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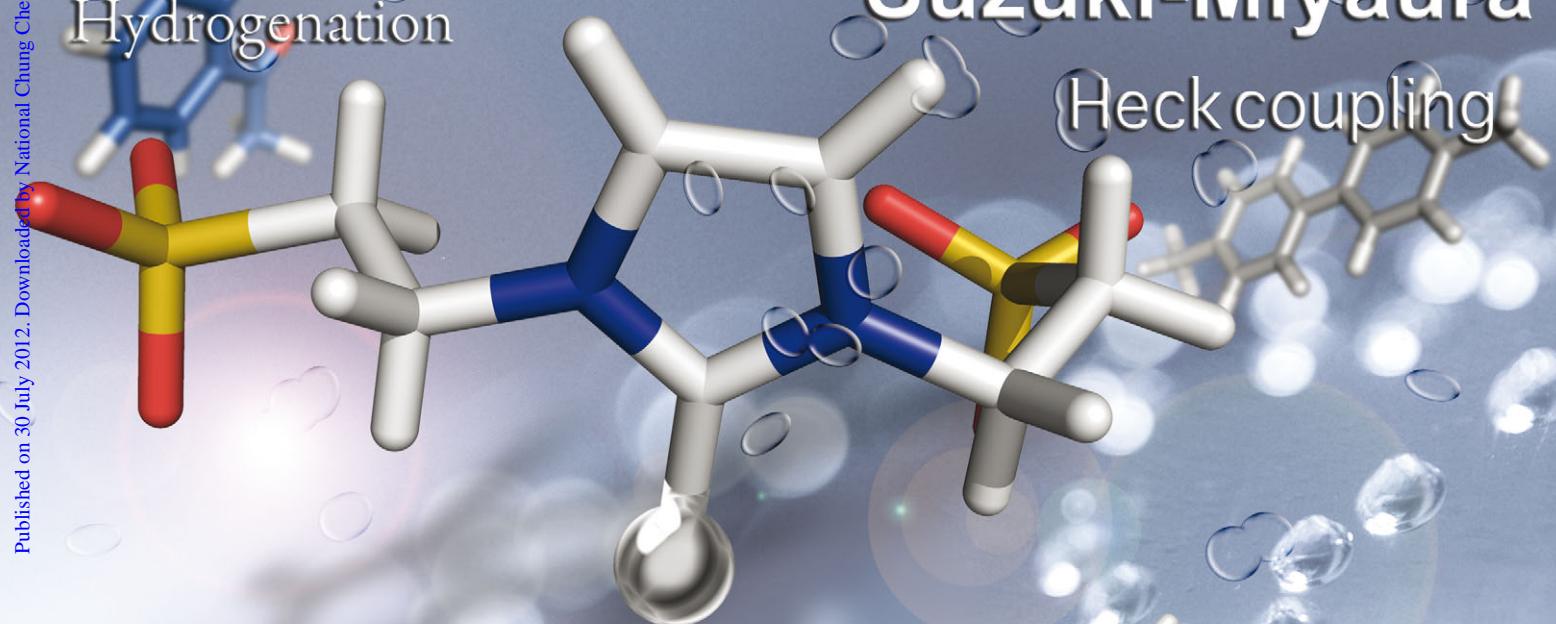
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CRITICAL REVIEW

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CRITICAL REVIEW

N-heterocyclic carbene transition metal complexes for catalysis in aqueous media

Heriberto Diaz Velazquez^d and Francis Verpoort*^{abcd}

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The last decade has seen an increasing number of reports on the use of NHC–metal complexes for catalysis in water, therefore this review is aimed to introduce the whole research on this area, in which the use of water or aqueous/organic media is to be applied. Since the first discovery of the NHC carbenes by Arduengo, work on the synthesis of NHC–metal organometallic compounds has revolutionized the field of catalysis, gradually displacing the typical phosphine and amine-type ligands in view of their higher stability and reactivity. Aqueous catalysis has become a hot topic in Green Chemistry due to the positive implications for the use of water as reaction media.

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Heriberto Diaz Velazquez

His main field of research is focused on aqueous organo-catalysis mediated by NHC–transition metal complexes.

1. Introduction

The majority of synthetic organic chemistry carried out in research laboratories or industrial processes utilize organic solvents since they have a number of attractive features: they will dissolve a wide range of organic compounds, they exhibit a variety of properties, and they are often volatile and easily removed. Unfortunately, organic solvents are often toxic, flammable, and non-renewable and have low heat capacities.



Francis Verpoort

Francis Verpoort (1963, Belgium) received his DPhil from Ghent University in 1996. In 1998, he became a full professor at the same university. In 2004, he founded ViaCatt NV, a spin-off company of Ghent University based on (latent) ruthenium olefin metathesis catalysts. In 2008, he became an Editor of *Applied Organometallic Chemistry*. Currently, next to Full Professor at Ghent University, he is a chair professor at the State Key

Laboratory of Advanced Technology for Material Synthesis and Processing (Wuhan University of Technology) and a Director of the Center for Chemical and Material Engineering (Wuhan University of Technology). Recently, he has been appointed as “Expert of the State” in the frame of “Thousand Talents” program, PR China. His main research interests concern the structure and mechanisms in organometallic material chemistry, homogeneous and heterogeneous catalysts, MOFs, water splitting, olefin metathesis and its applications, CO₂ conversion, inorganic and organic polymers.

In contrast, water is non-toxic and non-flammable, has a high heat capacity, and is relatively inexpensive. Of course water has some significant drawbacks as a solvent: it is a poor solvent for most organic molecules, and it is highly reactive with many classes of reagents. Because of these drawbacks, water is rarely used as a primary solvent in synthetic organic chemistry, although there is a growing body of work related to organic chemistry in water.¹

While solvent-less processes are a desirable goal, they are unlikely to be realized in most cases. Thus, one would like to use the most benign solvent possible. Water in its pure form is completely benign, so it would appear to be an attractive solvent. Furthermore, by simplifying the separation of the catalyst from the product, significant savings in the use of solvents and/or energy in the purification process can be realized. Water may not be the panacea solvent that it is often claimed to be, once it becomes in contact with organic materials, water becomes waste itself and can be very difficult to clean. The high heat capacity of water makes purification by distillation an energy intensive process. Incineration of organic-contaminated water is often required, which is complicated by the non-flammability of water. Thus the recycling of water used in chemical processes will likely be an important element in the design of aqueous-phase processes on an industrial scale.

Designing of catalysts containing ligands with hydrophilic substituents has been the most common approach to constrain a catalyst to the aqueous phase of a biphasic reaction. Such ligands have been typically based on the phosphine derivatives and nitrogen ligands, however, increasing efforts are devoted to the development of hydrophilic analogues such as N-heterocyclic carbenes (NHC).² Several NHC-containing transition metal complexes have been synthesized for catalytic reactions in aqueous media, however there is no document unifying the information concerning such compounds, making it an important study matter due to the increasing importance of the use of NHC–metal complexes for catalysis as well as the use of water as a green solvent for transition metal catalysed organocatalysis.

Over the past two decades, great achievements were made in catalysis using NHCs as ligands. Carbene complexes of late transition metals have been applied in many types of homogeneous catalytic reactions,² including olefin polymerization and metathesis by Ru-based catalysts (Section 1.3), hydrosilylation by Rh or Pt carbene complexes,³ Ir catalysed hydrogenation and hydrogen transfer,^{4–6} Pd catalysed carbon–carbon coupling reactions^{7–9} and an increasing number of enantioselective reactions.^{10–12} These types of reactions were traditionally carried out using phosphine based systems but NHC complexes exhibit some desirable properties not possessed by the former. Incorporation of NHC ligands improves the air and thermal stability of the complexes and makes them more resistant to oxidation. NHCs generally provide stronger bonding than the corresponding phosphines and unlike the latter remain bound to the metal center throughout catalytic cycles.^{13,14}

Persistent NHC-carbenes (Arduengo carbenes) have been tremendously used for complexation with most of the metals of the periodic table, nevertheless just a few of these complexes

have been designed so as to have a hydrophilic behaviour, in order to use them as aqueous-phase catalytic systems. It was until the end of the last decade that this area of research has attracted researchers' attention due to the great advantages of this kind of ligands compared to others used for catalysis in water, which during the 90's, seemed very remote to be accomplished. This review is aimed to give a full account on the development of NHC–transition metal chemistry intended for catalytic reactions in aqueous systems, ranging from ionic complexes to hydrophilic and immobilized complexes, and from homogeneous to heterogeneous systems.

2. Theoretical aspects determining the feasibility of NHC–metal complexes as good catalytic systems

Although it has been 21 years since the first isolation of a stable NHC carbene¹⁵ and 44 years from the first report on the isolation of NHC–transition metal complexes,¹⁶ along with the revolution in organometallic synthesis and catalysis that has derived from it, complete understanding of the factors that govern the high stability and at the same time the reactivities of these types of organometallics is far to be entirely achieved. Nevertheless, good progress has been accomplished during the last decade, in which both theoretical and experimental approaches have provided more clear evidence of the most important steric and electronic contributions to the NHC–metal bond. Originally thought of as a predominantly pure σ -donor, the NHC–metal bond was subjected to a more profound study and this simple idea was replaced due to the findings that π -interactions also contribute to the NHC–metal bond. It was found that there is a significant π -donor contribution and also a π^* back-donation from the d-orbital of the metals to the entire NHC–metal bonding.¹⁷ Fig. 1 shows the most important molecular orbitals involved in the NHC–metal bonding, with (a) representing the NHC to metal $\sigma \rightarrow d$ donation, (b) the metal to NHC $d \rightarrow \pi^*$ donation and (c) the NHC to metal $\pi \rightarrow d$ donation.

Meyer *et al.* showed with DFT (Density Functional Theory) calculations that NHCs can accept non-negligible electron density from electron rich metals through $d \rightarrow \pi^*$ backdonation.¹⁸ Similar conclusions were made from EDA (Energy Decomposition Analysis) calculations on NHC-containing group 11 metal complexes.¹⁹ Nolan *et al.* observed a remarkable $\pi \rightarrow d$ electron donation from the NHC to the metal for a NHC–Ir complex.²⁰ In parallel to Nolan, Cavallo *et al.* calculated that for systems with a low d electron count, both π -donation and π -backdonation are important while for systems with a high d electron count, back-donation makes the major contribution to the π -interaction. This allows the statement that NHC ligands can display an ambivalent π -bonding character.²¹ In addition, analysis of the BDE (Bond Dissociation Energy) of Ru and Ni complexes led to a correlation between the N-substituents in the NHC-ring and the stability of the complex, and only a small difference between saturated and unsaturated C4–C5 positions of only 1 kcal mol^{−1}. A comparison of the phosphine analogues of such complexes undoubtedly proved the higher stability of the NHC–metal complexes compared to phosphine based metal complexes.^{21,22} An important aspect regarding the BDEs and the substituents on the

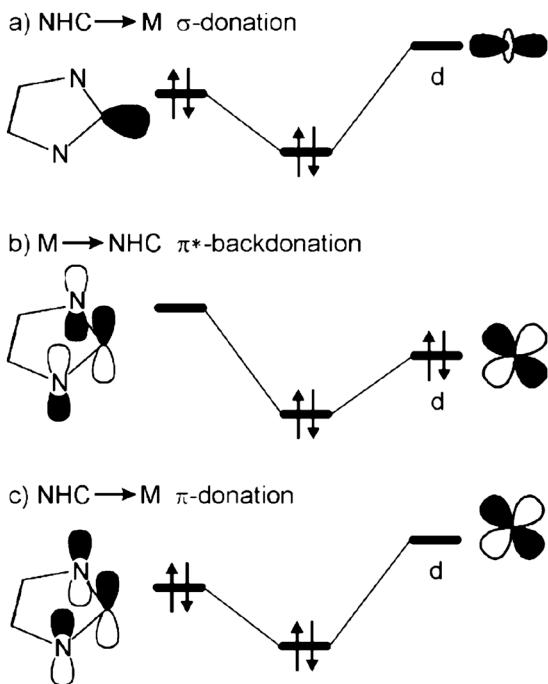


Fig. 1 MO contributions to the NHC–M bond.

N-atom of the NHC shows clearly that the BDEs of the ligands depend strongly on the bulkiness of the groups at the N atom, with higher BDEs found for less sterically hindered ligands.²² Theoretical studies on Ni(CO)_n(NHC) complexes made by Nolan and Crabtree separately showed that unsaturated NHC carbenes are marginally more net electron donating, which is in sharp contrast to conventional reasoning of their carbene donor capacity.²²

In spite of the many types of carbenes that have been reported, *e.g.*, the Bertrand carbenes and cyclic and acyclic diaminocarbenes,²³ special intrinsic characteristics related to the persistent NHC carbenes (or Arduengo carbenes) have rendered their huge application as ligands in organometallic

synthesis and catalysis, among those properties we can cite the dramatic shortening of the C_{carbene}–N bond as well as the C₄ and C₅ bond in the unsaturated carbenes, and the decline in the NCN bond angle, causing a more homogeneous bond angle. This makes NHC carbene ligands an extremely strong σ-donor with a considerable π-acceptor function in a direction perpendicular to the NHC plane. The in-plane π-direction can be considered to be electron-donating, making NHC ligands even more unique because in addition to π-donation, π-backbonding is not degenerated and so it has an important contribution to the metal–ligand bond. The result of all of these factors was the easy replacement of phosphines by NHC ligands and the high stability of the resultant complexes under many catalytic conditions.²⁴

The high stability featuring the NHC-carbenes has made them potential candidates for catalysis even on metal free catalytic systems, such as the imidazolium salts **1–8** reported by Hoveyda, Fig. 2.²⁵ In this very recent investigation the *in situ* NHC-carbene preparation in an aqueous reaction mixture was used for the metal-free Si–C bond formation by silyl conjugate addition to cyclohexene-2-one, Scheme 1. Symmetrical imidazolinium salt **7** gave the best yields and enantiomeric selectivity and was further tested on other cyclic and acyclic α,β-unsaturated carbonyl compounds. The catalytic activity of these NHC-carbene precursors was possible due to the activation of the B–B bond of the silylating agent by the formation of an intermediate stable NHC–B complex. This report signified the first metal-free C–Si bond forming reactions.

The feasibility of the formation of stable NHC–B bonds was further confirmed by Lacôte *et al.*²⁶ They reported the use of the NHC-borane **9** as a co-initiator for the photopolymerization of different acrylate monomers in the presence of a high concentration of water (Scheme 2). Determination of the rate constants confirmed that this NHC borane is an excellent co-initiator for free radical polymerizations in the presence of air and water, using either UV or visible light activation and di-*tert*-butyl peroxide as the radical initiator.

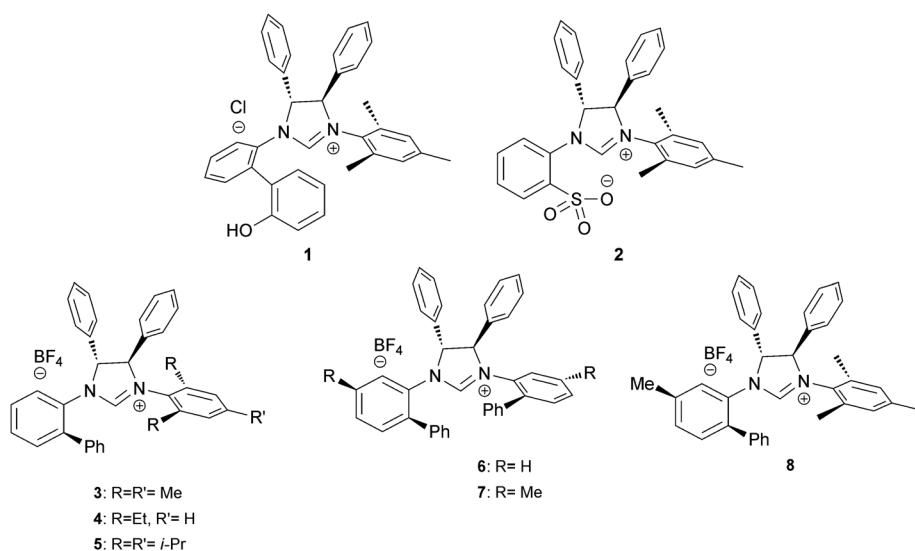
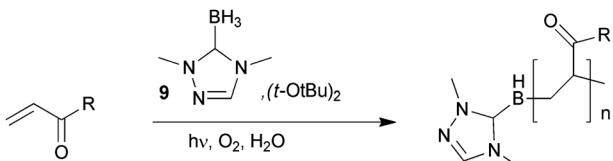


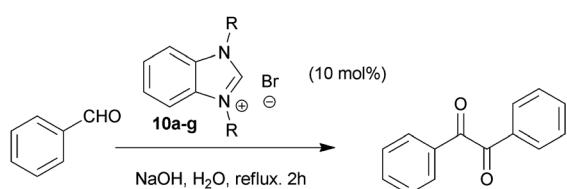
Fig. 2 Chiral imidazolinium salts as precursors for NHC carbene catalysts.



Scheme 1 C–Si bond formation by chiral NHC free carbenes under aqueous conditions.



Scheme 2 Photopolymerization of acryl monomers catalyzed by an NHC–borane as a co-initiator in water.



Scheme 3 Synthesis of benzyl by NHC–carbenes under metal-free conditions.

Jing *et al.* recently reported the synthesis of benzenes *via* NHC-catalysed benzaldehyde dimerization by using the alkyl-substituted benzimidazolium salts **10a–g** under a normal air atmosphere (Scheme 3). It was shown that air participates in the reaction by oxidizing the intermediate α -hydroxyketone to the benzyl ring. From the series of benzimidazolium salts used, the one holding an octyl group (**10e**) on both N-positions turned out to be the most active. Compound **10e** was further investigated with different aryl aldehydes, giving mixed results.²⁷

3. Group 8 metal–NHC complexes used in aqueous catalysis

An enormous number of reports on the use of Ru-based catalysts have been reported. In this regard, Ru(NHC) complexes have been the only metal–organic species reported as potential catalysts under aqueous conditions.

3.1 Ru(NHC) catalytic systems

3.1.1 Non-metathesis Ru(NHC) catalysts. The first report on an aqueous-phase metal catalysed reaction was made by Özdemir using the Ru complex **11** shown in Fig. 3.¹⁵ This complex was prepared starting from the corresponding tetraaminoethylene **11A**, which was reacted with $[\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-C}_6\text{Me}_6)]_2$ providing the neutral diamine-substituted imidazolin-2-ylidene complex (Scheme 4). Protonation with anhydrous HCl in ether gave the water-soluble diammonium salt **11**. Attempts to

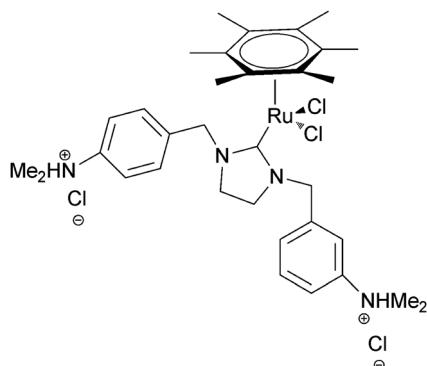
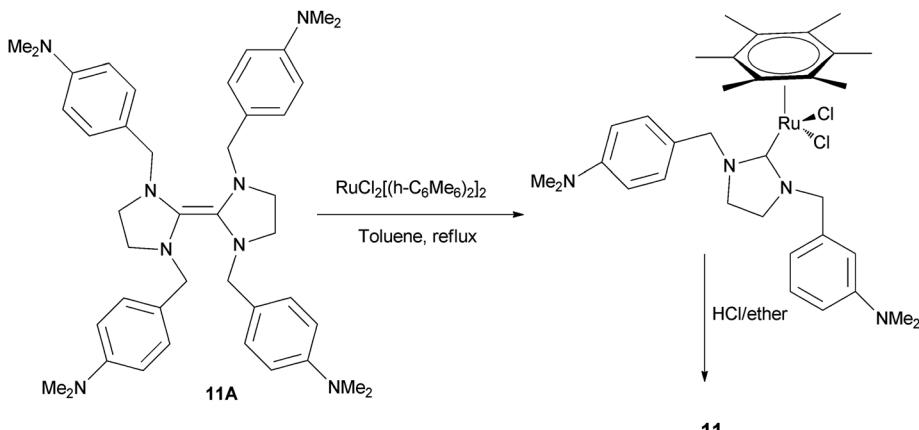
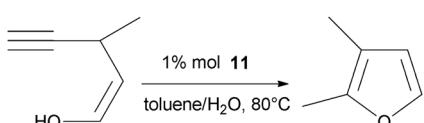
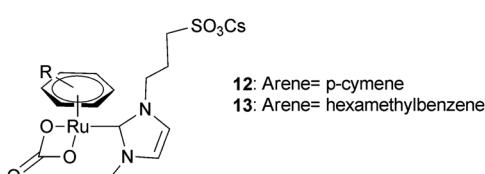
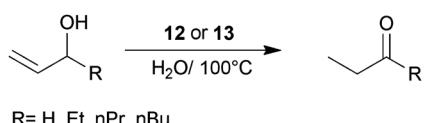
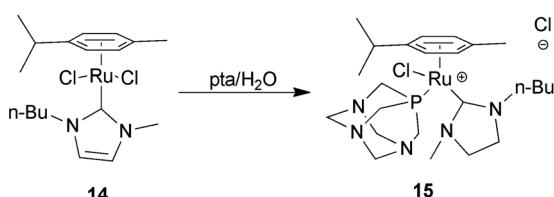


Fig. 3 Özdemir catalyst **11**.

