deeply investigated and used by Robert H. Grubbs and Richard R. Schrock [152,153], providing a large variety of new cyclic molecules, most of them impossible to be obtained by previously known procedures. This reaction leads

to the synthesis of interesting molecules containing rings with sizes from 5 to 7 atoms [154], but also with up to 90-membered macroheterocycles [155]. The obtained yields of this reaction are usually very large and the only major subproduct is ethylene. Therefore, the RCM is considered an example of atom efficient reaction.

A very elegant application of RCM reactions was developed in the last years involving biological molecules. Anthropogenic-biocatalysts are attractive compounds for synthetic processes developed from harnessing natural enzymes to new biocatalysts with tailor-made functions [156]. New achievements have enlarged the family of known artificial enzymes [157,158] by using three complementary approaches: reusing natural metalloenzymes for abiotic transformations [159]; redesign of metalloenzymes [160]; including abiotic cofactors into proteins [161]. Therefore, designing a wide variety of artificial metalloenzymes is possible, and can be useful for *in-vivo* non-natural reactions. Nevertheless, this option is limited due to the fact that many metal cofactors are inhibited by cellular components [162].

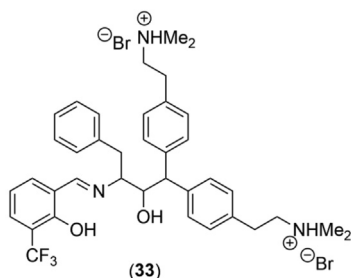
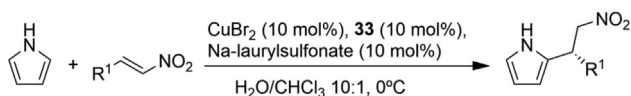


Scheme 20. Proposed mechanism for the α -alkylation of ketones with alcohols in water catalysed by **32** [134].

Table 18

Enantioselective Michael Addition of Pyrrole with Nitroalkenes catalysed by CuBr_2 in the presence of **33**. Conditions: pyrrole (0.6 mmol), nitroalkene (0.2 mmol), CuBr_2 (10 mol%), **33** (10 mol%), Na-laurylsulfonate (10 mol%) [146].

Substrate 1	Substrate 2	Product	T. (K)	Yield (%)	TON	T(h)
			273	97	9.7	72
			273	95	9.5	72
			273	88	98.8	72
			273	76	7.6	72



Scheme 21. Enantioselective Michael Reaction in $\text{H}_2\text{O}/\text{CHCl}_3$ catalysed by CuBr_2 in presence of the ligand **33** [146].

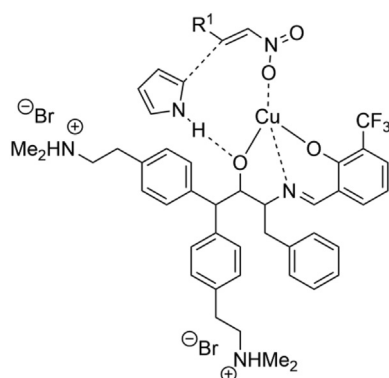
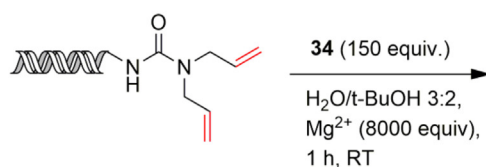


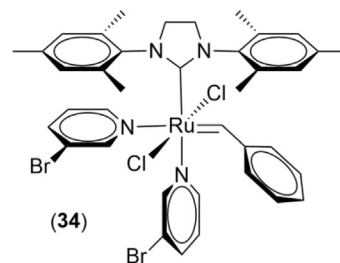
Fig. 10. Proposed intermediate for the enantioselective Michael reaction catalysed by the system $\text{CuBr}_2/\mathbf{33}$ [146].

As seen before, these new successes led to the use of transition metal homogeneous catalysis approaches to the development of DELs (DNA-encoded libraries) for pharmaceutical and biotechnological research [41–45]. In 2017 was described the first RCM and cross-metathesis (CM) reactions performed on-DNA, which were induced by the fast initiating Grubbs Ru catalysts **34** [163]. The reaction was accomplished in a water/*t*-butanol biphasic medium containing MgCl_2 to minimize the DNA backbone decomposition (Scheme 22). The success of this reaction provides the possibility of developing novel DELs, which could be useful for tackling challenging drug targets (Table 19) [164].