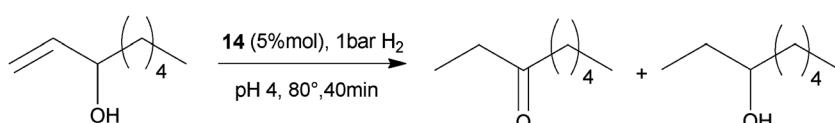
synthesize the Rh derivative by reacting the same ligand with $[\text{RhCl}(\text{COD})]_2$ followed by protonation of the $\text{Rh}(\text{NHC})\text{Cl}(\text{COD})$ were unsuccessful. Complex **11** was applied for the intramolecular cyclisation of (*Z*)-3-methylpenten-2-en-4-yn-1-ol into 2,3-dimethylfuran at 80 °C, in a biphasic toluene–H₂O system. The complex showed a better activity than its organic analogue, keeping a high yield for at least five catalytic cycles (Scheme 5).²⁸

There have been quite a few examples of catalysts from sulfonated-functionalized-NHC–metal complexes with metals other than Ag, Au or Pd. However, the Peris group managed to synthesize the first sulfonated functionalized-NHC-based Ru catalysts **12** and **13** for isomerization of allylic alcohols in water²⁹ (Fig. 4, Scheme 6) of which **12** is the most active catalyst. Nevertheless, the major contribution of this work is to show the ability of these catalysts to be recovered and recycled for a number of cycles depending on the catalyst loading and even without the use of an external base. So far **12** is the best performing catalyst due to its recyclability and there is no need for an external base compared with the rest of the reported catalysts.

Non-ionic functionalized metal–NHC complexes possessing hydrophilic behaviour have also been synthesized, some of the first reports were made by Joó *et al.*, by using the $[\text{bis}(\text{NHC})\text{Ag}]^+[\text{AgCl}_2]^-$ adduct to prepare complex **14** *via* a carbene transfer reaction, which was subsequently transformed into complex **15** in aqueous media, Scheme 7.³⁰ Both complexes were found to dissociate in aqueous solutions into different ionic species by coordination with one or two water molecules resulting in two different charged species. This explains their special hydrophilicity, so either structures of **14** or **15** adopt different configurations in aqueous solution. Complexes **14** and **15** were used in the hydrogenation of several substrates in both homogeneous and heterogeneous aqueous systems. Complex **15** is the most active one for several substrates, however it only showed a high selectivity for some of them. Complex **14** was further investigated for the redox isomerization of allylic alcohols in what it signified the first report of a water-soluble Ru(NHC) complex for this reaction in aqueous media. However, a trend towards product distribution of isomerization and hydrogenation was observed at the same time, depending strongly on the pH and the chloride concentration of the aqueous phase (Scheme 8). The highest selectivities and overall yields to carbonyls were obtained at

**Scheme 4** Synthesis of the Özdemir catalyst.**Scheme 5** Catalytic synthesis of 2,3-dimethylfuran with the water-soluble catalyst **1**.**Fig. 4** Sulfonated-NHC–Ru(arene) complexes.**Scheme 6** Isomerization of allylic alcohols by catalysts **12** and **13**.**Scheme 7** Hydrophilic Ru(NHC) complexes from the ionic liquid BMIM-Cl.

pH 7 and 0.2 M Cl. Likewise, complex **23** could be recycled for at least 4 times without a significant change in activity and selectivity (Table 1).³¹

**Scheme 8** Isomerization and hydrogenation of 1-octen-3-ol with catalyst **14**.

Among Ru complexes, cyclopentadienyl-type ligands have gained popularity because of the electronic stability of the species that can be obtained and their important catalytic properties. Peris and co-workers have synthesized different Cp–NHC–metal complexes with Ir, Rh and Mo, though they were not used for catalytic reactions until they reported an Ru complex **16** (Fig. 5).³² Complex **16** showed excellent activity in the catalytic isomerization of allylic alcohols in water, without the need for any base as a co-catalyst and with a catalyst loading as low as 0.2 mol% at 75 °C. The yield dropped dramatically when a substituted β-C to the OH group was used, even with elongation of the reaction time.

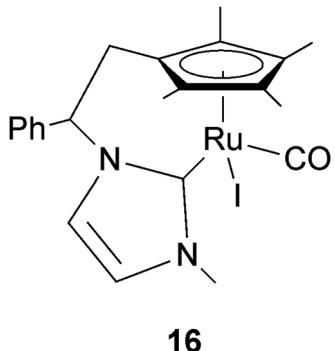
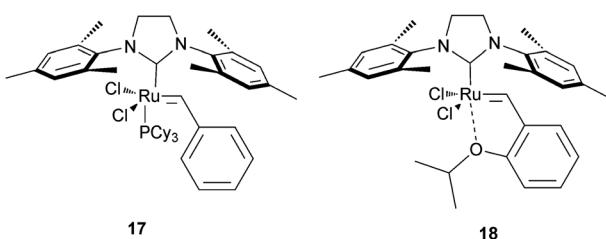
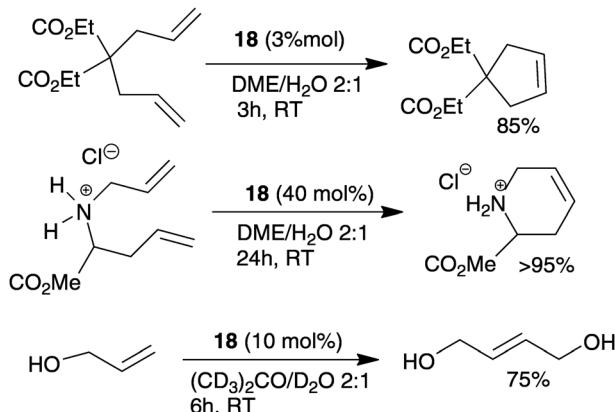
3.1.2 Ru(NHC) complexes for aqueous-phase olefin metathesis

3.1.2.1 Neutral Ru(NHC) catalysts. During the last two decades, one of the most studied C–C coupling reactions in both aqueous and organic solvents is olefin metathesis.³³ The first studies of metathesis reactions in aqueous media applied the widely known 2nd generation Grubbs and Grubbs–Hoveyda catalysts **17** and **18** respectively (Fig. 6). Their first generation homologues featuring tricyclohexylphosphine ligands are completely insoluble or only slightly soluble in water for olefin metathesis.³⁴ From these studies it turned out that the Hoveyda catalyst **18** has an excellent efficiency in the Ring Closing Metathesis (RCM) of a variety of dienes in aqueous dimethoxyethane (DME) and acetone (Scheme 9). Furthermore, the use of different co-solvents, e.g. THF or 1,4-dioxane, resulted in a much lower conversion. Blechert and Connon reported the synthesis of two modified Hoveyda type complexes **19** and **20** (Fig. 7), which were tested in the RCM of diallyl-tosylamine, and compared to **17** and **18**³⁵ (Scheme 10). Catalyst **20** was able to perform RCM in different aqueous–organic solvent mixtures and, although complex **18** was also active, when the substrate loses its miscibility in the solvent mixture the overall yield was higher with complex **20**.

Table 1 Recycling of catalyst **14** in the aqueous isomerization of 1-octene-2-ol

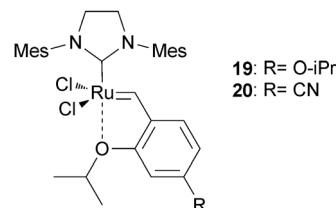
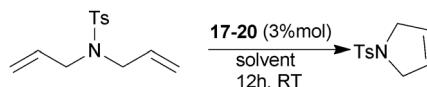
Run ^a	Conversion to 3-octanone (%)
1	93
2	91
3	90
4	89
5	83
6	36

^a Conditions: substrate/cat ratio = 52; 4 ml 0.1 M aqueous phosphate buffer, pH 6.9; $p(\text{H}_2)$ = 1 bar; T = 80 °C; t = 40 min.

**Fig. 5** Cp-functionalized NHC–Ru complex for isomerization of allylic alcohols in water.**Fig. 6** Grubbs and Grubbs–Hoveyda metathesis catalysts.**Scheme 9** Metathesis in aqueous mixtures with catalyst **18**.

Moreover, complexes **18** and **20** were active only when methanol was solely used as the solvent (Table 2).

Complexes **17** and **18** were further investigated as catalysts for metathesis reactions in heterogeneous mixtures containing water, either by using a simple mechanical stimulus of acoustic

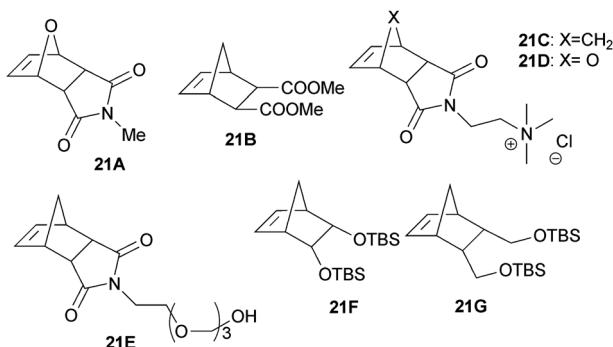
**Fig. 7** Blechert's complexes for aqueous metathesis reactions.**Scheme 10** RCM of diallyl-tosylamine with catalysts **17–20**.**Table 2** Conversions for the RCM of diallyl-tosylamine using catalysts **17–20**

Solvent	Conversion (%)			
	17	18	19	20
MeOH	94	60	96	20
MeOH–H ₂ O (3 : 1)	29	—	87	
MeOH–H ₂ O (3 : 1) ^a	77		94	
DMF–H ₂ O (3 : 1)	91		72	
DMF–H ₂ O (1 : 1)	29		68	
DMF–H ₂ O (1 : 3) ^a	82		94	

^a The substrate is not miscible with the solvent.

ultrasonication for the formation of microemulsions³⁶ or by using emulsifying agents or chemical surfactants,³⁷ both techniques were highly efficient in the Ring Opening Metathesis Polymerization (ROMP) of various hydrophilic and hydrophobic monomers (Fig. 8). Unfortunately, limitations were found applying the acoustic emulsification for metathesis reactions like RCM or CM, principally due to the low water-solubility of the substrates. The use of surfactants turned out to be the best technique for emulsion polymerizations as well as for RCM and Cross Metathesis.³⁸ These two-phase systems will be discussed later in this document.

3.1.2.2 Ionic-tagged Ru(NHC) catalysts. Grubbs and Jordan managed to synthesize the metathesis active Ru(NHC) complex **22**, which holds two ammonium groups to ensure good water-solubility. One ammonium group is α to the C-4 position of the NHC ring of the Grubbs–Hoveyda 2nd generation type catalyst while the other is at the *meta*-position

**Fig. 8** Hydrophilic (**21A–E**) and (**21F–G**) monomers for ROMP polymerizations in water.

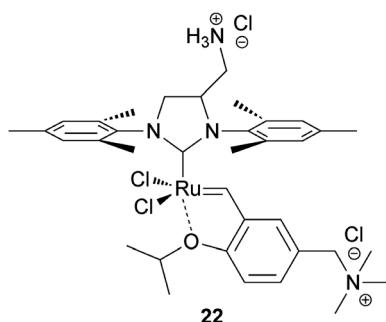
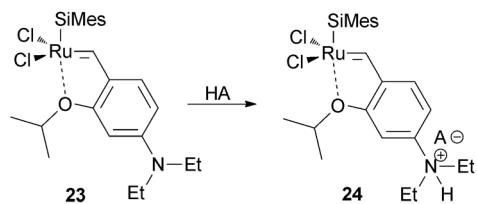


Fig. 9 Ammonium-tagged metathesis-active Ru–NHC complex.

of the isopropoxy-styrene ring.³⁹ Complex **22** displays a reasonable activity towards Ring Closing Metathesis (RCM) and Ring Opening Metathesis Polymerization (ROMP), however many disadvantages arose due to its limited activity towards certain substrates as well as low activity for Cross Metathesis (CM). One of the major disadvantages is the stability of **22** compared to other aqueous-metathesis catalysts (Fig. 9).

Following the investigation of a suitable and more convenient catalytic system for aqueous-phase olefin metathesis, several modified Ru-benzylidene, Grubbs 1st generation analogues and allenylidene complexes bearing functionalized phosphines were synthesized.^{40a,b} Grela reported the first example of an ionic functionalized NHC–Ru catalyst *in situ* (complex **24**, Scheme 11). Compound **23** demonstrated a very low or no activity under normal organic conditions, however, the salt-complex **24** formed *in situ* by treatment with a Brønsted acid showed a very high activity in contrast with the uncharged complex **23**. This activity change was possible due to the modification in



HA: Brønsted Acid

Scheme 11 Water-soluble catalyst **24** from the responsive complex **23**.

the electronic properties of the new salt **24** holding a strong electron-withdrawing group $-(\text{NEt}_2\text{H})^+$, totally opposite to the originally electron donating group $-(\text{NEt}_2)$.^{40c-e}

Extending the concept of switching the electronic properties along with changes in the solubility led to more research in this field. Grela and co-workers prepared catalyst **28** (Fig. 10) with a quaternary ammonium group, which was able to initiate metathesis reactions in organic media faster than the parent Hoveyda–Grubbs **19**. Moreover, **28** could even promote RCM, CM and enyne metathesis in aqueous mixtures and in neat water.⁴¹ The most representative examples of ionic tagged Ru–NHC metathesis catalysts reported up to now, complexes **25**,⁴² **26**,²⁷,⁴³ **28** and **29**,⁴⁴ are depicted in Fig. 10 along with the earlier described catalyst **17**,⁴⁵ they all perform metathesis reactions in aqueous media. Tables 3 and 4 display the comparison of the activities of the different complexes bearing a quaternary ammonium group. Among all these compounds, the earlier presented complex **17** reported the best water miscibility while **25**, **28** and **29** were only slightly soluble. Complexes **26** and **27**, initially designed for use in ionic liquids, were not soluble in neat water. Complex **25** reported the best stability under normal conditions and also the highest yields for RCM in aqueous media at high temperature.

For RCM in neat water complexes **28**, **29** and **22** were compared (Table 4). For the RCM of monomers **31a** to **31b** containing an ammonium centre in the allylic position, the reaction proceeds significantly slower with catalyst **28** than with complexes **29** or **22**. In general, the three catalysts perform RCM with relative high yields, however in some cases, using **29** and **22**, side-products due to isomerization are generated. Complexes **22** and **29** are also active catalysts in the ROMP polymerization of monomers **21C–D** in neat water, however **22** showed better stability under normal conditions.

3.1.2.3 *In-water active polymer-based Ru(NHC) catalytic systems.* Simultaneous to the development of polymer-based NHC–Pd catalysts for Suzuki and Heck coupling reactions, olefin metathesis has been widely studied with immobilized Ru catalysts for aqueous metathesis reactions. Most of the systems that have been generated are polyethylene glycol (PEG) based-NHC–Ru complexes given the advantages of PEG owing to its

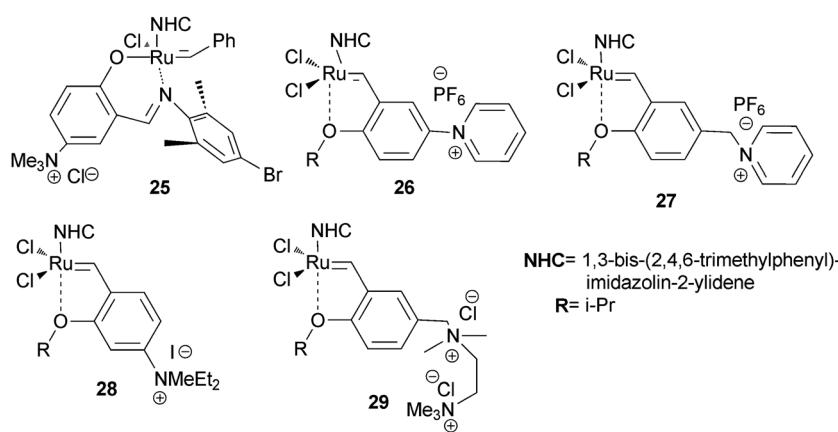


Fig. 10 Ammonium-functionalized NHC–Ru metathesis catalysts.

Table 3 Selected reactions mediated by catalysts **25–28** substituted with quaternary ammonium groups in aqueous media

Substrate	Product	Catalyst (mol%)	Solvent	<i>t</i> (h)	T [°C]	Conv. (%)
 30a	 30b	25 (5)	CD ₃ OD/D ₂ O 2 : 1	6	55	93
		26 (5)	EtOH/H ₂ O 5 : 2	24	25	50
		27 (5)	EtOH/H ₂ O 5 : 2	24	25	75
		28 (5)	EtOH/H ₂ O 5 : 2	24	25	83
 31a	 31b	25 (10)	CD ₃ OD/D ₂ O 5 : 2	6	55	>95
		26 (5)	EtOH/H ₂ O 5 : 2	0.5	25	99
		27 (5)	EtOH/H ₂ O 5 : 2	0.25	25	97
		28 (5)	EtOH/H ₂ O 5 : 2	0.5	25	99

Table 4 Selected reactions mediated by catalysts **28**, **29** and **22** substituted with quaternary ammonium groups in neat water

Entry	Substrate	Product	Catalyst (mol%)	<i>t</i> (h)	T (°C)	Conv. (%)
1			28 (5)	5	25	99
2			29 (5)	24	30	> 95
3			22 (5)	0.5	30	> 95
	30a	30b				
4			28 (5)	0.12	110	44
5			29 (5)	24	30	> 95
6			22 (5)	4	30	36 (59)
	31a	31b				
7			28 (2.5)	3.5	25	> 99
8			29 (5)	24	45	82 (4)
9			22 (5)	6	45	69 (12)
10			28 (2.5)	8	25	99
11			29 (5)	24	45	92
12			22 (5)	2	45	94

intrinsic hydrophilic behavior.⁴⁵ The first report was given by Blechert and Connon,⁴⁶ who used a modified PEG named PEGA (polyethylene glycol–acrylamide copolymer) to obtain the polymeric catalyst **38** (Fig. 11) by an amide bond on the benzylidene ligand of the Grubbs–Hoveyda 2nd generation catalyst. With this polymer-based catalytic system, metathesis of selected olefins was possible with good yields. Using **38**, sterically hindered and electron deficient substrates gave only poor yields. RCM of the diallylammonium chloride, which had not been able to be cyclized by other catalysts, gave satisfactory yield in methanol (69%). When applying water as the solvent, **38** was weakly active even at 45 °C for 12 h, and maximum conversion of only 11% was obtained. Grubbs and co-workers developed the PEG-functionalized-NHC–Ru complex **35**, which was tested for ROMP of the *exo*-monomer **21C**. A quantitative yield was obtained for the polymerization of the *exo*-monomer **21C** under acidic aqueous conditions (HCl–substrate 1 : 1). Even for the challenging *endo*-**21C**, system **35** was able to polymerize this monomer in high yield (87%).⁴⁷ The activity of catalyst **38** was higher compared to the previous water-soluble phosphine-based catalyst **35** but was limited to its stability under acidic conditions. Emrick and Breitenkamp developed the catalytic systems **36** and **37**.^{48a} System **36** was obtained as a mixture of unreacted PEG tagged-pyridine ligands and was able to perform ROMP of monomer **22F** under aqueous acidic conditions ($\text{pH} \leq 2$). Unfortunately, no control over the molecular weight and polydispersity was achieved. System **37** showed a similar

behaviour to **36** with monomer **21F** under acidic conditions. Addition of a phosphine scavenger, *e.g.* CuBr, under neutral conditions provided satisfactory results in yields as well as PDI (< 2).^{48b} More recently, Grubbs and co-workers developed the modified Grubbs–Hoveyda second generation catalyst **26** in order to get the PEG modified-NHC–Ru complex **34**. The latter is active and highly stable in water (no decomposition after one week in D₂O).⁴⁹ Complex **34** demonstrated a higher activity than the previous catalytic systems since substrates like the *endo*-monomer **21C** were easily polymerized in quantitative yield in water without the need for acidic conditions. RCM of several water soluble α,ω -dienes in water was also achieved with good to excellent yields with **34**, similar results were obtained for the self-metathesis of allyl alcohol and *cis-trans* isomerization of *cis*-2-butene-1,4-diol by self-metathesis. Complex **34**, however, was highly substrate-dependent, since it was unable to homodimerize other kinds of water-soluble olefins even under acidic conditions.