A similar approach led to the first RCM synthesis in the water of an unprotected peptide (Scheme 23), which is catalysed by complex **35**. The reaction was favoured in acidic conditions and by addition of MgCl_2 [165]. Interestingly, the authors proposed that this reaction proceeds better in water with unprotected pep-



Scheme 22. Examples of on-DNA RCM catalysed by **34**.



tides, rather than protected in organic solvents. Another advantage of the reaction is related to the fact that peptides are more soluble in water than in organic solvents and therefore the method could have a larger and general applicability for the peptide synthesis.

In 2016 S. Panke et al. published a very interesting paper that reported a representative organometallic reaction unknown in nature: the catalytic olefin metathesis catalysed by an artificial metalloenzyme and its evolution *in vivo* in *Escherichia Coli* [166,167]. The same team previously published an artificial metallohydrolase useful for catalysing functional metatheses *in vivo* [160], which constituted the efficient application and evolution of an artificial metalloenzyme catalysing an abiotic reaction *in vivo*. This reaction may be applied to non-natural metabolism. Olefin metathesis was catalysed by application of the streptavidin–biotin technology by an unknown reaction mechanism in natural enzymes. The wild-type artificial metalloenzyme biot–Ru–SAVperi leads the cell to be an adequate reaction environment in which perform metathesis reactions (Scheme 24). These results were proposed to be the first step to develop and implement a set of bio-orthogonal tools for non-natural metabolic synthesis.

Another very interesting synthetic process was presented in 2019 and concerns RCM to achieve enantioselective cyclopropanation of diazo esters and Weinreb amides in water/ Et_2O biphasic medium catalysed by the Ru(II) complex **37**. The obtained products (Table 20 summarizes some significant examples) are bicyclo [3.1.0]hexa-lactones and lactames, which can be recovered from the reaction in high yields (up to 99%) and excellent enantioselectivities (up to 99% ee) at room temperature (Scheme 25) [168]. The experimental study of the reaction suggested that the ammonium at the Amm–Pheox ligand is a key functionalization step to achieve good conversions. Catalyst **37** can be reused up to six recycling runs maintaining high values of yield and enantioselectivity.

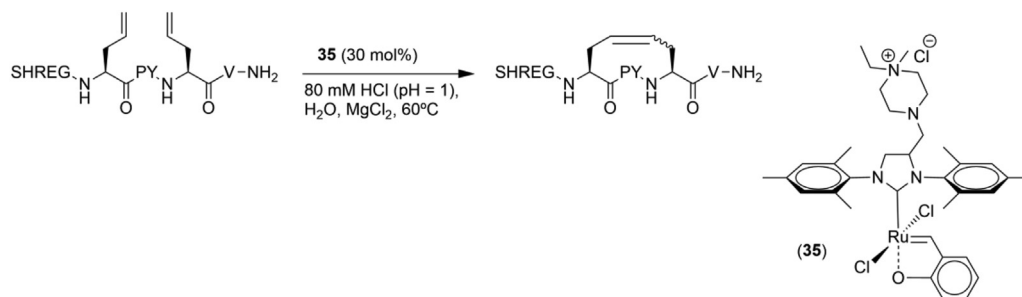
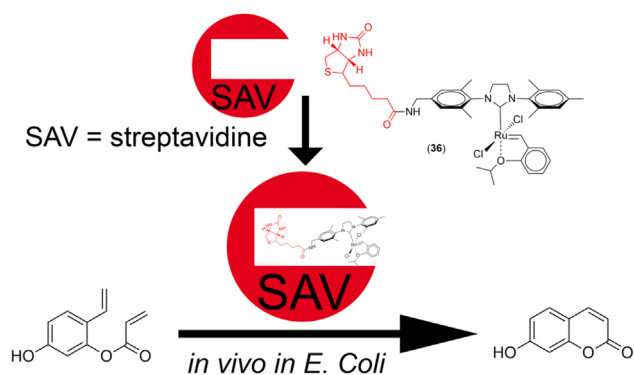
9. Ring opening metathesis polymerization

Another really important family of synthetic reactions are collected by the generic description of Ring Opening Metathesis Polymerization (ROMP). The ROMP C–C coupling, under mild conditions, is capable to produce a wide variety of polymers with different topologies and functionalities [169–171]. The ROMP is catalysed by metal complexes, being those containing Ru the most used as they can catalyse a wide range of substrates, are active under air and moisture [172], in water [173] and biological media [174]. The most known catalysts suitable in water usually contain hydrophilic ligands and do not commonly achieve adequate control of the polymer molecular weight and dispersity. This fact is imputed to the low initiation efficiency and to the reaction rate of these catalysts that lead to a loss of living character [175]. A proposed possible solution to these problems consists in initiating the reaction in a water-miscible organic solvent via ring-opening of a few hydrophilic monomers by using a known ROMP catalyst. The reaction leads to a living hydrosoluble oligomer attached to the

Table 19

Examples of on-DNA RCM catalysed by **34**. Conditions: water:t-butanol = 3:2, MgCl₂ (8000 equiv). Catalyst loading: 150 equiv. Conversions determined by LC/MS. (TON: Number of turnovers) [163].

Substrates	Product	T (K)	t (h)	TON	Conv %
		RT	1	0.085	85
		RT	1	0.065	65
		RT	1	0.050	50
		RT	1	0.055	55
		RT	1	0.050	50

**Scheme 23.** RCM on linear peptides catalysed by **35** [165].**Scheme 24.** Structure of complex **36**. And conjugation with streptavidin to obtain an artificial metalloenzyme useful for *in vivo* RCM in *Escherichia Coli* (SAV = streptavidine).

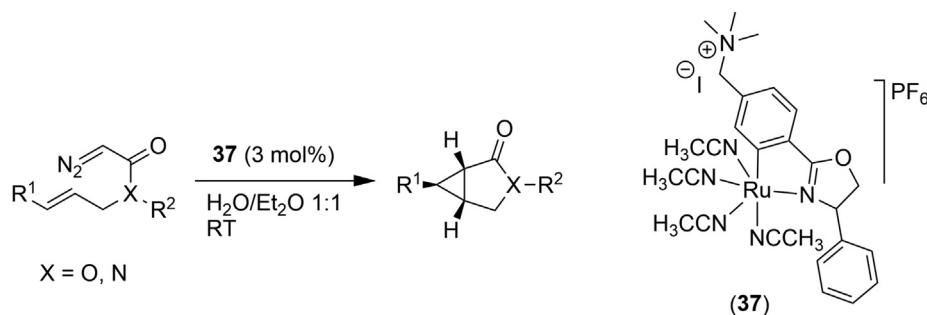
catalyst through the propagating alkylidene that can be introduced in a water solution of the monomers to be polymerized. One of the most interesting advantages of this method is that it could be used for polymerization reactions in the biological environment, which can mediate interesting reactions such as the conjugation of polymers to proteins or DNA. New biomaterials are needed in medicine and pharmacy and, in principle, the ROMP should be an adequate synthetic method for obtaining this class of compounds as it is fast and tolerant with functional groups.

In 2018 R. K. O'Reilly et al. described the synthesis of block copolymers in water by a general strategy that uses the commercial ROMP catalysts **38** (Scheme 26). The catalyst initiates the polymerization process in an organic solvent, which allows obtaining a water-soluble macroinitiator that further mediates a living ROMP in H₂O [176]. This reaction allows obtaining block-copolymers in water with excellent control of their molecular weight distributions. Adding a different second monomer a water-insoluble poly-

Table 20

Examples of intramolecular cyclopropanation catalysed by **37**. Conditions: diazo amide (1 mmol), H₂O/Et₂O 1:1 (2 mL). Catalyst loading: 0.3 mol%. Isolated yields are reported; ee % determined by chiral HPLC. (TON: Number of turnovers) [168].