For non-PEG polymeric catalytic systems, Buchmeiser and Nuyken reported the synthesis of the water-insoluble polyoxazoline-based copolymer **39** (Fig. 12), which was used for the polymerization of diethyl-dipropargyl-malonate, **40**, under aqueous micellar conditions (Scheme 12). The polymeric product **41**, prepared as stable latex particles, showed a lower polydispersity index (<1.4) compared to the polymers acquired from non-immobilized catalysts in organic solvents.⁵⁰

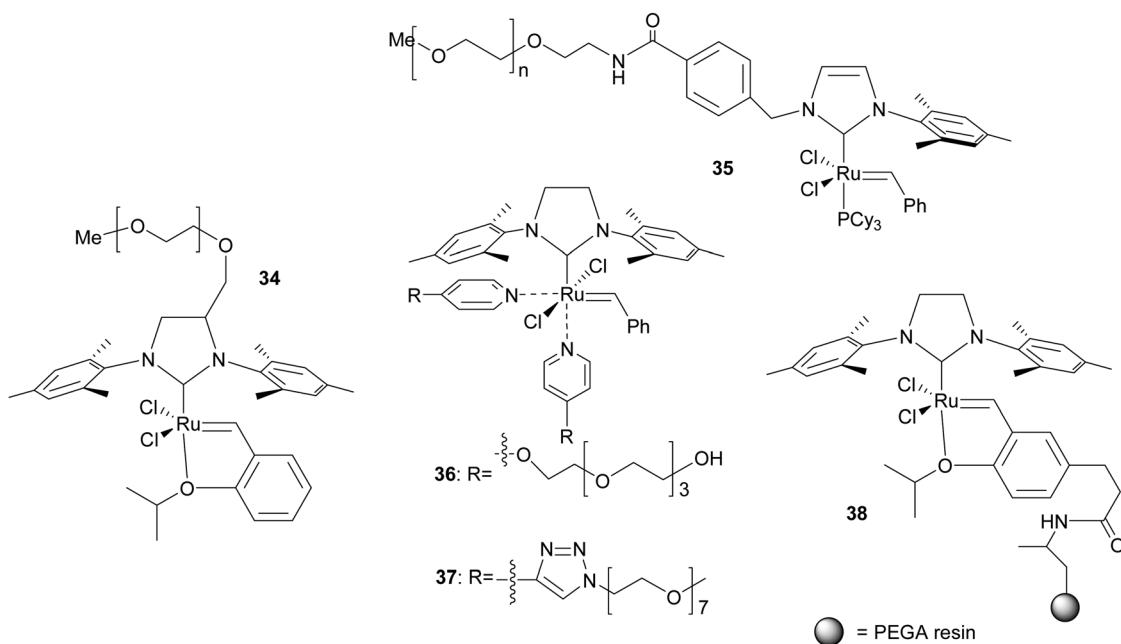


Fig. 11 PEG-tagged polymer Ru–NHC catalysts for olefin metathesis in aqueous media.

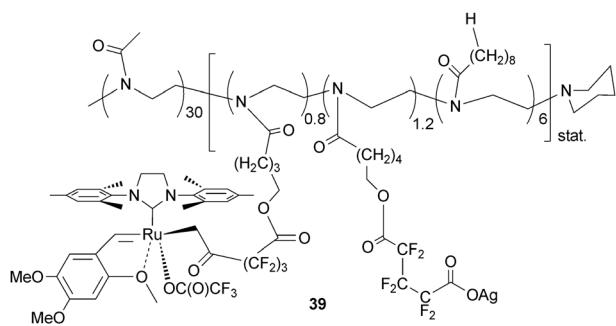
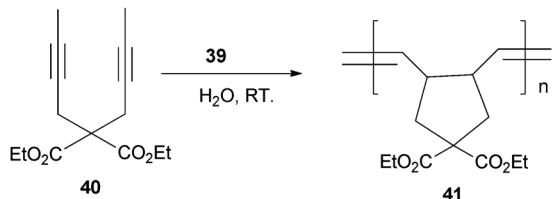


Fig. 12 Polyoxazoline-based Ru–NHC complex for alkene metathesis under aqueous micellar conditions.



Scheme 12 Cyclopolymerization catalyzed by polymeric system 39 under aqueous micellar conditions.

4. Group 9 metal–NHC complexes (Co, Rh, Ir)

Reports on aqueous catalysis using metals from this group are scarcely found in the literature. The most recent examples of NHC metal complexes of group 9 used in the aqueous phase were found for Ir and Rh.

4.1 Water-soluble sulfonated-tagged Ir(NHC) complexes

Very recently, a sulfonated ligand precursor was introduced for the synthesis of the Ir complex 42 (Fig. 13).⁵¹ An innovative blocking of the C-2 position of the imidazolium ring ligand by a methyl group changed the reactive sites of this ligand to the C4/C5 carbons, so that the new complex 43 holds an “abnormal” bis-NHC type ligand, Fig. 13. Both “normal” and “abnormal” complexes turned out to be highly active in the reduction of CO₂ to potassium formate, either by using hydrogen gas (1CO₂ : 1H₂ mol/mol, KOH 1 N) or isopropanol as hydrogen source (50 atm CO₂, iPrOH : H₂O 1 : 9 v/v, KOH 0.5N), Scheme 13. Comparison of the activity of complexes 42 and 43 with that of the non-sulfonated complexes reported by Crabtree *et al.*⁵² demonstrated that the solubility in water has a key effect on the efficiency of the catalyst, giving rise to much higher TONs for the sulfonated complexes, and among them, complex 43 was the best performing catalyst using hydrogen

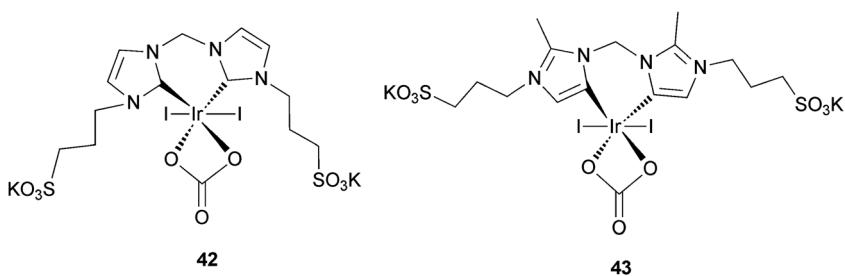
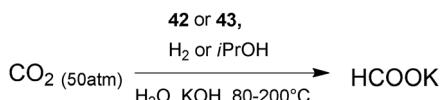


Fig. 13 Sulfonate functionalized NHC–Ir complexes.



Scheme 13 Reduction of carbon dioxide with catalysts **23** and **24** in water.

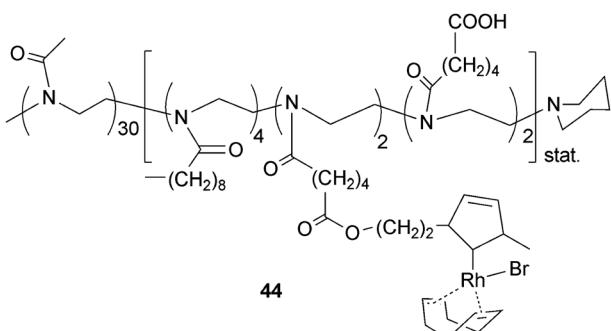


Fig. 14 Amphiphilic polyoxazoline-NHC–Rh catalytic system for hydroformylation in an aqueous–organic biphasic medium.

and *i*-propanol as hydrogen source. Complex **43** displays the best activity reported so far for the reduction of CO_2 with *i*-propanol, and a comparable efficiency with the best catalysts using H_2 . Complexes **42** and **43** were also successfully tested in the deuteration of heterocyclic substrates using D_2O as deuterating agent. For all the processes, complex **43** demonstrates that the bis-“abnormal” NHC–metal complexes exhibit high stability and activity towards many chemical processes compared with the “normal” NHC–metal catalytic systems.

4.2 Polymer-based Rh(NHC) complexes

After the report from Nuyken on polyoxazoline-based Ru complex **39**, Weberskirch *et al.* used this polymeric precursor to immobilize a Rh–NHC complex in order to get the amphiphilic block-copolymer catalytic system **44** (Fig. 14), which was used for the hydroformylation of 1-octene in an aqueous two-phase system.⁵³ NMR analysis revealed that two Rh–NHC complexes were linked to one polymer chain. Hydroformylation of 1-octene with a substrate : Rh ratio of 10^4 : 1 was able to provide up to 43.7% yield. A low selectivity was found for the *n* : *iso*, having the highest selectivity for the first run (*n* : *iso* ratio 72 : 28). Recycling was possible up to 4 cycles until the TOF remained constant (2360 h^{-1}). Product separation from the aqueous solution was simply done by just decantation. Leaching experiments showed a negligible leaching of 4 ppm.

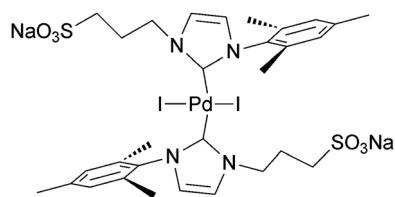


Fig. 15 First reported water-soluble Pd–NHC complex.

The activity of **44** was limited to its water stability, since hydroformylation experiments followed by NMR showed that after 18 h, 25% of the ester bonds which link the complex to the polymer had hydrolysed, corresponding to 2.7% of rhodium loss after each reaction cycle of 2 h.

5. Group 10 metal–NHC complexes (Ni, Pd, Pt)

Among group 10 metals, extensive work has been made on C–C coupling reactions with Pd(NHC) systems. The first sulfonic-tagged NHC–metal complex was initially reported by Herrmann in 1997.⁵⁴ In 2006 Shaughnessy *et al.*⁵⁵ reported the synthesis of water-soluble alkyl sulfonate and alkyl carboxylate functionalized-NHC–Ag complexes, along with the alkyl-sulfonate functionalized-NHC–Pd complex shown in Fig. 15. However, these complexes were not tested in any catalytic reaction. The most significant contribution of Shaughnessy's work was to provide good evidence that water can be used as solvent for the synthesis of NHC–metal complexes provided that the NHC precursor has a good compatibility with water, as was first described by Youngs in 2003.⁵⁶ Later on, in this document, we will discuss the *in situ* formation of a NHC–Pd complex as the catalytic active species in Suzuki coupling reactions in water.

5.1 Non-(C–C) coupling reaction catalysts

5.1.1 Pt(NHC) catalysts. Taking into consideration the feasibility of sulfonated NHC-precursor ligands to be introduced into any transition metal centre, Flores and de Jesus explored this possibility with a Pt(0) species, namely the commercial Karstedt® complex $[\text{Pt}_2(\text{dvtms})_3]$ (dvs = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane), and used it as starting material to isolate what was the first example of water-soluble NHC platinum (0) complexes **45** and **46** (Fig. 16).⁵⁷ These complexes showed, as expected, high stability towards air and moisture, as well as high catalytic activity towards hydrosilylation of terminal alkynes with triethylsilane (Scheme 14). Complex **46** showed higher catalytic activity than the Karstedt® complex

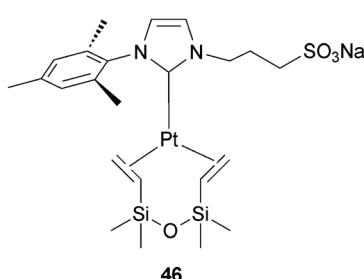
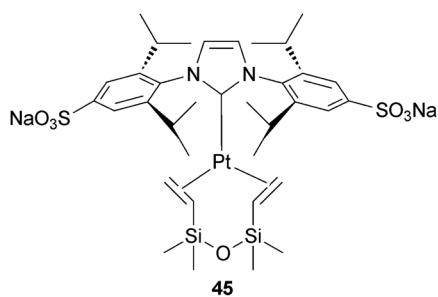
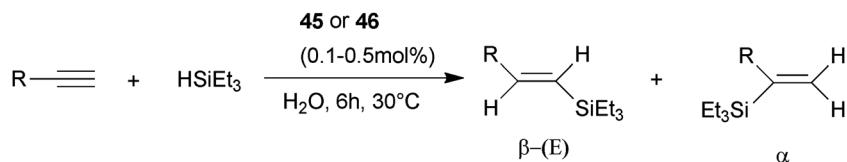


Fig. 16 Water-soluble sulfonated-NHC–Pt(0) complexes.



R: hexyl, trimethylsilyl, bromomethyl, *p*-methoxyphenyl, thiophene-yl, naphthalene-yl

Scheme 14 Hydrosilylation of terminal alkynes in water by complexes **45** and **46**.

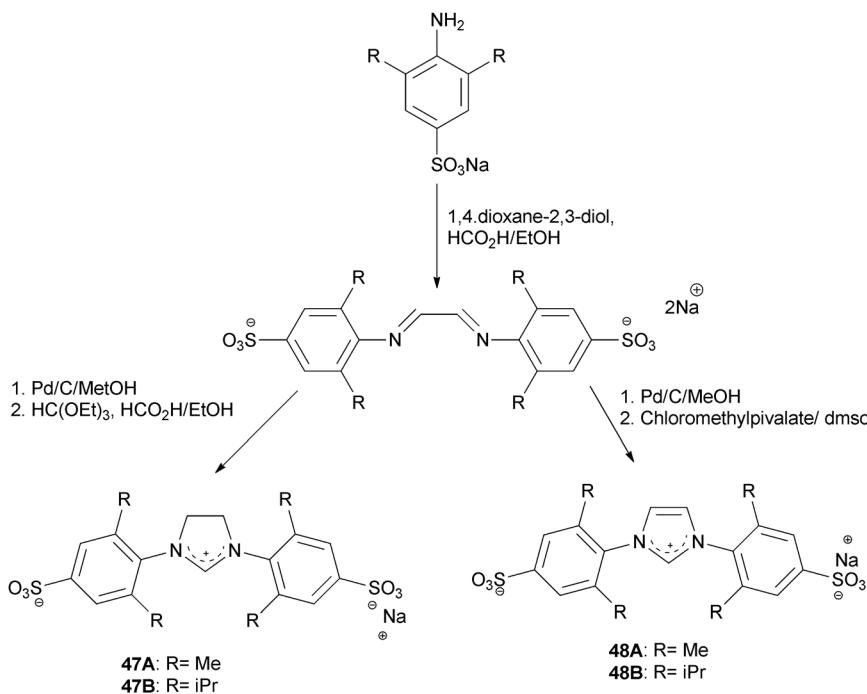
for the hydrosilylation of phenylacetylene in water under the same conditions, and **45** had an intermediate efficiency. In most of the cases the regioselectivity was directed to the β -*E* isomer with respect to the α isomers, however, **45** showed a lower selectivity than **46**. Recyclability studies confirmed that **45** and **46** have a better recycling capacity than the Karstedt complex, however this ability is restricted to selected substrates.

5.2 Aqueous C–C coupling reactions catalysed by Pd(NHC) catalysts

5.2.1 Ionic-tagged Pd(NHC) catalysts. The first report on *in situ* generated sulfonic-functionalized NHC–metal complexes for Suzuki coupling reactions in water was made by Plenio's group,⁵⁸ the ligand synthesis started with the sulfonation of the corresponding anilines, followed by the diimine formation by reaction with 1,4-dioxane-2,3-diol. Reduction of the diimine to the diamine and cyclization of the latter resulted in the desired zwitterionic imidazolinium salts (Scheme 15). In a similar fashion the mesityl analogue of the saturated NHC-precursor **49** was synthesized (Fig. 17).

The catalytic performance of such carbene precursors was tested as *in situ* catalytic systems using Na₂PdCl₄ in water with

KOH as the base for the Suzuki coupling reactions of different aryl chlorides with two different aryl boronic acids. **47B**, **48B** and **49** were the imidazolinium salts under investigation (Table 5). The conversion rate was calculated as the average of two runs. From Table 5, it is obvious that this kind of ligands, namely **48B** and **49**, are able to afford the Suzuki coupling products with almost full conversion and with a catalyst loading as low as 0.1 mol% for ligand **48B**. These results proved that a high performance could be achieved for a catalytic coupling reaction in water when the NHC precursor has a suitable affinity with water and thus, the formed catalytic species are stable enough to complete the reaction. A few years later Plenio and Roy reported an alternative procedure for the synthesis of the same ligands in a one-step protocol by sulfonation of the respective imidazolium and imidazolinium salts with the sulfonating agent HSO₃Cl.⁵⁹ The results reveal that for the synthesis of sulfonated SiMes and IMes, this single step procedure is more convenient, however it is not applicable for the 2,6-*i*propyl derivatives since a mixture of products is formed. In this new report the synthesis and isolation of the (NHC)PdCl(cinnamyl) complex **50** is presented by reaction of 4-sulfonated-2,6-diisopropyl-phenylimidazolium salt **48B** with [PdCl(cinnamyl)]₂ in the presence of a base (Scheme 16). Such a complex was tested for the Suzuki coupling in a solvent



Scheme 15 Synthesis of the sulfonated ligands for Suzuki coupling in water.

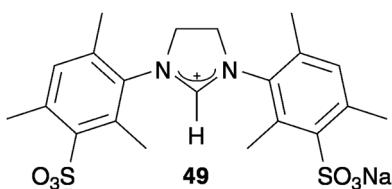
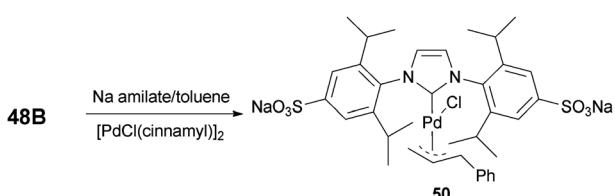


Fig. 17 Sulfonated SiMes ligand for Suzuki coupling.