Substrates	Product	T (K)	t (h)	TON	Yield
		RT	1–5	33	99% (99% ee)
		RT	1–5	32.3	97% (95% ee)
		RT	1–5	32	96% (91% ee)
		RT	1–5	31	93% (90% ee)
		RT	1–5	18.6	56% (97% ee)
		RT	1–5	12.7	38% (96% ee)
		RT	1–5	6	18 (88% ee)

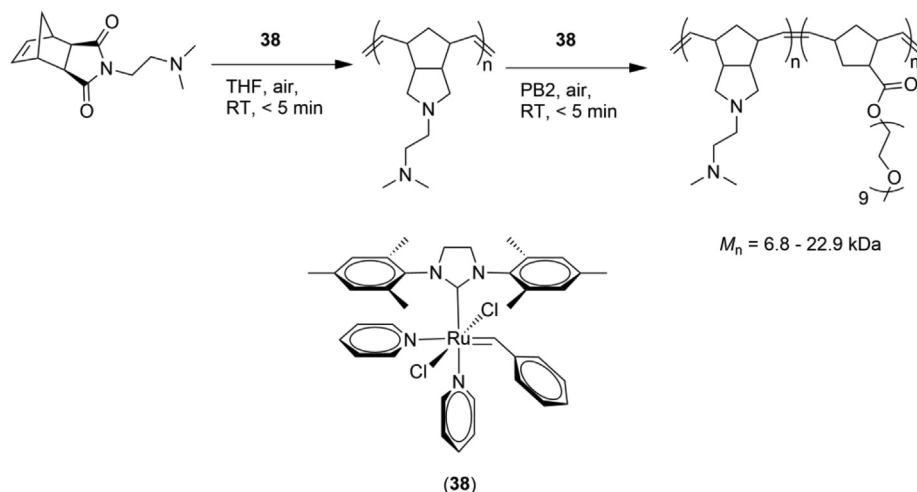
**Scheme 25.** Enantioselective intramolecular cyclopropanation catalysed by **37** [168].

mer is formed. This strategy, named polymerization-induced self-assembly (PISA), offers a new path for the synthesis of functional nanostructures, providing a variety of self-assembled nano-objects morphologies such as spheres, worms, vesicles, etc.

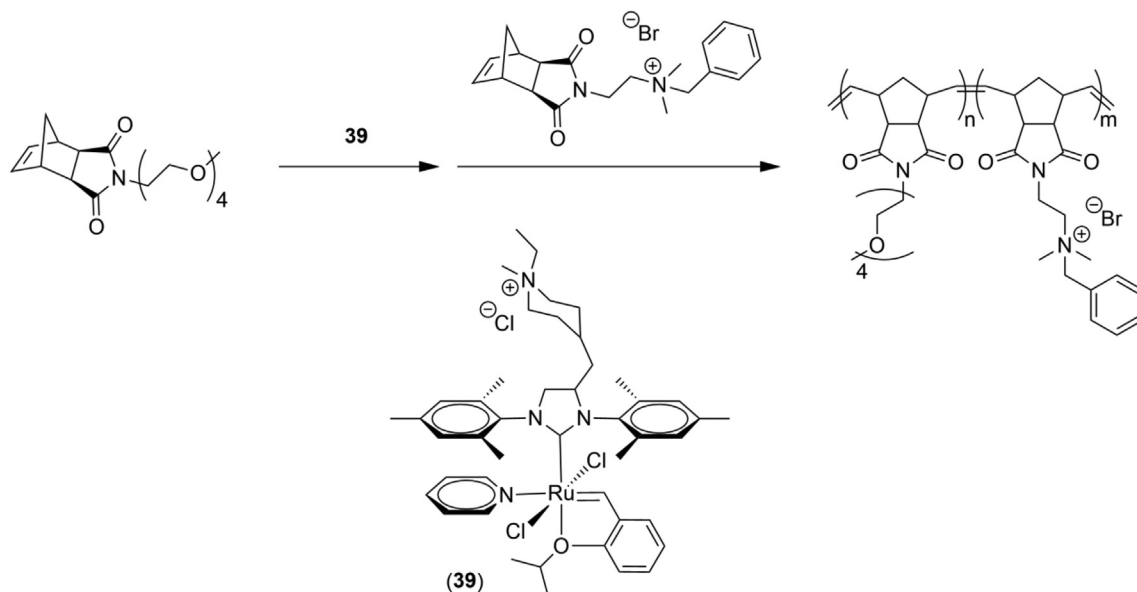
In the same year, the protocol defined as Ring-Opening Metathesis Polymerization-Induced Self-Assembly (ROMPISA) was performed for the first time in an aqueous medium by using a Ru catalyst. The reaction was carried out at room temperature and with high solids concentration and the obtained compounds were well-defined micellar polymer nanoparticles (20 w/w%) [177]. The catalyst used is a new polymerization initiator (Scheme 27), similar to the water-soluble cationic second-generation Hoveyda-Grubbs catalysts. This new complex catalyses the formation of di-block copolymers from norbornenyl monomers in water. The large variety of obtained self-assembled polymeric