Table 5 Suzuki coupling reactions with different aryl chlorides using **47B**, **48B** and **49**

Entry	Aryl chloride	Boronic acid	Conversion	
			NHC	Mol% (%)
1	4-Chlorotoluene	4-Tolyl	49	1 >99
2	4-Chloroanisole	4-Tolyl	49	1 >99
3	4-Chloroacetophenone	4-Tolyl	49	1 >99
4	4-Chlorobenzonitrile	4-Tolyl	49	1 >99
5	4-Chlorotoluene	4-Tolyl	49	0.5 84
6	4-Chloroacetophenone	4-Tolyl	47B	1 63
7	4-Chlorotoluene	4-Tolyl	47B	1 56
8	4-Chlorotoluene	4-Tolyl	48B	1 >99
9	4-Chlorotoluene	4-Tolyl	48B	0.1 91
10	4-Chloroacetophenone	4-Tolyl	48B	0.1 >99
11	4-Chlorobenzene-sulfonamide	4-Tolyl	48B	0.1 >99
12	4-Chloroanisole	4-Tolyl	48B	0.1 74
13	4-Chloroaniline	4-Tolyl	48B	0.5 80
14	2-Chloropyridine	4-Tolyl	48B	0.1 >99
15	2-Chloropyridine	1-Naphthyl	48B	0.5 >99
16	4-Amino-2-chloropyridine	1-Naphthyl	48B	1 85
17	2-Chloro-4-methylquinoline	1-Naphthyl	48B	0.5 >99



Scheme 16 Synthesis of a sulfonate functionalized-NHC–Pd complex.

mixture water–*n*-butanol 1 : 1, displaying an improved reactivity with respect to the *in situ* catalysts screened in the previous report, however its efficiency still remains below that of the non-aqueous coupling reactions.

On the quest for more efficient and stable water-soluble functionalized NHC–Pd complexes for Suzuki coupling reactions, Peris *et al.* recently isolated the complexes depicted in Fig. 18, which contain bis-sulfonate functionalized NHCs, with a monodentate (**51**), a bidentate (**52**) and two pyridine-bridged pincer type ligands (**53**, **54**).⁶⁰ These complexes were

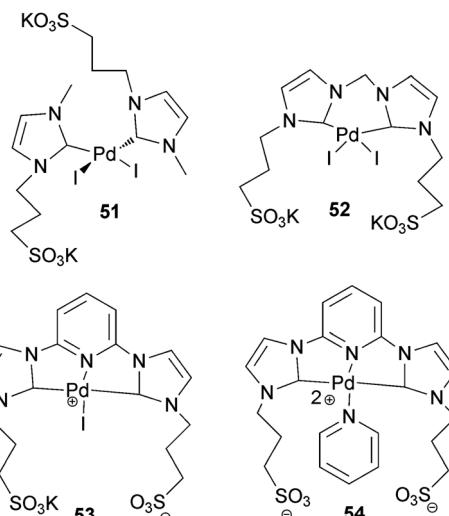
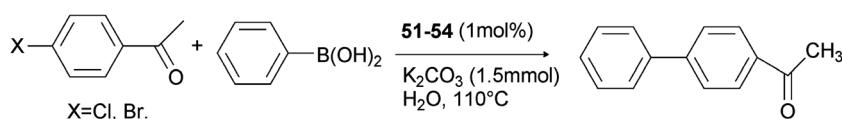


Fig. 18 Functionalized bis-NHC–Pd complexes.

used in the Suzuki coupling of the 4-bromo and 4-chloro-acetophenone (Scheme 17). Complexes **51**, **53** and **54** were very active in the arylation of 4-acetophenone (above 90%) while complex **52** provides only a moderate yield (54%). However when more inert substrates were used, complex **51** turned out to be the most active catalyst. Unfortunately, complex **54** did not afford the best yields, which is contradictory to the predicted PEPPSI effect (Pyridine-Enhanced Precatalyst Preparation, Stabilization and Initiation). The catalytic activity of complex **51** is competitive for reaction systems in aqueous medium, but still lower compared to the catalysts that operate under non-aqueous media. Direct comparison of these results with those of Plenio's group was not feasible since the yield in this work is determined from the products while Plenios's group reported conversions that are calculated from the starting reactants.

5.2.2 Non-ionic-tagged Pd(NHC) catalysts. The Sonogashira cross-coupling reaction, along with olefin metathesis, has been deeply studied due to its great importance in the production of natural products, pharmaceuticals, biologically active molecules and molecular electronics. Pd catalyses the typical Sonogashira coupling reaction in a basic medium and in the presence of copper as a co-catalyst. However, the intermediate copper-acetylidyne species makes the Sonogashira reactions sensitive to air and moisture, consequently efforts were made in order to avoid the use of Cu by enhancing the reactivity of the catalytic system, however an excess of amines had to be used. Recently, Ghosh and co-workers developed a series of catalysts as N/O-functionalized bis-NHC–Pd complexes **55**–**56** and their Py–NHC–Pd analogues **57**–**58** (Fig. 19) in order to study the PEPPSI effect (Pyridine-Enhanced Precatalyst Preparation, Stabilization and Initiation) on this class of complexes.⁶¹



Scheme 17 Aqueous Suzuki–Miyaura coupling reactions with complexes **51**–**54**.

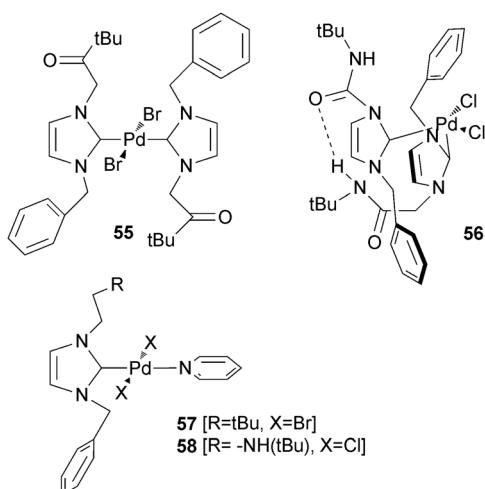


Fig. 19 N/O functionalized NHC–Pd complexes for Suzuki coupling reactions in aqueous media.

From the resulting isolated yields given in Table 6, it is clear that opposed to the so-called PEPPSI effect, complexes **55–56** exhibited better activity than their corresponding mono-NHC–pyridine derivatives **57–58**. The higher electron density in the Pd metal centre for complexes **55–56** compared to **57–58** is an acceptable explanation. This may promote more conveniently the oxidative addition of the aryl chloride, which is a key step in the cross-coupling reaction. Similarly, complexes **55–56** demonstrated comparable activities to the phosphine based precatalysts, which indeed require more strict and strong conditions as well as longer reaction times.

Following the investigation of a more suitable catalytic system for amine and copper-free Sonogashira cross coupling reactions, Ghosh published a series of imidazoline and triazole NHC–Py–Pd complexes **59–64**⁶² (Fig. 20). DFT analysis of the complexes showed that the strong σ -donating ability of the NHC ligand makes the pyridine a “*throwaway*” ligand by

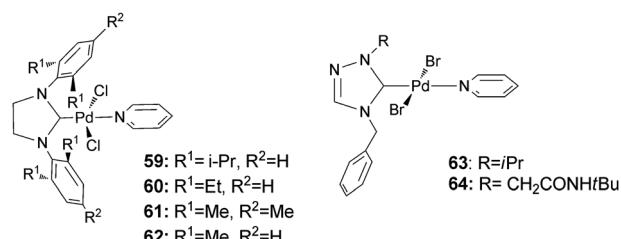
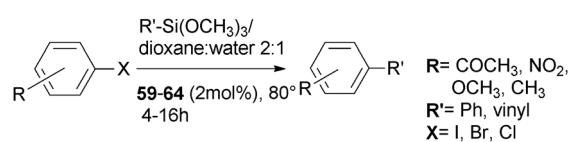


Fig. 20 Imidazoline- and triazole-NHC–Pd complexes for aqueous Hiyama and Sonogashira coupling reactions.



Scheme 18 Hiyama coupling reactions with precatalysts **59–64**.

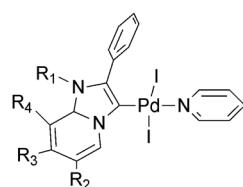
weakening its bonding with the Pd metal center. This work was the first example of well-defined NHC–metal complexes for an amine and copper-free Sonogashira coupling, showing good to excellent yields in aerobic and aqueous media using CsCO_3 as base instead of amines. This series of complexes was also tested for Hiyama coupling (Scheme 18), displaying good yields comparable to the results of the *in situ* complexes generated by LAC conditions (Ligand Assisted Catalysis) and circumventing the use of a fluoride co-initiator.

The same group later reported an unusual variety of NHC–Pd complexes **65–68** with an abnormal NHC precursor for the desirable amine and copper-free Sonogashira coupling (Fig. 21).⁶³ DFT studies as well as FT-IR and single crystal X-Ray analysis proved that these complexes contain a more electron rich NHC–carbene moiety and therefore a stronger NHC–Pd bond than the “normal N–C–N” NHC, which is generated due to the stronger σ -donating carbon of the “atypical” carbene. This represents the first report on the

Table 6 Selected results for the Sonogashira coupling reaction (ArX , $\text{X} = \text{I}$) using catalysts **55–58**

Cross coupling of Aryl halides (ArX , $\text{X} = \text{I}$)			Yield ^a			
Reagent	Reagent	Cross-coupled product	55	56	57	58
			98	84 ^b	4	27
			80	88	76	66
			75	94	42	11
			97	81	Nr	Nr
			85	81	28	24

^a Reaction conditions: ArX , $\text{X} = \text{I}$ (0.49 mmol), phenylacetylene (0.98 mmol), Cs_2CO_3 (2 mmol), cat (3 mol%), CuBr (10 mol%), $\text{DMF-H}_2\text{O}$ (3 : 1, 10 ml), 100 °C, 2 h. ^b Reaction time: 12 h.



65: R₁=Me, R₂=R₃=R₄=H
66: R₁=R₄=Me, R₂=R₃=H
67: R₁=Et, R₃=R₄=H, R₂=Me
68: R₁=Et, R₂=R₄=H, R₃=Me

Fig. 21 Abnormal NHC–Pd complexes for Sonogashira coupling.

use of abnormal NHC–Pd complexes for Sonogashira cross coupling reactions (Scheme 19). Specifically for aryl iodides and aryl bromides with terminal acetylenes in mixed aqueous media under the highly desirable Cu-free and amine-free conditions, complexes **65–68** catalysed these reactions very well (Scheme 19). Moreover, when aryl iodides and terminal acetylene were heated to 90 °C with 2 mol% of the catalyst in DMF–H₂O (3 : 1 v/v) a clean conversion was reached within 1 h!

Given the proven activity enhancement provided by the complexes with N-donor ligands, further research focused on the synthesis of more stable complexes containing both NHC and N-donor ligands. Chen *et al.* were the first to successfully isolate pincer NHC–metal complexes with triazole and pyrimidine moieties as N-donor ligands (Fig. 22).⁶⁴ From this series of complexes, the highly stable Pd complex **69** was used as catalyst for the Suzuki–Miyaura cross coupling reaction of 4-bromoacetophenone and 4-bromoanisole (Scheme 20), giving full conversion at 200 °C within 20 minutes using 1 mol%. Knowing the extremely high reactivity of complex **69**, double coupling of arylboronic acids with 1,1-dibromo-1-alkenes was investigated. Trisubstituted alkenes were obtained in good to excellent yields in an air atmosphere, with substrates holding both electron donating and electron withdrawing groups.

Palladium catalysts have been more investigated for Suzuki reactions than for any other coupling reaction. In this regard, aqueous Suzuki reactions have been a matter of study in recent years. Taking into consideration the enhancement of the catalytic activity of Pd coordinated to tridentate ligands, Domínguez and co-workers designed hydrophilic pincer complexes **70–73** (Fig. 23).⁶⁵ Unlike previous C–N–C pincer complexes, **70–73** have a carboxylate moiety in the 4-position of the pyridine ligand, which provoke their hydrophilicity. Complex **70** showed excellent catalytic activity for several aryl bromides in neat water, up to quantitative yields were obtained with a catalyst loading as low as 10⁻⁷ mol%. Furthermore, this complex showed an extremely high stability under normal conditions and at high temperatures. Complexes **71** and **72** bearing an ester and carboxylic acid functionalization, respectively, showed also very high yields at low catalyst loading. Experiments on reuse of these complexes

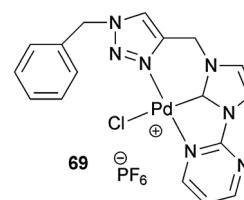
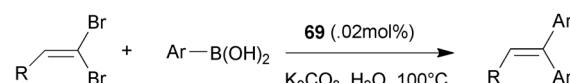


Fig. 22 Non-symmetrical-pincer-NHC–Pd complex for Suzuki and double Suzuki coupling reactions in water.



R: Ph-, p-Br(C₆H₄)-, p-Cl(C₆H₄)-, octyl-, p-MeO(C₆H₄)-, thiophene-2-yl-; Ar: Ph-, o-Me(C₆H₅), m-MeO(C₆H₄), p-Cl(C₆H₄), p-CF₃(C₆H₄), naphthyl

Scheme 20 Double Suzuki–Miyaura couplings of 1,1-dibromo-1-alkenes with aryl boronic acids.

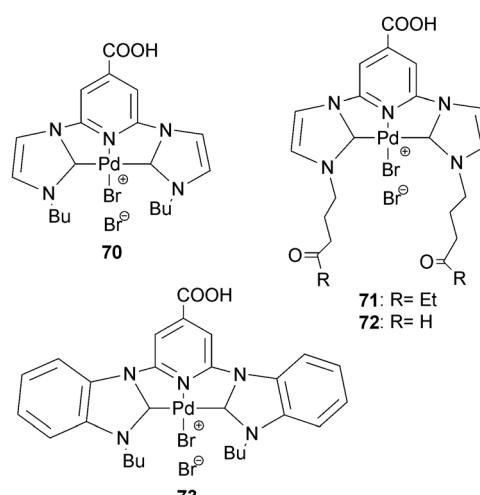


Fig. 23 Pincer bis-NHC–Pd complexes for Suzuki coupling in neat water.

demonstrated that by increasing the reaction time in every run, it is possible to get reasonable yields. However by applying the same reaction conditions only complex **72** could be reused up to 5 runs with good yields. Tu and co-workers⁶⁶ reported complex **73**, exhibiting an excellent activity for several substrates with catalyst loading as low as 5 × 10⁻³ mol%. However, recyclability experiments were moderate since only good yields were attained until the 3rd run. Still, complex **73** was successfully used as the first NHC–Pd complex catalysing the Heck reaction in neat water.⁶⁷ From the results depicted in Table 7 one can see that good to excellent yields



Scheme 19 Sonogashira coupling reactions with catalysts **65–68**.

Table 7 Heck reaction of iodo-arenes with *tert*-butyl acrylate catalysed by the pincer complex **73**

Entry	Iodo-arene	Time (h)	Yield
1	4-Iodotoluene	5	94
2	4-Iodotoluene	18	>99
3	3-Iodotoluene	8	61
4	2-Iodotoluene	18	96
5	2-Iodoanisole	8	85
6	1-Chloro-4-iodobenzene	24	93
7	1-Fluoro-4-iodobenzene	18	96
8	1-Iodo-2-(trifluoromethyl)benzene	5	80
9	4-Iodoacetophenone	12	79
10	1-Ethyl-4-iodobenzoate	8	87
11	1-Iodonaphthalene	8	29
12	3-Iodopyridine	8	3

are obtained except for the more sterically demanding 1-iodonaphthalene (entry 11) and the heterocyclic 3-iodopyridine (entry 12). The relative position of the substituent slightly affected the coupling process.

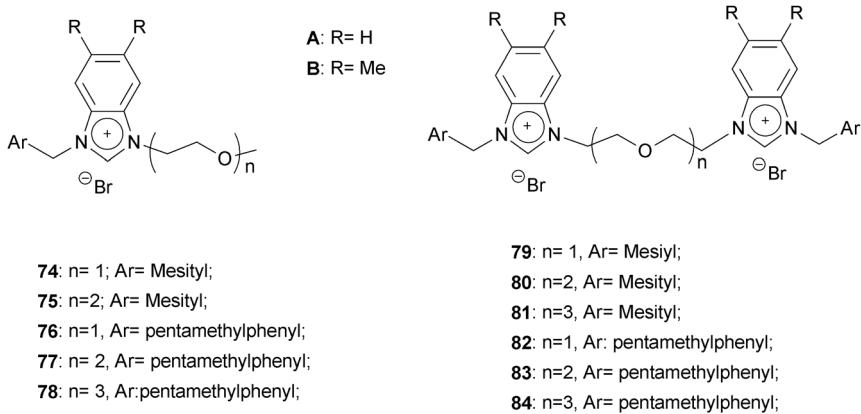
Another important contribution to the development of Heck coupling reactions in water was made by Güçemal *et al.*,⁶⁸ who developed a series of ligands based on *N*-oligoether-substituted benzimidazolium bromides **74–84** (Fig. 24) and used them as *in situ* precursor catalysts in conjunction with Pd(OAc)₂ and Cs₂CO₃ in the Heck coupling of styrene and 4'-bromoacetophenone in water. By exploiting the ligand precursors **75** and **77**, the synthesis of the preformed catalysts **85** and **86** was possible by carbene transfer from the Ag–NHC adducts. Catalysts **89** and **90** were synthesized directly by the cleavage of the dimeric complexes **87** and **88**, respectively, by reaction with PPh₃, Scheme 21.

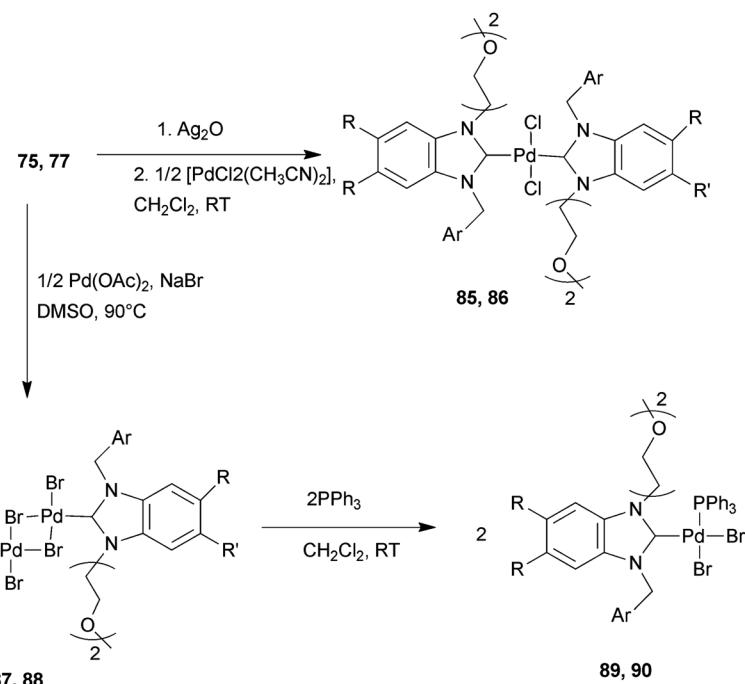
Table 8 illustrates the most representative yields for the Heck coupling reaction of styrene and 4'-bromoacetophenone in water. Surprisingly, preformed catalysts **85–86** and **89–90** turned out to be less active than the *in situ* generated catalytic systems, here presented in comparison with the ligand precursors **75** and **77**. This behaviour could be explained due to the presence of the species AcO[−]/AcOH in Pd(AOc)₂ used

as the metal precursor. Indeed, it is clear that the longer oligoether chain, the bulky N-benzyl substituents and the presence of methyl groups in the benzimidazole ring have a positive effect on the catalytic activity of both *in situ* and preformed catalysts.

Hor and co-workers reported the synthesis of a benzimidazole-functionalized NHC–Pd complex **92** from the Ag adduct **91** in good yields⁶⁹ (Scheme 22). Complex **92** displayed good to excellent catalytic activity towards Suzuki coupling reactions when these were carried out in a polar solvent. However when water was added as co-solvent, the yield increased compared to that of sole organic solvent, and decreased again when neat water was used as the sole solvent. Nevertheless, the main contribution of **92** was the ability to perform such coupling reactions at room temperature, and its tolerance to a wide range of functional groups making it a valuable material for sensitive substrates. The catalytic performance of complex **92** had already reached its maximum at a reaction time as short as 1 h, with a catalyst loading of 0.2% mol. Despite these advantages, this complex was highly active only with aryl bromides, since aryl iodides required a higher catalyst loading as well as longer reaction times and the use of TBAB (tetrabutyl ammonium bromide) as an additive in order to achieve yields not higher than 61%. Following the work on the development of suitable NHC–Pd catalytic systems in combination with the PEPPSI effect for reactions in aqueous systems, Cetinkaya and co-workers developed a series of NHC–Pd complexes with a carboxylate-functionalized pyridine **93** to **95a–c** and bicarboxylate-pyridine **96a–c** from the parent di-nuclear complex [PdBr₂(NHC)₂]₂ (Fig. 25), all of these complexes were insoluble in non-polar solvents but soluble in DMF, ethanol, and water.⁷⁰ Suzuki couplings at room temperature with complexes **94** and **96** exhibited high yield for the homocoupling of the arylboronic acid, however, the yield for the desired coupling product increased with temperature, reaching the maximum at 100 °C. In general complexes **93a–c** and **96a–c** gave the highest yields meanwhile **94a–c** and **95a–c** gave moderate to good yields.

The scope of NHC–Pd complexes for Suzuki reactions was further extended to a more robust class of complexes that still remain scarcely investigated. Huynh *et al.* reported the synthesis of the dimeric [PdBr₄(NHC)₂]₂ **97**,⁷¹ (Fig. 26) which was

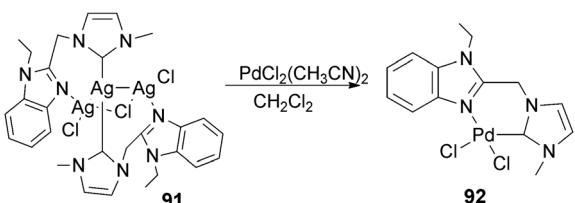
**Fig. 24** Oligoether substituted benzimidazolium salts for *in situ* catalyzed Heck coupling reactions.



Scheme 21 Synthesis of the preformed Pd(II)-NHC catalysts for Heck reactions in water.

Table 8 Heck coupling reaction of styrene and aryl bromide

Entry	Catalyst	Yield (%)
1	75A	84
2	75B	88
3	77A	92
4	77B	95
5	85A	56
6	85B	59
7	86A	61
8	86B	63
9	89A	73
10	89B	80
11	90A	77
12	90B	81



Scheme 22 Synthesis of benzimidazole-functionalized NHC-Pd complex 92.

fortuitously obtained in an attempt to synthesize the respective monomeric Pd-NHC complex, by reaction of the respective benzimidazolium salt with Pd(AcO)₂ in the presence of 4 eq. of NaBr in DMSO at 90 °C. This dimer was further cleaved to three different monomeric species using acetonitrile, starting benzimidazolium salt and triphenylphosphine, though only the catalytic activity of 97 was investigated. Standard experiments

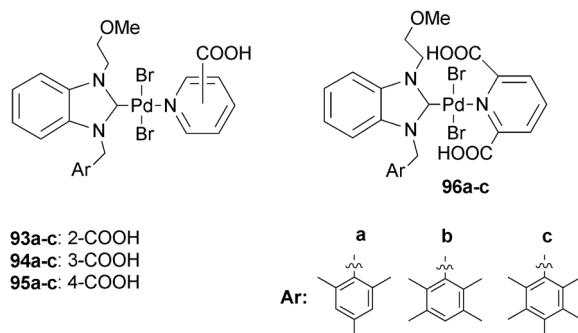


Fig. 25 Functionalized pyridine-NHC-Pd complexes for aqueous phase Suzuki coupling reactions.

with 4-bromobenzaldehyde and phenylboronic acid to study the effect of the solvent showed that acetonitrile–water and neat water gave the best yields with a catalyst loading of 0.5 mol%, at room temperature and a reaction time of 6 h. Experiments with neat acetonitrile did generate poor yields, therefore water turned out to be the sole solvent for the catalytic reactions. When higher temperatures were necessary in order to obtain better yields with non-activated aryl bromides, adding TBAB was useful since quantitative yields were attained for aryl bromides at 85 °C, conversely low yields prevailed with aryl chlorides.

In order to get more active catalysts for Suzuki coupling reactions, Huynh reported the synthesis of the dimeric sulphur bridged complex 98 from the corresponding thiol-functionalized benzimidazolium salt by two different procedures.⁷² Complex 98 was subjected to further treatment with an equimolar amount of AgO₂CCF₃ to afford the trifluoroacetate substituted complex 99. Attempts to alkylate complex 98 with Me₃OB₄ were unsuccessful and instead of the desired product, a tetrameric

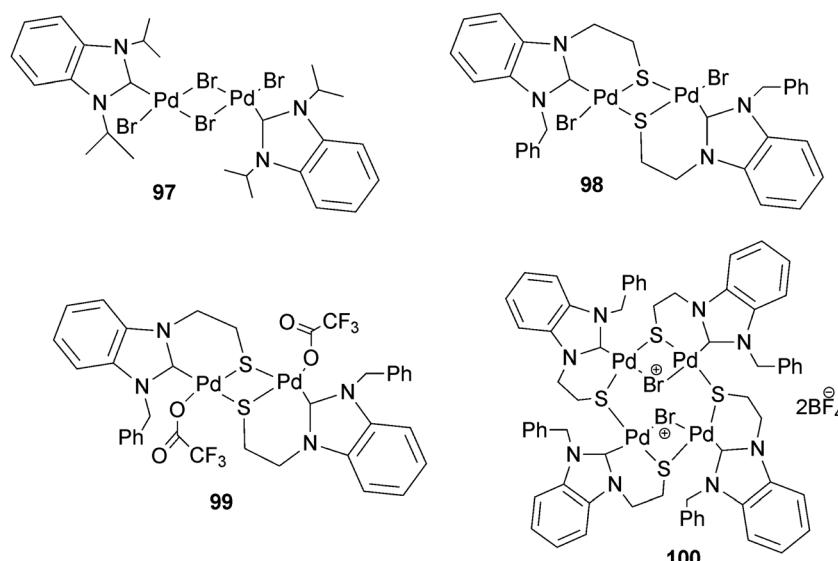


Fig. 26 Dinuclear and tetranuclear NHC–Pd complexes for Suzuki–Miyaura couplings in aqueous media.

Table 9 Suzuki–Miyaura coupling of several aryl halides catalysed by **99**

Entry	Aryl halide	Cat. loading (mol%)	Temp (°C)	t (h)	Yield (%)	TON
1	4-Bromobenzonitrile	0.001	60	24	> 99	100 000
2	1-Bromo-4-nitrobenzene	0.001	60	42	90	90 000
3	4-Bromobenzaldehyde	0.001	80	23	> 99	100 000
4	2,6-Dibromopyridine	0.0025	100	48	> 99	20 000
5	4-Bromotoluene	0.0025	100	20	97	38 800
6	4-Bromoanisole	0.0025	100	24	86	34 400
7	1-Bromo-4-chlorobenzene	0.0025	100	24	72	28 800
8	4-Chlorobenzaldehyde	0.1	100	72	41	410

sulphur and bromide-bridged complex **100** was obtained. Studies of the influence of temperature and solvent on Suzuki coupling showed that water is the preferred solvent since it is able to afford high yields with a reaction temperature as low as 60 °C, below this temperature the yield drops dramatically. Comparison of the catalytic activity of complexes **98** to **100** showed that complex **99** exhibits the best catalytic performance probably due to its more labile trifluorocarboxylate group. Table 9 displays the yields for Suzuki coupling reactions of several substrates using complex **99**. Good activities were attained with activated Br substrates, for non-activated substrates higher catalyst loadings and temperature were needed. Poor activities were displayed with aryl chlorides, requiring TBAB as a promoter to raise the activity.

Recently, Luo and collaborators reported the catalytic properties of a bis-NHC–Pd complex **101** derived from caffeine (Fig. 27), for Suzuki, Heck and Sonogashira coupling reactions in aqueous media.⁷³ Although there have been more publications on the synthesis of NHC–metal complexes derived from caffeine as a readily available xanthine from natural sources, this is the first time that the catalytic properties of this novel class of compounds were investigated. Suzuki coupling reactions in water gave good yields as the temperature of the reaction was increased up to 65 °C and KOH used as base, addition of sodium *tert*-butoxide as base gave similar yields at room temperature. Sonogashira reactions require a

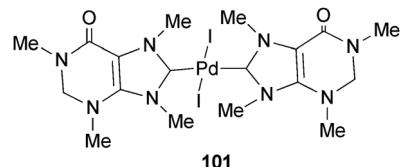


Fig. 27 Bis-NHC–Pd complex derived from caffeine.

non-ionic surfactant like Brij-30, sodium *tert*-butoxide as the base and temperature as high as 90 °C to improve the catalytic activity. For Mizuroki–Heck reactions, the use of KOH, K₂CO₃ or Et₃N as base was adequate to acquire the desired coupling product in more than 90% isolated yields. A catalyst loading of 2 mol% was indispensable for all the reactions.

Lu and co-workers reported the synthesis of imidazolium salts derived from N-phenyl and N-benzyl substituted proline from which complexes **102** and **103** were synthesized (Fig. 28).^{74a,b} They found out that substitution on the N-atom of the proline ligand precursor affects the coordination pattern of the Pd centre. In order to prove this, the dinuclear Pd(NHC) complex **104** holding a NHC-substituted proline ligand was isolated.^{74c} This indicated that non-electron rich substituents on the N-atom of the pyrrolidine ring give place to dimeric species, possibly due to a combination of electronic and steric effects around the N atom. Interestingly, when a phenyl group was inserted in the N-position of the proline ligand precursor, a cleavage of the C–N bond occurred,

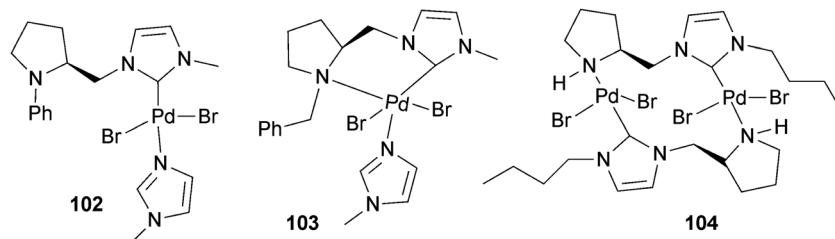
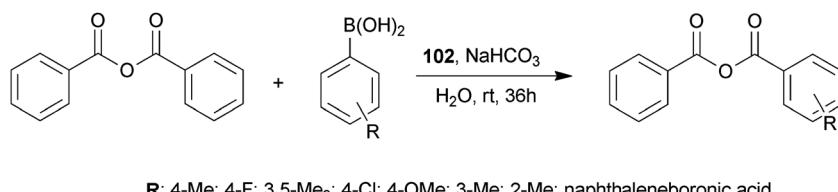


Fig. 28 Proline based Pd(NHC) complexes for C–C coupling reactions in water.

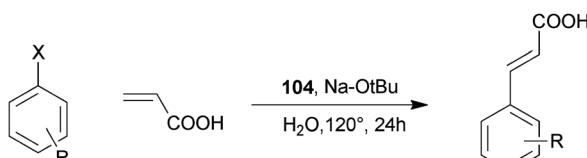


Scheme 23 Coupling reactions of benzoic anhydride with phenyl boronic acids in water catalyzed by complex **102**.

originating a second N-donor ligand, which was coordinated to the Pd centre as methylimidazole (**102**, Fig. 28).

Complex **102** was screened as a catalyst for C–C coupling reactions of benzoic anhydride with phenyl boronic acids. Preliminary experiments showed that NaHCO_3 as base and 36 h of reaction time at room temperature were the most suitable reaction conditions. In general, electron-donating substituents on the phenyl boronic acid gave lower yields than electron withdrawing groups, the best yield (84%) was found for the 4-chloro substituted phenylboronic acid. Complex **103** was used as catalyst for the Suzuki coupling reactions of a variety of aryl bromides and aryl iodides with aryl boronic acids at room temperature (Scheme 23). Good to excellent yields were achieved with no influence of the electronic properties of the substrates and with a minor steric influence on the overall yields. However, complex **103** failed when tested for coupling with aryl chlorides, since yields no higher than 43% were obtained using stronger conditions (refluxing water and 0.5 mol% of catalyst). Medium scale reactions (10 mmol of substrate) were performed without a significant decrease in yield.

The catalytic activity towards Mizuroki–Heck coupling reactions in water (Scheme 24) was tested for complex **104**. The complex showed moderate to good performance when $\text{NaO}^\circ\text{Bu}$ was used as base instead of direct NaOH , which confirms that the hydrolysis of $\text{NaO}^\circ\text{Bu}$ increases the activity of the complex. Also the use of iodo-arenes with electron withdrawing groups as substrates has a positive effect on the yield of the reaction.



$\text{X}=\text{Br}, \text{I}$

$\text{R}=\text{H}, 4\text{-MeO}, 4\text{-Me}, 4\text{-F}, 4\text{-Cl}, 4\text{-CF}_3, 3\text{-Me}, 3\text{-MeO}$

Scheme 24 Mizoroki–Heck reactions with complex **104**.

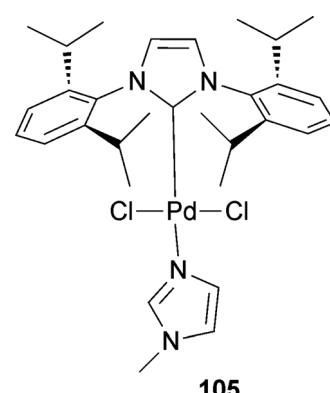


Fig. 29 NHC–Pd-imidazol complex for Suzuki–Miyaura coupling reactions in water.

Since the C–C coupling reactions of aryl chlorides remained unsuccessful with complexes **102**, **103** and **104**, Shao's group used a symmetric imidazolium salt as ligand precursor to isolate complex **105** (Fig. 29).^{74d} **105** was able to perform Suzuki–Miyaura couplings of aryl and heteroaryl chlorides with different arylboronic acids using $t\text{-BuOK}$, water at $80\text{ }^\circ\text{C}$ and reaction times ranging from 12–24 h. Good to excellent yields were obtained with no selectivity for substrates as a result of their steric or electronic effects. It is also interesting to note that complex **105** is competitive with the best catalytic systems reported so far under non-aqueous conditions.

The investigations for new functionalized NHC–metal complexes for use in aqueous catalysis led to a new field where molecules of biological importance were investigated. In this regard, sugars were one of the first type of biomolecules investigated because of their biological activity, but also because of their increased solubility in water caused by their multiple hydroxyl groups.⁷⁵ The last property has motivated the research on the use of ligands of this kind as chiral auxiliaries for catalysis. Lin and co-workers have reported the synthesis of glucopyranoside-incorporated NHC–Pd complexes **106–108** (Fig. 30) which were used for Suzuki coupling in water.⁷⁶ The ligand synthesis started from the reaction of

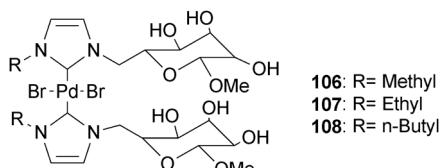


Fig. 30 Glucopyranoside-incorporated NHC–Pd complexes for Suzuki–Miyaura couplings in water.

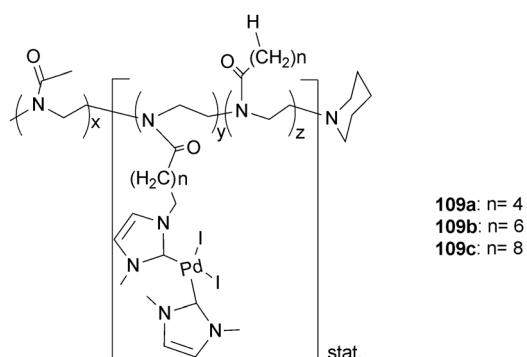
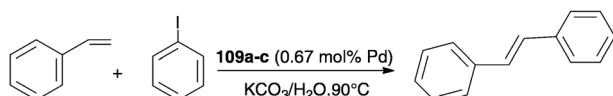


Fig. 31 Poly(oxazoline) based copolymer catalytic system for Heck and Suzuki couplings.

imidazole with the sugar 1-methyl-2,3,4-tri-*O*-benzoyl-6-bromo-6-deoxy- α -D-glucopyranoside followed by reaction with the respective alkyl halide to give the imidazolium salt. The latter was converted into the carbene bis(NHC)–Ag adduct with Ag_2O and transmetalated to Pd using PdBr_2 , the hydrolysis of the resulting product yielded **106**–**108** in good yields. Complexes **107** and **108** showed good catalytic activity in Suzuki–Miyaura coupling reactions in aqueous solutions especially when sodium methoxide was used as base in the coupling reaction of *p*-bromobenzoic acid with phenylboronic acid using 0.05 mol% of catalyst loading. With hydrophobic substrates like 2-chlorophenol, TBAB was needed as auxiliary base in order to reach yields as high as 94%. These complexes were suitable for recycling up to three cycles keeping good yields.

5.3 Polymer-based and solid-supported Pd(NHC) catalysts

Due to the disadvantages involved in the use of homogeneous catalysts like difficult separation and recycling of the catalyst, leading to contamination of the products, high production costs and environmental damage due to the use of organic solvents, several catalytic systems have been developed in order to avoid such difficulties. Webberskirch and co-workers developed a complex amphiphilic catalytic system based on 2-oxazoline diblock co-polymer **109a**–**c** bearing monomeric NHC–Pd complexes, Fig. 31. **109a**–**c** were synthesized by co-polymerization of 2-oxazoline derivatives, including an oxazoline-functionalized bis-NHC–Pd complex with an alkyl chain spacer bearing a piperidine terminating unit. Dynamic Light Scattering analysis proved that micellar aggregates were formed with hydrodynamic radii of particles between 10–30 nm. In a first approach, the polymeric macroligands **109a**–**c** were tested in the Heck reaction of styrene with iodobenzene (Scheme 25). In a micellar catalytic fashion, using short reaction times, TOF as high as 570 for copolymers **109b**–**c**



Scheme 25 Heck coupling of styrene and iodobenzene with copolymers **109a**–**c**.

and low concentrations of by-products were obtained, indicating a high catalytic activity. The length of the alkyl chain spacer in **109a** seems to be too short to separate the catalyst sufficiently from the polymer backbone and as a result it requires a longer time to accomplish the same performance as **109b**–**c**. Nonetheless, catalytic recycling of these copolymers was only affordable for the first three cycles, which was thought to occur because of the inefficient phase separation of the catalytic species and solvent, making the next substrate loading less soluble.⁷⁷

Further investigation of this catalytic system showed that both, base and temperature, play a major role in the performance, as well as the catalyst loading. Experiments with bromoarenes were unsuccessful and gave low yields. Suzuki coupling of bromobenzenes with phenylboronic acid showed that **109a**–**c** possess better catalytic activities for this reaction than for Heck coupling, displaying a TOF of up to 5200 h⁻¹.⁷⁷ Once more, temperature and catalyst loading played a significant role in the catalytic activity.

Among the polymer supported NHC–metal complexes for catalysis in aqueous media, Lee and co-workers have reported the synthesis of the simple polystyrene based NHC–Pd complex **110**^{78a,b} which was able to perform Suzuki coupling reactions in excellent yields with the non-activated phenyl iodide and phenylboronic acid (Fig. 32). When using activated aryl iodides the yield decreased, moreover, in all cases DMF–water mixtures had to be used in order to achieve the highest yields while use of neat water leads to poor yields. In order to overcome the limitations on the reactivity of the catalytic system, the polymer-based system **111** with a similar structure to **110** was reported by the same group. The difference of **111** lies in the hydrophobic ionic liquid moiety and the polymerization technique used. System **111** was synthesized by suspension polymerization using styrene as the organic phase, a polystyrene grafted resin bed (PS) was obtained in which the poly-(methylimidazolium-methylstyrene)chloride was deposited on the surface, followed by complexation with $\text{Pd}(\text{AcO})_2$ in DMSO. The resulting active polymer resin was able to perform highly efficient Suzuki couplings with a variety of iodobenzenes and phenylboronic acid at 50 °C. Unfortunately, the reaction led to a poor yield when neat water was applied as solvent. Reusability of system **111** was achieved up to 10 times under the optimal conditions. Couplings between activated and deactivated aryl iodides and bromides with electron deficient arylboronic acids were also achieved very rapidly under mild conditions.