nanostructure morphologies were systematized by a phase diagram. The experimental studies of the reaction mechanism showed how an aqueous initiator initiates the living polymerization.

Nevertheless, and despite the precedent results, olefin metathesis is still a challenging process in water. It is evident to this point that great efforts are devoted to developing new catalyst and reactions in water [178–181], nevertheless the influence of water molecules on the activity and stability of the Ru catalysts remains largely unexplored. The comparison of the results obtained in water with those in organic solvents sheds of evidence that in aqueous-medium the catalytic intermediates are different to those in organic solvents [182,183]. Therefore, it is rather probable that reaction conditions in an organic solvent are quite different from those desirable for accomplishing the same reaction in water. Understanding how water affects the catalytic activity in



Scheme 26. Preparation of a diblock copolymer via PISA, through the prior preparation of a hydrosoluble macroinitiator. (PB2: acidic phosphate buffer at pH = 2) [176].



Scheme 27. The diblock copolymer obtained by aqueous ROMPISA catalysed by 39 [177].

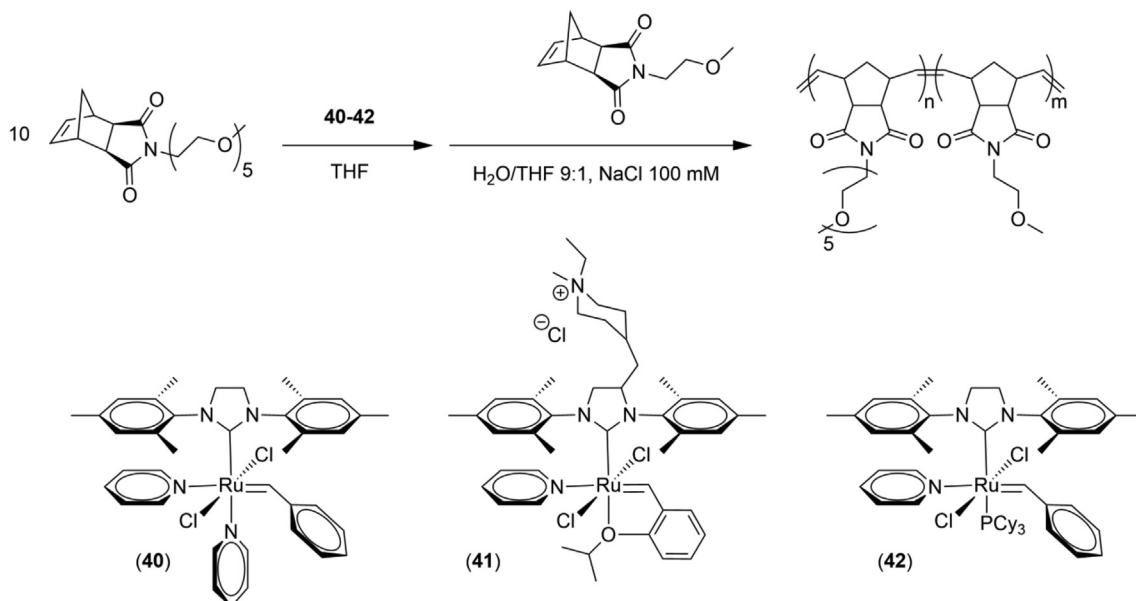
aqueous-medium is without any doubt mandatory but also to determine how the reaction is altered by the pH and the presence of other species such as anions is important. Obtained results should provide important information to enable a controlled polymerization in water under neutral conditions.