In an attempt to overcome the problem of water miscibility, the polystyrene–polyethylene glycol–NHC–Pd species **112** was reported later by the same group,^{78c,d} where the PEG moiety provided a better water miscibility and converted this species into an amphiphilic catalytic system. For this purpose Merrifield Resins[®] PEG-200 and PEG-600 were used as the

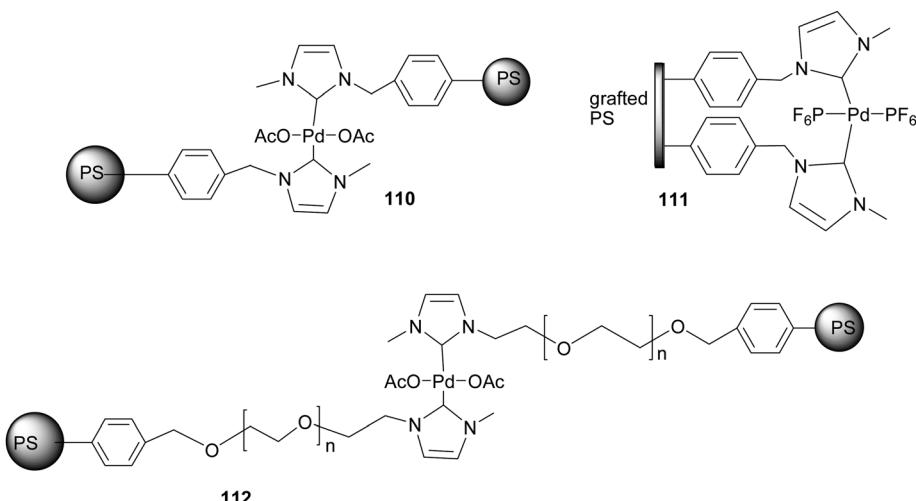
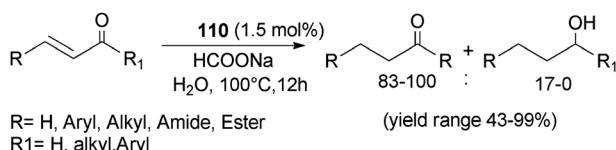


Fig. 32 PS- and PS-PEG-NHC-Pd complexes for Suzuki coupling in aqueous media.



Scheme 26 Chemoselective hydrogenation of α,β -unsaturated carbonyl compounds with catalyst **110**.

hydrophilic polymer matrix. PS-PEG-600-NHC-Pd **112** provided excellent yields for activated and non-activated aryl iodides under mild conditions by using water exclusively with only a negligible amount of DMF for dissolving the substrate. Indeed, recycling of the catalyst was possible up to 5 cycles keeping good yield.

In 2005, Sharpless and co-workers presented the concept “*on-water*” to explain the unusual reaction rate enhancement compared to the same reaction in an organic solvent or under solvent free conditions. This concept allows not only for a better reproducibility but also a more convenient product separation from the media.⁷⁹ Quite recently, Bhanage *et al.* reported a new catalytic use for the polymer-supported-Pd–NHC **110** in the chemoselective conjugated reduction of α,β -unsaturated carbonyls by using HCOONa as hydrogen source and water as the solvent (Scheme 26).⁸⁰ Surprisingly, water had an extra effect on the conversion and selectivity, since organic solvents provided much lower reaction yields and even aqueous mixtures gave lower yields than water itself. Electron-donating and electron-withdrawing enones all gave excellent yields of the corresponding ketone; α,β -unsaturated aldehydes and heterocyclic enones were also successfully reduced. However, conversion decreased considerably when aromatic α,β -unsaturated amides and enoates were applied. Successful recyclability was achieved till four cycles without significant loss of activity and selectivity.

In order to reach the advantages of the homogeneous and heterogeneous catalysts, Hagg and co-workers reported the synthesis of the water soluble species **113** and **114** (Fig. 33), based on hyperbranched polyglycerol and polyethylene glycol respectively.⁸¹ The main advantage of the dendritic structure in **113** is its solubility in a huge variety of solvents ranging from toluene to water and the possibility of running continuous

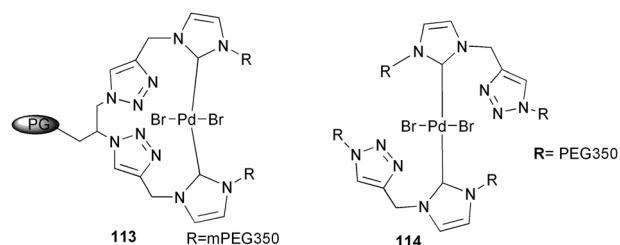
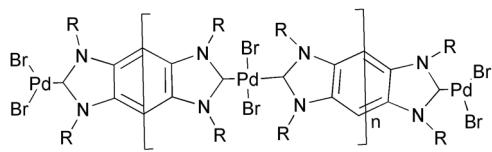


Fig. 33 Hyperbranched polyglycerol and linear polyethylene glycol catalytic NHC–Pd systems.

reactions in membrane reactors. Catalyst **113** contained 65 Pd centres per polyglycerol molecule. Both the dendritic catalyst **113** and the linear **114** showed full conversion for Suzuki couplings at high concentrations of the catalyst with TONs of 59 000 for **113** and 50 000 for **114**. Reusing **114** was not feasible due to the difficult separation of the catalyst from the substrates. In contrast, **113** was able to perform catalytic reactions with excellent yields for up to 4 cycles. Using pyridine boronic acids and other less reactive substrates, the dendritic catalyst **113** turned out to be the most active catalyst. Therefore, in terms of activity, recyclability and stability, **113** was the best performing catalytic system for Suzuki coupling.⁸¹

Organic–inorganic hybrid materials have gained a great deal of attention due to their high stability against hydrolysis and thermal decomposition as well as their tunable electronic and chemical properties, yet their catalytic properties have barely been explored. Karimi and Akhavan reported first the synthesis of the NHC-based organometallic polymer (NHC-MCOP) **115**, and investigated its potential application to Suzuki coupling in water (Fig. 34).^{82a} This polymeric catalyst showed an excellent activity for aryl iodides and a quite high efficiency even for the deactivated aryl chlorides and aryl fluorides. An average yield of 92% was obtained after 6 cycles for activated aryl chlorides. In a further report NHC-MCOP **77** was compared with the newly synthesized **116** and **117** NHC-MCOP. From those results, it turned out that the benzyl and alkyl groups of the NHC ligands played a key role in the catalytic behaviour of these species. In general, NHC–Pd–MCOP **117** displayed the highest efficiency even



115: R= Benzyl Mw= 136000 Da
116: R= n-hexyl Mw= 88000 Da
117: R= n-dodecyl Mw= 85000 Da

Fig. 34 Main chain organometallic-NHC–Pd polymers for Suzuki couplings in water.

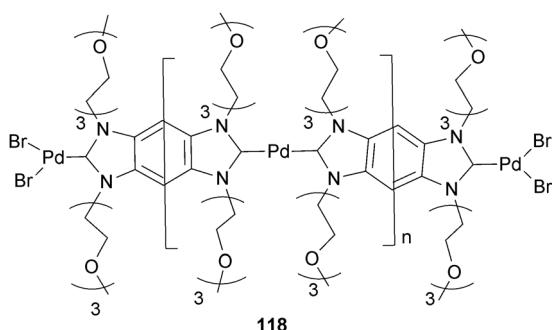


Fig. 35 Triethylene glycol functionalized Pd–NHC-based organometallic polymer.

with the most challenging substrates, *e.g.* 2-substituted aryl bromides, and a recyclability of 4 cycles without any loss of activity. Hot filtration experiments, as well as poisoning and catalytic screening with a monomeric analogue demonstrated that the catalytic species works in a partially heterogeneous fashion with the formation of trace amounts of Pd nanoclusters. The increase of the catalytic activity in the case of **117** is due to the high concentration of coupling partners in the hydrophobic region of the polymer capsules producing an improved contact with the Pd nanoclusters.^{82b}

In order to overcome the limitations involving the number of reaction cycles in which **115–117** can be used with high catalytic activity, MCOP **115** was modified by exchanging the *N*-benzyl group in the benzimidazole ring (R in Fig. 34) by triethylene glycol moieties (TEGs), generating the water-soluble NHC–Pd-MCOP **118**, (Fig. 35). The new polymeric species, with an average molecular weight of 107 000 Da exhibited good to excellent yields in the Suzuki coupling reactions of substituted aryl bromides and aryl halides, including deactivated and hindered substrates with aryl boronic acids at room temperature. More sterically hindered substrates required higher catalyst loadings and temperatures of up to 80 °C. The new TEG substituted MCOP **118** showed better activity than its congener **115**, which demonstrates that the triethylene glycol moieties have a positive effect on the catalytic performance of **115**. Simple extraction with hexane and purification by dialysis allowed a total of 17 subsequent reaction cycles with 4-chlorobenzaldehyde and phenylboronic acid with a consistent yield of *ca.* 90%. Finally, poisoning experiments with Hg revealed that no Pd nanoclusters are responsible for the catalytic activity, different from MCOPs **115–117**.⁸³

Inorganic supports for organometallic catalysts have been investigated in parallel to the developments on polymer supported catalytic systems. The first reported work on

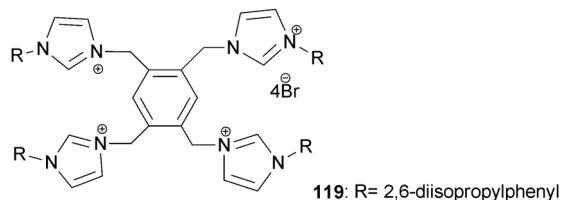


Fig. 36 Ligand used for the silica supported NHC–Pd catalyst for Suzuki couplings in water.

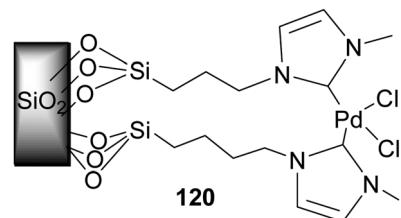


Fig. 37 Silica gel supported NHC–Pd catalyst for C–C coupling reactions in aqueous media.

inorganic-supported-NHC–transition metal complexes for aqueous catalysis was made by Zhang and co-workers.⁸⁴ By reacting $\text{Pd}(\text{AcO})_2$ with ligand **119** (Fig. 36) in dichloroethane for 24 h followed by addition of silica or alumina to the reaction mixture, a silica or alumina-supported Suzuki coupling catalyst system was obtained. Attempts to get good Suzuki coupling reactions in neat water by reacting $\text{Pd}(\text{AcO})_2$ and **119** failed to afford good yields. Upon addition of the inorganic support, the catalyst became stable enough to perform coupling reactions without the need for phase transfer agents. This system has the possibility to work on an industrial scale because of its high stability; however the reusability is limited to 3 cycles.

Silica has been widely used as an inorganic support for a huge variety of catalysts, owed to its special electronic properties as well as its high stability and occurrence. Jin *et al.* developed a method to synthesize a NHC–Pd complex supported on a silica matrix **120** by reacting silica gel (Merck® 9385) with triethoxysilylpropylimidazolium chloride followed by reaction with $\text{Pd}(\text{OAc})_2$ in DMSO (Fig. 37).⁸⁵ ICP analysis yielded a 3.65 atom% of Pd in the sample, which is equal to 3.34 mmol of Pd anchored on 1 g of **120**. Excellent catalytic activities of this system were achieved even with a Pd loading as low as 0.01% and under mild conditions for activated and non-activated aryl bromides in DMF : H_2O 1 : 1 (v/v). In many cases a quantitative yield was obtained by increasing the reaction time up to 1 h. These high yields were limited to aryl bromides, since reaction times of 12 h were needed in order to achieve good yields with aryl chlorides, and a poor activity was found for substituted aryl chlorides. Recyclability studies of **120** with iodobenzene and 1-bromo-4-nitrobenzene with phenylboronic acid demonstrated that this system can be used up to 6 cycles without significant loss of activity, besides, no Pd leaching was detected. Molecular polyoxometalates (POMs) are another interesting option for inorganic supports for heterogeneous catalysts due to their stability and polyionic properties like the Keggin polyanion $[\gamma\text{-SiW}_{10}\text{O}_{36}]^{8-}$, used by Albrecht, Bonchio and co-workers⁸⁶ managed to synthesize the catalytic system **121** (Fig. 38), by anchoring

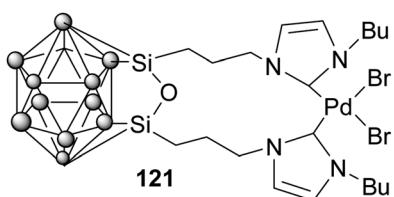


Fig. 38 Polyoxometalate-based NHC–Pd complex for C–C coupling in aqueous media.

the trialkoxysilyl-functionalized-bis-NHC–Pd complex to the mentioned Keggin polyanion. Characterization by FT–IR, ^1H , ^{13}C , ^{29}Si and ^{183}W , as well as XPS spectroscopy and DFT experiments demonstrated the identity of the catalytic species, where the halide ligands were in the *trans* configuration.

The catalytic behaviour of this species was investigated for a number of phenyl halides in DMF: : H_2O 1: : 1 (1/1) and under microwave induced dielectric heating (75 – 80 °C), chosen due to its proven advantages towards polycharged catalysts. Aryl bromides and iodides were efficiently converted into their diphenyl-coupled product with phenylboronic acid in a range of 80–99% yield. TON and TOF numbers of 1980 and 11 880 h⁻¹ were reached respectively. Since aryl chlorides required a higher catalyst loading, dehalogenated by-products were present in a relevant amount. Optimization of the necessary conditions to make dehalogenation the major product yielded high conversion for only activated aryl chlorides.

The use of ionic liquids as alternative and eco-friendly reaction solvent has led to increasing investigation in this field.⁸⁷ Jin and co-workers developed a catalytic system based on Fe_3O_4 nanoparticles coated with the ionic liquid [BMIM][PF₆]. Immobilizing the NHC–Pd complex (**cat**, Fig. 39) into thin layers of [BMIM][PF₆] (**IL**), coated on the surface of nano-sized Fe_3O_4 ,

resulted in the catalytic NHC–Pd immersed into an ionic liquid functionalized-Fe nanoparticles **122**.⁸⁸ Catalytic system **122** demonstrated an excellent efficiency with activated and non-activated aryl bromides by adding TBAB as a phase transfer agent in a range of temperatures from 40 to 90 °C and 0.5 mol% of active species in neat water. Reusability was studied with 4-bromoanisole and phenylboronic acid, which afforded excellent yields until the fifth run. The simple separation of catalytic system **122** from the reaction mixture by external magnets is one of its main advantages that makes it a potential candidate for industrial-level reactions.

6. Group 11 M–NHC complexes (Ag, Au, Cu)

From the reports published so far, all the members of this group have released at least one publication concerning the synthesis of NHC–M complexes and their use in catalytic reactions. Ag(NHC) complexes have been widely mentioned as carbene transfer agents, but their use as catalysts has been quite limited. Au and Cu catalysts are widely reported in the literature, but still there is quite few publications regarding their use in catalysis under aqueous conditions using NHC-based systems.

6.1 Ionic tagged M(NHC) complexes

6.1.1 Ag and Au(NHC) complexes. New catalytic applications of the water-soluble ionic-tagged Au(NHC) complexes were found very recently. Joó *et al.*⁸⁹ isolated different sulfonated functionalized zwitterionic imidazolium salts **123A–F** (Fig. 40) as precursor ligands for carbene transfer reactions from their respective Ag complexes (**124A–F**). Ag complexes (**124A–F**) were synthesised in order to get the Au(NHC)Cl complexes to be used as catalysts for the hydration of terminal

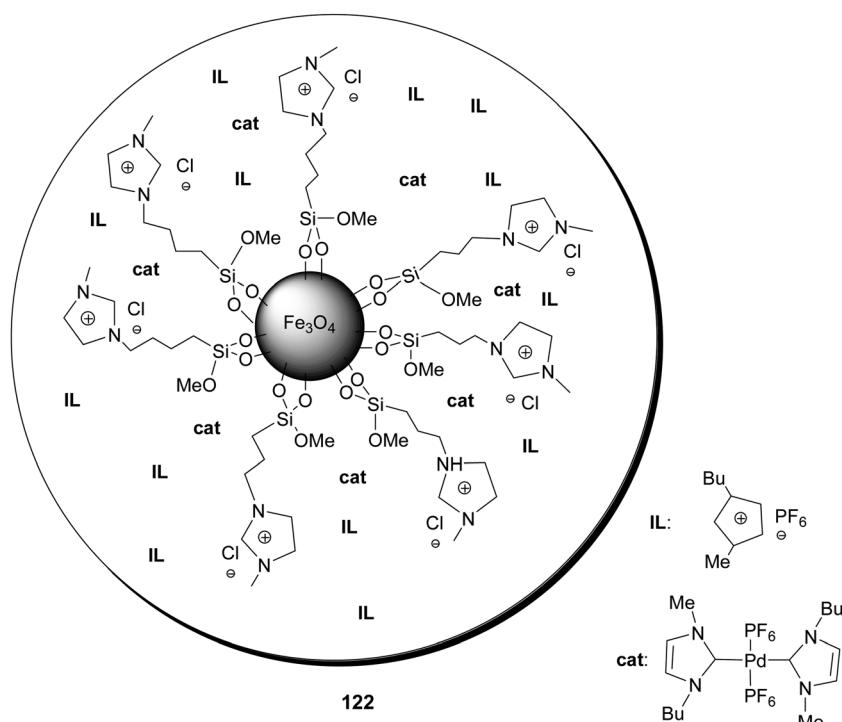


Fig. 39 Fe_3O_4 nanoparticle–ionic liquid matrix for the NHC–Pd catalyst for C–C couplings in water.

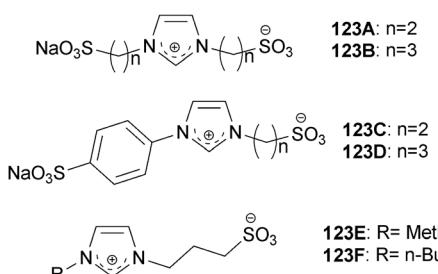
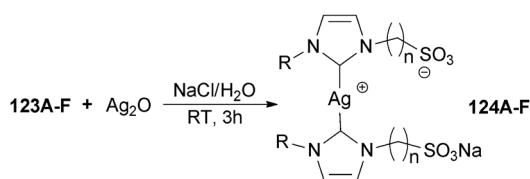


Fig. 40 Imidazolium sulfonate zwitterionic ligands.



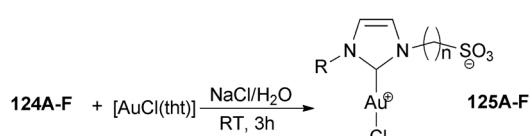
Scheme 27 Synthesis of the bis(NHC)–Ag complexes.

alkynes in aqueous media. Scheme 27 shows the formation of the Ag adducts from **123A–F**, from which complexes **124B** and **124E–F** were isolated and were used immediately as prepared (Table 10). The carbene transfer reactions to [AuCl(tht)] were performed in a similar mode as those for the synthesis of the Ag adducts **124A–E** (Scheme 28). The single complex, [AuCl(NHC)] **125F**, could not be obtained, instead a bis(NHC)–Au complex was formed (see Table 11).

In Scheme 29 the general reaction conditions for the hydration of terminal alkynes using the Au(NHC)Cl **125A–E** are presented. Among the screened complexes, **18C** and **18E** displayed the highest catalytic activity, with the utmost conversion for **125E** of 94%. The best contribution of these

Table 10 Isolated yields from the synthesis of complexes **124A–F**

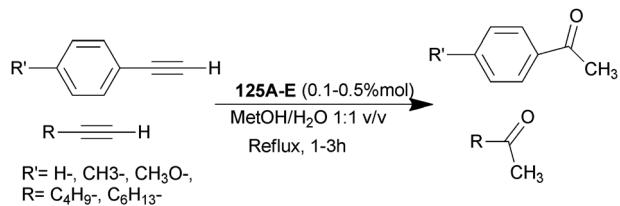
Complex	Ligand	Yield
124A	123A	60%
124B	123B	Not isolated
124C	123C	43%
124D	123D	56%
124E	123E	Not isolated
124F	123F	Not isolated



Scheme 28 Preparation of the catalytic species Au(NHC)Cl **125A–E**.