Despite water-soluble Ru-complexes **40–42** (Scheme 28) were used for the catalytic cross-metathesis (CM) and ring-closing metathesis (RCM) of olefins, few data were determined on how is the activity and stability of these complexes during the ROMP process [184]. It is important to point out that the reaction was found to be significantly affected by the concentration of chlorides and, in minor grade, by pH (Scheme 29), suggesting that exchange of the chlorides in the complex by hydroxide or H₂O affords an unstable intermediate that decomposes quickly releasing a carbene ligand and stopping the metathesis. To avoid this problem, the addition of chloride (NaCl, KCl, etc) is required to stabilize the intermediate, which improves ROMP conversion and control. In these reaction conditions, the complex can catalyze in water the formation of

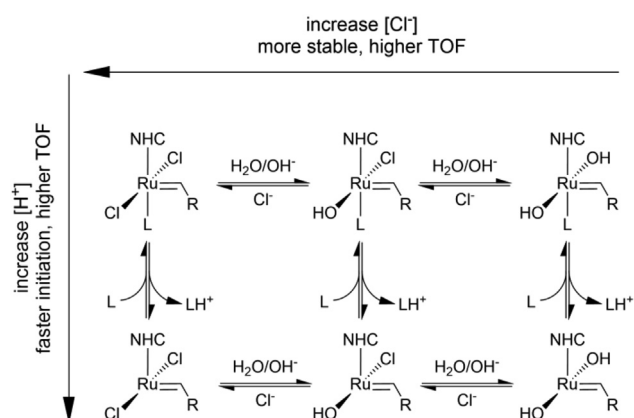
diblock copolymers (Scheme 28) in low concentration of the starting compound, low catalyst concentrations (1 mol %) and moderate to low catalyst loadings. This finding is claimed to be very important to enable the use of this reaction in biological media as it proceeds at neutral pH, which is an important result as the olefin metathesis has an increasing application in biochemical research [185–187]. For example, metathesis in water has been used to implant in biological media polymers from proteins [174,188] This strategy led to molecular transformations within living cells [167], and to obtain polymeric nanoparticles via ROMPISA [189].

10. Conclusions and perspective

The formation of the C–C bond in water, mediated by water-soluble homogeneous transition metal catalysts, is one of the most interesting and potentially important synthetic methods, offering a versatile and elegant route to synthesizing a large variety of new



Scheme 28. Aqueous ROMPISA catalysed by 40–42.

Scheme 29. Role of H^+ and Cl^- in the ROMOP catalysed by 40–42. (TOF: Frequency of turnovers) [184].

organic molecules by environmentally friendly procedures. Only recently, water has been used as a reaction medium despite the importance of this solvent in chemistry and biology, and the social pressure to develop new more economical and ecological methods. Using water as solvent can provide larger yields, reactivity and, in some cases, milder reaction conditions than dry solvents. At the moment only complexes containing Ru, Pd and Ir, and in minor grade Cu, Ni, Co, have been shown to be catalytically active in the formation of C–C bonds in water. Catalytic reaction mechanisms in water have been proposed to be similar to those in organic solvents, sometimes also on the basis of the experimental studies made in these solvents. Nevertheless, significant differences have been found, supporting that genuine mechanisms involving water are still to be determined. It is very significant to stress that water is the life medium and therefore C–C coupling reactions can be used in promoting abiotic reactions in the living cell. This possibility has been evaluated by using metal complexes in combination with biological molecules, such as DNA, to obtain new catalysts useful to perform the formation of C–C bonds under physiological conditions. These exciting findings open the door to developing some sort of molecular surgery. There are also examples for obtaining asymmetric molecules in water catalyzed only

by metal complexes, but it can be expected that a novel and more efficient generation of catalysts will provide better results soon. Despite the long time passed from the first achievements on catalytic synthesis in water, the aqueous organometallic chemistry has a long way ahead and a brilliant future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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