Table 11 Isolated yields from the synthesis of complexes **125A–E**

Ag(NHC) adduct	Au(NHC)Cl	Yield (%)
124A	125A	78
124B	125B	82
124C	125C	80
124D	125D	47
124E	125E	59
124F	Au-bis(NHC)	34



Scheme 29 General conditions for the hydration of alkynes catalyzed by **125A–E**.

complexes is their ability to activate the alkynes without the need for an acid co-catalyst. This is advantageous in the case of acid sensitive substrates. Unfortunately, testing of catalyst **125A** with different co-catalysts did not provide the expected increased activity.

Following this work, Joó reported a new modified synthetic path for the synthesis of sulfonated SiMes (sSiMes) and sulfonated IMes (sIMes) first described by Plenio.⁹⁰ These ligands were used for the synthesis of the new complexes [Au(sSiMes)Cl] **126** and [Au(sIMes)Cl] **127** (Fig. 41), from their respective Ag adducts by carbene transfer reactions to [AuCl(tht)]. Complexes **126** and **127** were used for the catalytic hydration of alkynes showing excellent catalytic activities for the hydration of terminal alkynes, bearing aromatic as well as aliphatic groups, in water–methanol mixtures (Scheme 30). This is a very competitive protocol compared to other aqueous alkyne hydrations,⁹¹ even in the absence of acid, which is a common co-catalyst for most hydration reactions. However, in this case acid had a clear beneficial effect on the reaction velocity providing up to full conversion.

6.1.2 Cu(NHC) complexes. Since 2001, “Click” chemistry has become one of the most important cycloadditions studied due to its high applicability in the production of biologically active molecules, and among them, Cu(i) catalyzed azide–alkyne cycloaddition (CuAAC) has become the most popular click reaction. Recently, Li and co-workers⁹² reported the synthesis of the ammonium-tagged NHC–Cu(i) complexes for the three component click reaction of different benzyl bromides and terminal alkynes in water using NaN₃ as the azide source (**128–133**, Fig. 42). It is worth mentioning that the use of methanol was crucial for the efficient synthesis of all these complexes. Table 12 shows the most relevant results for the model click reaction of benzyl bromide and phenylacetylene in water using NaN₃. There is a clear effect of the length of the alkyl group R and the halogen X on the overall yield and the reaction time, where the best results were generated by complex **128** holding two triethylammonium groups and a chloride as the counter-anion. Moreover, compound **128** gave acceptable results with a catalyst loading as low as 0.5 mol%, although, considerably longer reaction times were required (48 h). Further analysis of the catalytic scope of **128** was carried out with several benzyl bromides holding both electron-withdrawing and electron-donating groups as well as hydroxy-functionalized alkynes, alkylacetylenes and heterocyclic alkynes, affording good to excellent yields. Reuse of **128** was possible up to four catalytic cycles, nonetheless a strong decrease in the yield was observed in each consecutive run.

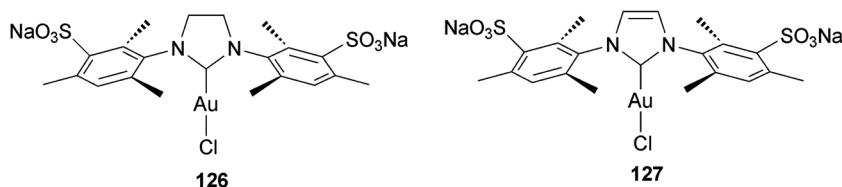
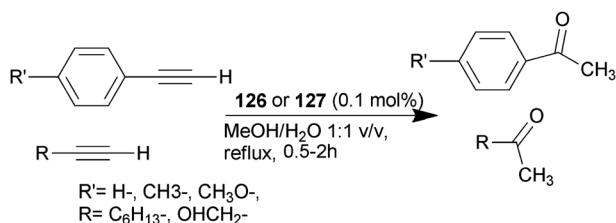


Fig. 41 Water soluble Au(sSiMes)Cl (**126**) and Au(sIMes)Cl (**127**) for hydration of alkynes.



Scheme 30 General reaction conditions for the hydration of alkynes catalyzed by complexes **126** and **127**.

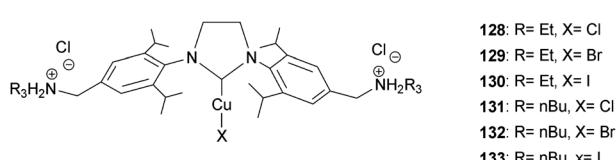


Fig. 42 Ammonium-tagged [(NHC)CuX] complexes for the three component click reaction.

Table 12 Isolated yield for the three-component click reaction of benzyl bromide and phenylacetylene

Entry	Catalyst	Time (h)	Yield (%)
1	128	3	98
2	129	6	Trace
3	130	6	92
4	131	6	94
5	132	6	Trace
6	133	6	66

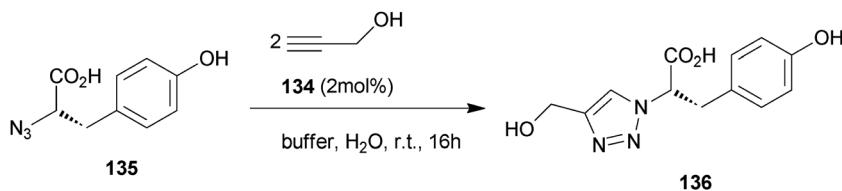
Due to the extreme importance of the CuAAC reactions for the click chemistry of molecules with biological significance, synthesis of suitable catalytic systems is of main concern. In this regard, Gautier *et al.*⁹³ developed the symmetric complex **134**, holding a two triazole-functionalized NHC ligand with an ammonium group on each side. The complex structure of the ligand in **134** induced water-solubility and high stability

towards oxidation of Cu(I). Preliminary experiments, to identify the optimum catalytic conditions, were carried out by the CuAAC of **135** (Scheme 31) and propargyl alcohol, from which it was found that HEPES buffer (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) at pH = 7.6 in water was able to afford the best results. The effect of solvent additives was also investigated, from which it could be concluded that MeOH, DMSO, NMP and HFIP 25% v/v were well compatible for the reaction. Knowing that α -amino acids chelate copper cations, the influence of some L-amino acids on the formation of **136** was studied. To overcome chelation to all Cu(I) centers, 0.5 mol% of catalyst per mol of α -amino acid was used (Fig. 43).

Finally, in order to study the applicability of **134** for peptide ligation reactions, reactions of alkyne containing peptides with **135** and its benzyl analogue in 0.2 M HEPES as buffer at pH 7.6 and HFIP as a solvent additive were carried out. Peptides containing methionine, cysteine, tyrosine, arginine, tryptophan and histidine (**137**–**139** and **140**, Fig. 44) were successfully synthesized and even peptides containing residues sensitive to copper-mediated oxidation (His, Met, Cys). Thiol and sulfide-containing peptides **137** and **138a–b** were not over-oxidized and even peptides **140a–b** were produced with no sign of chelation with Cu species.

6.2 Non-ionic tagged complexes

6.2.1 Cu and Ag(NHC) catalysts. Following previous works on the development of the ionic-tagged NHC–Cu complexes, Nolan *et al.*⁹⁴ published a report on the use of NHC–Cu species with the traditional NHC precursors SiMes, IMes, and IPr ligands as shown in Fig. 45. These complexes were tested in the click reaction of benzyl azide and phenyl acetylene in mixtures of *tert*-butanol and water at 5 mol% (Table 13). Preliminary comparison of organic solvents and water led to a strong acceleration of the reaction when aqueous mixtures were used, water alone was able to afford the best yield for the reaction. Neat reactions were also possible by employing low catalyst loading, this reaction required the lowest reaction time. The results in Table 13 show an evident effect of the NHC ligand and the halogen employed, leading to complex **144** as the most active species.



Scheme 31 CuAAC reaction of **135** using complex **134**.

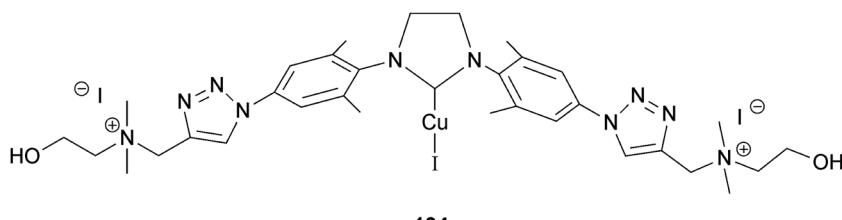
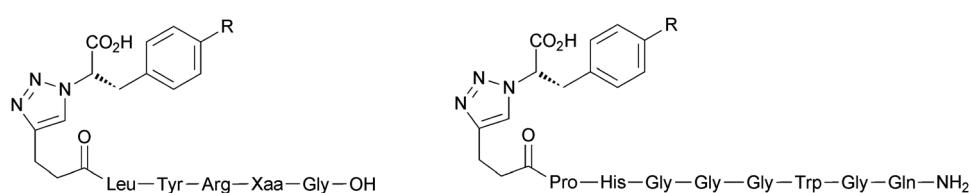


Fig. 43 Triazole functionalized NHC–Cu(μ) complex for the CuAAC of unprotected peptides



137a: Xaa= Cys, R= OH; **137b:** Xaa= Cys, R= H **140a:** R= OH
138a: Xaa= Met, R= OH; **138b:** Xaa= Met, R= H **140b:** R= H
139a: Xaa= His, R= OH; **139b:** Xaa= His, R= H

Fig. 44 Synthesized peptides using complex **134** in the presence of 0.2 M HEPES and HFIP 25% v/v.

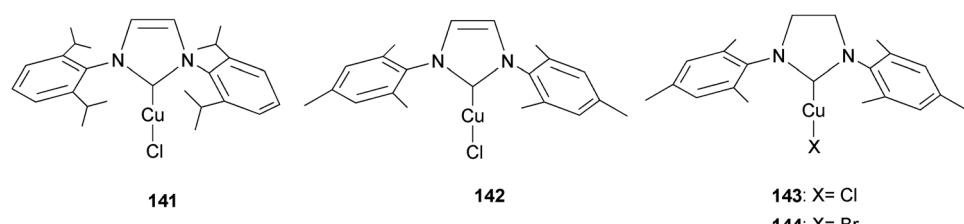
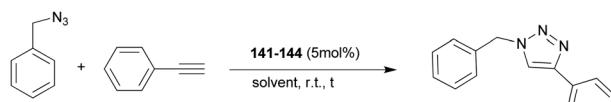


Fig. 45 $[(\text{NHC})\text{CuX}]$ complexes as click catalysts.

Table 13 Catalytic study of **141–144** for the click reaction of benzyl azide and phenylacetylene



Entry	Catalyst	Solvent	<i>t</i> (h)	Yield (%)
1	141	Water/ <i>t</i> -BuOH	18	18
2	142	Water/ <i>t</i> -BuOH	18	65
3	143	Water/ <i>t</i> -BuOH	18	93
4	144	Water/ <i>t</i> -BuOH	9	95
5	144	Water	0.5	98
6	144^a	Neat	0.3	98

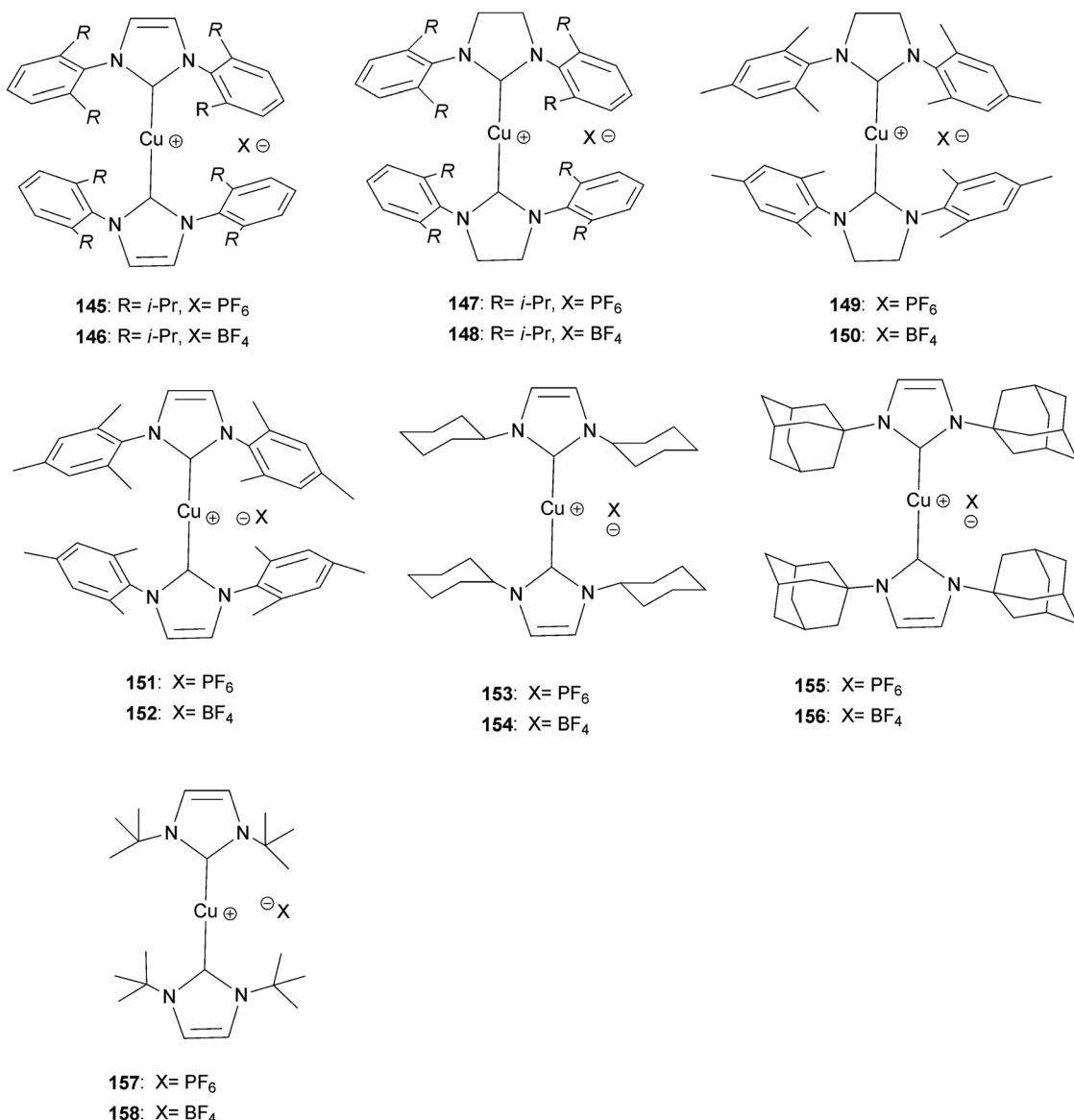
^a 0.8 mol% of the catalyst.

144 was further investigated for the three component reaction as was described above for **128–133**. Comparison of the result of the same reaction described in Table 13 shows that **144** required 1 h to achieve 92% yield, which is competitive with the water soluble complex **128**. This complex was also tested for cycloadditions using internal alkynes under neat conditions, giving fair to good yields and no acceleration was observed when using water as solvent.

Aimed at improving the conditions for the click reactions such as low catalyst loading, short reaction times without

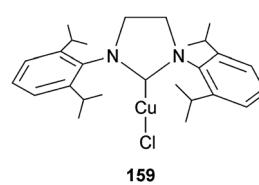
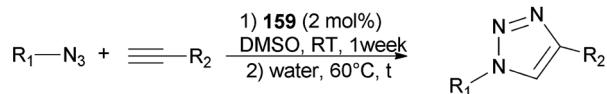
loss of activity, Nolan *et al.*⁹⁵ published a series of complexes of the type bis(NHC)-CuX holding a polyatomic counter-ion, using different NHC ligands and two different Cu(i) salts as metal precursors. In total, 14 different complexes were tested as catalysts for the CuAAC of benzyl azide in water, at room temperature, with a catalyst loading of 2 mol%. From all the complexes tested, **153** turned out to be the best performing catalyst as it was able to complete the cycloaddition in quantitative yield within only 1.5 h. Although this is longer than the time required for **144** (Table 13, entry 5) a lower catalyst loading can be used. The synthesis of different triazoles by catalyst **144** was possible, finding no effect on the electronic properties of the reactants, and completing the reactions within times ranging from 5 min to 9 h. The requirement for low catalyst loading motivated the investigation for the synthesis of triazoles under catalyst loading as low as 40 ppm for benzyl azide and phenyl acetylene, giving good results at 50 °C. According to the NMR analysis of a reaction between phenyl acetylene and **153**, one of the NHC ligand is dissociated during the reaction, and possibly this ligand may act as the base for the deprotonation of the acetylene (Fig. 46).

Another type of catalysts which have been less studied are the so-called "latent" catalysts, which are inert under normal conditions such as ambient temperature and light, but become active when an external stimulus such as heat or irradiation is applied.^{96a}

**Fig. 46** Bis-NHC–CuX complexes for CuAAC reactions.

In this regard, Nolan and co-workers found out that the Cu complex **159** (Fig. 42) was active for the formation of triazoles from the [3 + 2] cycloaddition of azides to alkynes only when water (v/v 1 : 1) was added to the catalytic system at 60 °C (Scheme 31). In case DMSO was applied as inert solvent (no reaction took place under normal conditions), the reaction only gave 21% yield when the temperature was raised to 60 °C. However, almost quantitative yield was obtained when water was added to the system. Water by itself was not a good solvent for the reaction, since low yields were obtained under normal conditions (Fig. 47 and Scheme 32).^{96b}

The investigation of NHC–Ag catalyzed organic reactions had remained scarcely explored. Very recently Li and co-workers have reported the first NHC–Ag catalyzed alkynylation of isatins “on-water”.⁹⁷ Complexes **160–166** were initially used for the alkynylation of *N*-benzylisatin with phenylacetylene in water under an Ar atmosphere with diisopropylethylamine (DIPEA). The catalytic activity is strongly dependent on the

**Fig. 47** [(NHC)CuCl] complex as a latent click catalyst.

R₁: -Benzyl, -CH₂Ar, -Alkyl, -Ts, -(CH₂)₂Ph

R₂: -Ph, -CH₂OH, -Ar, -cyclohexenyl

Scheme 32 Triazole formation by latent catalyst **159**.

structure of the silver complex, Table 14. **160** gave the best yield under the given conditions, even under an air atmosphere

Table 14 Catalytic performance of the silver complexes **160–166** for alkynylation of N-benzylisatin

Entry	Catalyst	Time (h)	Yield (%)
1	160	4	98
2	161	4	93
3	162	4	92
4	163	4	94
5	164	6	<10
6	165	6	Trace
7	166	6	N.R.

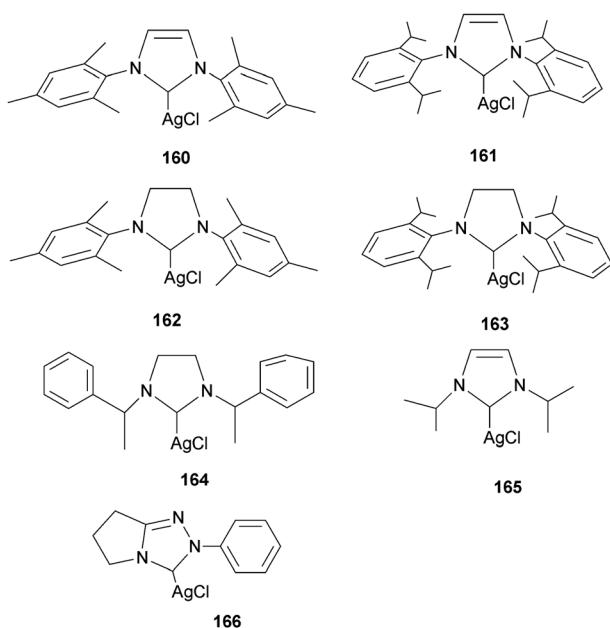


Fig. 48 NHC–Ag complexes for the “on-water” alkynylation of isatins.

there was no change in activity. Water plays a key role in increasing the yield of the reaction, since the use of ordinary organic solvents led to poor or negligible reaction yields. Aromatic and heteroaromatic alkynes afforded excellent yields and reactions with alkylacetylenes proceeded smoothly generating good to excellent yields. The major influence on the reactivity was given by the N-substituent, since very low yield was obtained when substituting benzyl by hydrogen (Fig. 48).

7. Conclusions and outlook

According to the reports that have been published during the last three decades, nearly any catalytic reaction involving late transition metals can be adapted to the use of water as the reaction solvent provided the reactants themselves are water stable. Continuing efforts are focused on the development of new ligand architectures and adapting new reactions to the aqueous phase. Such a research area started with the synthesis of hydrophilic phosphine and nitrogen derivatives and continued

with N-heterocyclic carbene ligands. In this regard, and considering the advantages of the NHC–metal complexes such as high thermal and chemical stability given by the nature of the metal–carbene bond, this class of complexes represent a promising selection for the synthesis of aqueous-phase organometallic catalysts. At present, most of the work on aqueous catalysis by NHC–transition metal complexes has evoked C–C coupling reactions such as Suzuki, Heck and Sonogashira couplings as well as olefin metathesis owing to the suitability of the involved substrates as well as the high performance of the active species. Nevertheless, reactions such as isomerization of allylic alcohols, olefin hydrogenation, hydration of alkynes, hydroformylation, hydrosilylation and alkynylation of carbonyl compounds, and even alkyne–azide cycloadditions in aqueous systems have also been explored using this class of complexes. Although most of the transition metals have been coordinated with NHC ligands and most of the resulting complexes used in organometallic catalysis, only a few of them, predominantly with Ru and Pd and in a few examples with Ag, Au, Cu and Rh, Pt and Ir have been investigated in aqueous phase catalysis. This opens a huge window of opportunities in this field, since water has become a green alternative for many chemical processes, either for one or two-phase reaction systems. Currently there are several chemical processes using water reaction medium, so the outlook for the near future is based on an increased number of such processes. A better understanding of the role of water as reaction medium may improve the performance of the chemical processes, such as product separation, treatment of by-products and recycling of catalysts and solvent.

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References

- For related reviews, see: (a) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751; (b) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095; (c) K. Shaughnessy, *Chem. Rev.*, 2009, **109**, 643.
- W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1290.
- I. E. Markó, S. Stérin, O. Buisine, G. Mignani, P. Branlard, B. Tinant and J.-P. Declercq, *Science*, 2002, **298**, 204.
- A. C. Hillier, H. M. Lee, E. D. Stevens and S. P. Nolan, *Organometallics*, 2001, **20**, 4246.
- H. M. Lee, T. Jiang, E. D. Stevens and S. P. Nolan, *Organometallics*, 2001, **20**, 1255.
- L. D. Vasquez-Serrano, B. T. Owens and J. M. Buriak, *Chem. Commun.*, 2002, **21**, 2518.
- G. Grasa, M. S. Viciu, J. Huang and S. P. Nolan, *J. Org. Chem.*, 2001, **66**, 7729.
- G. Grasa, M. S. Viciu, J. Huang, C. Zhang, M. L. Trudell and S. P. Nolan, *Organometallics*, 2002, **21**, 2866.
- O. Navarro, R. Kelly III and S. P. Nolan, *J. Am. Chem. Soc.*, 2003, **125**, 16194.

- 10 V. César, S. Bellemin-Laponnaz and L. Gade, *Chem. Soc. Rev.*, 2004, **33**, 619.
- 11 D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534.
- 12 M. C. Perry and K. Burgess, *Tetrahedron: Asymmetry*, 2003, **14**, 951.
- 13 S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402.
- 14 W. A. Herrmann, D. Baskakov, E. Herdtweck, S. D. Hoffmann, T. Bunlaksananusorn, F. Rampf and L. Rodefeld, *Organometallics*, 2006, **25**, 2449.
- 15 (a) A. J. Arduengo, M. Kline, J. C. Galabrese and F. Davidson, *J. Am. Chem. Soc.*, 1991, **113**, 9704; (b) A. J. Arduengo, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361.
- 16 (a) K. Öfele, *J. Organomet. Chem.*, 1968, **12**, 42; (b) H. W. Wanzlick and H.-J. Schönher, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 141.
- 17 L. Cavallo, A. Correa, C. Costabile and H. Jacobsen, *J. Organomet. Chem.*, 2005, **690**, 5407.
- 18 (a) X. Hu, Y. Tang, P. Gantzel and K. Meyer, *Organometallics*, 2003, **22**, 612–614; (b) X. Hu, I. Castro-Rodriguez, K. Olsen and K. Meyer, *Organometallics*, 2004, **23**, 755–764.
- 19 D. Nemcsok, K. Wichmann and G. Frenking, *Organometallics*, 2004, **23**, 3640–3646.
- 20 N. M. Scott, R. Dorta, E. D. Stevens, A. Correa, L. Cavallo and S. P. Nolan, *J. Am. Chem. Soc.*, 2005, **127**, 3516–3526.
- 21 (a) D.-G. Silvia and S. P. Nolan, *Coord. Chem. Rev.*, 2007, **251**, 874; (b) H. Jacobsen, A. Correa, A. Poater, C. Costabile and L. Cavallo, *Coord. Chem. Rev.*, 2009, **293**, 687–703.
- 22 (a) R. Dorta, E. D. Stevens, N. M. Scott, C. Costabile, L. Cavallo, C. D. Hoff and S. P. Nolan, *J. Am. Chem. Soc.*, 2005, **127**, 2485–2495; (b) O. Eisenstein, J. Loch and R. H. Crabtree, *Inorg. Chem.*, 2001, **40**, 5806–5811.
- 23 (a) T. Kato, H. Gornitzka, A. Baceiredo, A. Savin and G. Bertrand, *J. Am. Chem. Soc.*, 2000, **122**, 998–999; (b) Y. Canac, M. Soleilhavoup, S. Conejero and G. Bertrand, *J. Organomet. Chem.*, 2004, **689**, 3857–3865.
- 24 C. Heinemann, T. Müller, Y. Apeloig and H. Schwarz, *J. Am. Chem. Soc.*, 1996, **118**, 2023–2038.
- 25 J. M. O'Brien and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, **133**, 7712.
- 26 M.-A. Tehre, J. Monot, M. Malacia, L. Fensterbank, J.-P. Fouassier, D. P. Curran, E. Lacôte and J. Lalevée, *MacroLett.*, 2012, **1**, 92–95.
- 27 X. Bi, L. Wu, C. Yan, X. Jing and H. Zhu, *J. Chil. Chem. Soc.*, 2011, **6**, 664.
- 28 I. Özdemir, *J. Organomet. Chem.*, 2001, **633**, 27.
- 29 E. Peris, A. Arturo and S. Sanz, *Organometallics*, 2010, **29**, 3661.
- 30 F. Joó and P. Csabai, *Organometallics*, 2004, **23**, 5640–5643.
- 31 F. Joó and M. Fekete, *Catal. Commun.*, 2006, **7**, 783.
- 32 E. Peris, B. Royo, J. A. Mata and A. Pontes da Costa, *Organometallics*, 2010, **29**, 1832.
- 33 (a) *Handbook of Metathesis*, ed. R. H. Grubbs, Wiley-VCH, Weinheim, Germany, 2003; (b) A. Hoveyda and R. Zhugralin, *Nature*, 2007, **450**, 243.
- 34 R. T. Raines, J. B. Binder and J. J. Blank, *Org. Lett.*, 2007, **9**, 4885.
- 35 S. Blechert, S. J. Connolly, M. Rivard and M. Zaja, *Adv. Synth. Catal.*, 2003, **345**, 572.
- 36 (a) K. Grela, Ł. Gutajski, P. Śledź and A. Lupa, *Green Chem.*, 2008, **10**, 271; (b) Y. Hayashi, *Angew. Chem.*, 2006, **118**, 8281; (c) Y. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 8103; (d) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275; (e) D. G. Blackmond, A. Armstrong, V. Coombe and A. Wells, *Angew. Chem., Int. Ed.*, 2007, **46**, 3798.
- 37 (a) R. H. Grubbs, D. M. Lynn and S. Kanaoka, *J. Am. Chem. Soc.*, 1996, **118**, 784; (b) D. D. Manning, X. Hu, P. Beck and L. L. Kiessling, *J. Am. Chem. Soc.*, 1997, **119**, 3161; (c) J. P. Claverie, S. Viala, V. Maurel and C. Novat, *Macromolecules*, 2001, **34**, 382; (d) D. Quemener, V. Heroguez and Y. Gnanou, *Macromolecules*, 2005, **38**, 7977.
- 38 (a) K. J. Davis and D. Sinou, *J. Mol. Catal. A: Chem.*, 2002, **177**, 173; (b) B. H. Lipshutz, G. T. Aguinaldo, S. Ghorai and K. Voigtlander, *Org. Lett.*, 2008, **10**, 1325.
- 39 R. H. Grubbs and J. P. Jordan, *Angew. Chem., Int. Ed.*, 2007, **46**, 5152.
- 40 (a) *Aqueous Organometallic Chemistry and Catalysis*, ed. I. T. Horvat and F. Joó, Amsterdam, 1995, p. 15; (b) B. Mohr, D. M. Lynn and R. H. Grubbs, *Organometallics*, 1996, **15**, 4317; (c) L. Gulajski, A. Michrowska, R. Bujok and K. Grela, *J. Mol. Catal. A: Chem.*, 2006, **254**, 118; (d) A. Michrowska, K. Mennecke, U. Kunz, A. Kirschning and K. Grela, *J. Am. Chem. Soc.*, 2006, **128**, 13262; (e) A. Kirshning, K. Harmrolfs, K. Mennecke, J. Messinger, U. Schön and K. Grela, *Tetrahedron Lett.*, 2008, **49**, 3019.
- 41 (a) K. Grela, A. Michrowska, L. Gulajski, Z. Kaczmarśka, K. Mennecke and A. Kirschning, *Green Chem.*, 2006, **8**, 685; (b) K. Grela, A. Michrowska and L. Gulajski, *Chem. Today*, 2006, **24**, 19.
- 42 R. T. Raines, J. B. Binder and I. A. Guzei, *Adv. Synth. Catal.*, 2007, **349**, 395.
- 43 (a) D. Rix, H. Clavier, L. Gulajski, K. Grela and M. Mauduit, *J. Organomet. Chem.*, 2006, **691**, 5397; (b) D. Rix, F. Caño, I. Laurent, L. Gulajski, K. Grela and M. Mauduit, *Chem. Commun.*, 2007, 3771.
- 44 R. H. Grubbs and J. P. Jordan, *Angew. Chem.*, 2007, **119**, 5244.
- 45 K. Grela and D. Burtscher, *Angew. Chem., Int. Ed.*, 2009, **48**, 442.
- 46 S. Blechert and S. J. Connolly, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1873.
- 47 R. H. Grubbs, J. P. Jordan and J. P. Gallivan, *Tetrahedron Lett.*, 2005, **46**, 2577.
- 48 (a) T. Emrick and K. Breitenkamp, *J. Polym. Sci., Part A: Polym. Chem.*, 2005, **43**, 5715; (b) T. Emrick, X. Zhang, K. Kratz and D. Samanta, *Macromolecules*, 2008, **41**, 530–532.
- 49 R. H. Grubbs and S. Hyek, *J. Am. Chem. Soc.*, 2006, **128**, 3508.
- 50 M. R. Buchmeiser, O. Nuyken, R. Weberskirch, U. Anders, M. T. Zarka and J. O. Krause, *Angew. Chem., Int. Ed.*, 2003, **42**, 5965.
- 51 A. Azua, S. Sanz and E. Peris, *Chem.–Eur. J.*, 2011, **17**, 3963–3967.
- 52 M. Albrecht, J. R. Miecznikowski, A. Samuel, J. W. Faller and R. H. Crabtree, *Organometallics*, 2010, **29**, 3661–3664.
- 53 R. Weberskirch, O. Nuyken, M. Bortenschlager, M. T. Zarka and K. Wurst, *Organometallics*, 2004, **23**, 4817.
- 54 W. A. Herrmann and K. Christian, *J. Organomet. Chem.*, 1997, **532**, 261.
- 55 K. H. Shaughnessy, L. R. Moore, S. M. Cooks, M. S. Anderson, H. H.-J. Schanz, S. T. Griffin, R. D. Rogers and M. C. Kirk, *Organometallics*, 2006, **25**, 5151.
- 56 J. W. Youngs, *J. Organomet. Chem.*, 2003, **673**, 1.
- 57 F. Silbertri, J. C. Flores and E. de Jesus, *Organometallics*, 2012, **31**, 3355–3360.
- 58 H. Plenio and S. Roy, *Chem. Commun.*, 2007, 2870.
- 59 H. Plenio and S. Roy, *Adv. Synth. Catal.*, 2010, **352**, 1014–1022.
- 60 E. Peris, P. Maracena, S. Candela and G. Fernando, *Organometallics*, 2011, **30**, 684.
- 61 P. Ghosh, M. S. Mobin, B. Samir and R. Lipika, *Chem.–Eur. J.*, 2008, **14**, 6646.
- 62 P. Ghosh, M. S. Mobin and S. Chandrakanta, *Eur. J. Inorg. Chem.*, 2009, **12**, 1608.
- 63 P. Ghosh, M. S. Mobin and J. Alex, *Dalton Trans.*, 2009, **47**, 10581.
- 64 S. Gu, H. Xu, N. Zhang and W. Chen, *Chem.–Asian J.*, 2010, **5**, 1677–1686.
- 65 (a) F. Churruca, R. SanMartin, B. Inés, I. Tellitu and E. Domínguez, *Adv. Synth. Catal.*, 2006, **348**, 1836; (b) E. Domínguez, R. San Martin, M. J. Moure and B. Inés, *Adv. Synth. Catal.*, 2009, **351**, 2124.
- 66 T. Tu, X. Feng, Z. Wang and X. Liu, *Dalton Trans.*, 2010, **39**, 10598.
- 67 Z. Wang, X. Feng, W. Fang and T. Tu, *Synlett*, 2011, 951.
- 68 S. Güçemal, S. Kahraman, J.-C. Daran, E. Çetinkaya and B. Çetinkaya, *J. Organomet. Chem.*, 2009, **694**, 3580–3589.
- 69 F. Li, S. Bai and T. S. Andy Hor, *Organometallics*, 2008, **27**, 672.
- 70 H. Türkmen, R. Can and B. Çetinkaya, *Dalton Trans.*, 2009, **35**, 7039.
- 71 H. V. Huynh, Y. Han, J. H. H. Ho and G. K. Tan, *Organometallics*, 2006, **25**, 3267.
- 72 H. V. Huynh and D. Yuan, *Organometallics*, 2010, **29**, 6020.
- 73 F. T. Luo and H.-K. Lo, *J. Organomet. Chem.*, 2011, **696**, 1262.
- 74 (a) L.-X. Shao, S. Xiao-Bao, G. Ting-Ting and L. Jian-Mei, *Appl. Organomet. Chem.*, 2011, **25**, 497–501; (b) Y.-Q. Tang, H. Lv, J.-M. Lu and L.-X. Shao, *J. Organomet. Chem.*, 2011, **696**, 2576–2579; (c) M. T. Ma and J. M. Lu, *Appl. Organomet. Chem.*,

- 2012, **26**, 175–179; (d) L.-X. Shao and X.-X. Zhou, *Synthesis*, 2011, 3138–3142.
- 75 (a) F. Tewes, A. Schlecker, K. Harms and F. Glorius, *J. Organomet. Chem.*, 2007, **692**, 4593; (b) T. Nishioka, T. Shibata and I. Kinoshita, *Organometallics*, 2007, **26**, 1126; (c) B. K. Keitz and R. H. Grubbs, *Organometallics*, 2010, **29**, 403; (d) J.-C. Shi, N. Lei, Q. Tong, Y. Peng, J. Wei and L. Jia, *Eur. J. Inorg. Chem.*, 2007, 2221.
- 76 J. B. I. Lin, L. Fu-Chen, L. Pey-Syuan and Y. Chien-Chan, *Organometallics*, 2010, **29**, 5959.
- 77 (a) R. Weberkirch, O. Nuyken and D. Schönfelder, *J. Organomet. Chem.*, 2005, **690**, 4648; (b) R. Weberkirch, O. Nuyken, M. Schmidt, K. Fischer and S. Daniel, *Macromolecules*, 2005, **38**, 254.
- 78 (a) Y.-S. Lee and J.-W. Byun, *Tetrahedron Lett.*, 2004, **45**, 1837; (b) Y.-S. Lee, J.-W. Byun, B.-H. Jun and J.-H. Kim, *Tetrahedron Lett.*, 2004, **45**, 5827; (c) Y.-S. Lee, M. Shokouhimehr, J.-W. Kim and J.-H. Kim, *J. Org. Chem.*, 2005, **70**, 6714; (d) Y.-S. Lee, D.-H. Lee, J.-H. Kim and J.-W. Kim, *Tetrahedron Lett.*, 2006, **47**, 4745.
- 79 S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275.
- 80 B. M. Bhanage, S. R. Khan, K. P. Dhake, Z. S. Qureshi and D. B. Bagal, *Green Chem.*, 2011, **13**, 1490.
- 81 R. Haag and M. Meise, *ChemSusChem*, 2008, **1**, 637.
- 82 (a) B. Karimi and P. F. Akhavan, *Chem. Commun.*, 2009, **25**, 3750–3752; (b) B. Karimi and P. F. Akhavan, *Inorg. Chem.*, 2011, **50**, 6063.
- 83 B. Karimi and P. F. Akhavan, *Chem. Commun.*, 2011, **47**, 7686–7688.
- 84 H. Zhang, Y. Zhao, Y. Zhou, D. Ma, J. Liu, L. Li and T. Y. Zhang, *Org. Biomol. Chem.*, 2003, **1**, 1643.
- 85 M.-J. Jin, D.-H. Lee, S. M. Sarkar and H. Qiu, *Green Chem.*, 2008, **10**, 37.
- 86 M. Bonchio, M. Albrecht, G. Scorrano, A. Sartorel, M. Iglesias, M. Carraro and S. Berardi, *Chem.–Eur. J.*, 2010, **16**, 10662.
- 87 For reviews on ionic liquids, see: (a) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (b) C. Hardacre and V. I. Pârvulescu, *Chem. Rev.*, 2007, **107**, 2615.
- 88 M.-J. Jin, W.-S. Ahn, J.-Y. Jung, J.-B. Kim and A. Taher, *Synlett*, 2009, 2477.
- 89 F. Joó, A. C. Benyei, C. E. Nagy and A. Almassy, *Organometallics*, 2010, **29**, 2484.
- 90 F. Joó, K. Ágnes, P. Gábor and E. C. Csilla, *J. Mol. Catal.*, 2011, **340**, 1.
- 91 S. Sanz, L. A. Jones, F. Mohr and M. Laguna, *Organometallics*, 2007, **26**, 952.
- 92 F. Li, C. Xia, J. Wu and W. Wang, *Green Chem.*, 2011, **13**, 3440–3445.
- 93 A. Gautier, F. Cisnetti, V. Aucagne, C. Gaulier, A. Hospital, B. Legeret and A. F. Delmas, *Chem. Commun.*, 2012, **48**, 4005–4007.
- 94 S. P. Nolan, L. Cavallo, A. Correa and S. Diez-Gonzalez, *Chem.–Eur. J.*, 2006, **12**, 7558–7564.
- 95 S. P. Nolan and S. Diez-Gonzalez, *Angew. Chem., Int. Ed.*, 2008, **47**, 8881–8884.
- 96 (a) S. Monsaert, A. Lozano Vila, R. Drozdak, P. Van Der Voort and F. Verpoort, *Chem. Soc. Rev.*, 2009, **38**, 3360–3372; (b) S. P. Nolan, S. Diez-González and E. D. Stevens, *Chem. Commun.*, 2008, 4747.
- 97 C.-J. Li, L. Liu, Y.-J. Chen, D. Wang and X.-P. Fu, *Green Chem.*, 2011, **13**, 549.