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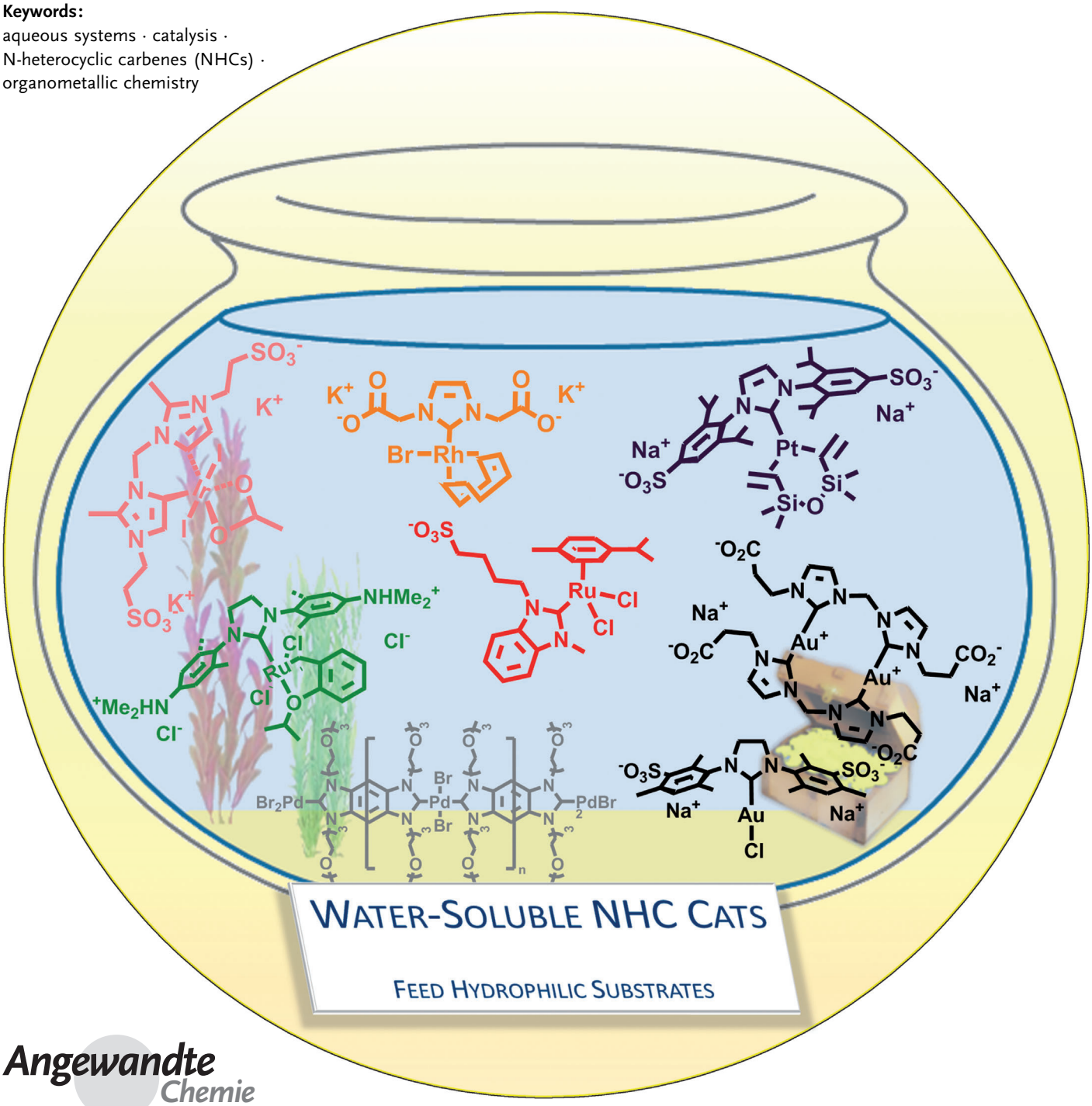
Organometallic Chemistry

Synthesis and Application of Water-Soluble NHC Transition-Metal Complexes

Lars-Arne Schaper, Sebastian J. Hock, Wolfgang A. Herrmann, and Fritz E. Kühn**

Keywords:
aqueous systems · catalysis · N-heterocyclic carbenes (NHCs) · organometallic chemistry



We provide an overview on the state-of-the-art in transition-metal complexes formed with water-soluble NHC ligands. Paths to introducing water solubility by ligand design are elucidated and some general properties of water-soluble NHC complexes are highlighted. The enhanced hydrophilicity of water-soluble catalysts offers advantages in applications. While studies based on C–C coupling reactions still dominate the field, recent reports show water-soluble NHC complexes can be applied in metathesis and hydrogenation reactions and turn out to be among the best performing catalysts known. Nevertheless, wide areas of this young field remain to be investigated, offering great potential for future research.

From the Contents

1. Introduction

The utilization of water—the "greenest" and most abundant of all solvents—as a reaction medium in chemical applications is of greatest interest, not only for traditional proponents of *Green Chemistry Principles*,[1] but also for the chemical industry. Switching from "volatile organic compounds" (VOCs), currently used in most industrial processes, to water as the solvent reveals an enormous saving potential for the chemical industry, given that recent estimates of the worldwide cost of VOCs amounts to up to five billion Euros per year.[2] Furthermore, the usage of VOCs is associated with enormous safety and health risks and requires precautions, since most organic solvents are harmful if not toxic, carcinogenic, flammable, or explosive. Clearly, application of water also has some drawbacks, such as its high distillation energy, high specific heat capacity (difficulties in quick heating or cooling), and the necessity to purify waste water. However, in addition to its abundance, water offers exceptional chemical reactivity and selectivity through its unique properties: its ability to solvate salts and polar compounds or its high dielectric constant.[3]

Homogeneous catalysis presents further advantages to achieve the goals of green chemistry, such as high atom economy and high E factors.[4] Yet, one of its intrinsic problems is costly catalyst recycling. Utilization of water-soluble homogeneous catalysts in aqueous or multiphase media[5]—as most substrates show only low solubility in water—can overcome this limitation and exploit new and efficient ways of chemical operations.[6] Thus, homogeneously catalyzed industrial processes performed in water are not exceptional anymore and are applied on plant scale, for example the rhodium-catalyzed Ruhrchemie/Rhône–Poulenc process for hydroformylation of propylene,[7] or the Shell Higher Olefins Process (SHOP).[8] In these processes, the water-solubility of transition-metal catalysts is enhanced through suitable ligand design. Although the application of N-heterocyclic carbenes (NHCs) as ligands offers attractive features, such as high electron donation and complex stability,[9] and although many NHC-based transition-metal catalysts are already produced on an industrial scale,[10] no industrial application of transition-metal catalysts equipped with water-soluble NHCs has been reported to date.

Ever since the significance of NHCs as steering ligands in catalysis was discovered and research in this area picked up pace,[11] their substituents have been used for two major purposes: providing stability or influencing steric and electronic properties of the carbene ligands. Most importantly, substituents were used to vary buried volume[12] or donor strength,[13] induce chirality,[14] provide stability through chelate effects,[15] or increase solubility.[16] However, solubility in aqueous solvents was of minor interest throughout the first decade of intensified NHC research and work in this area only recently experienced growth (Figure 1).

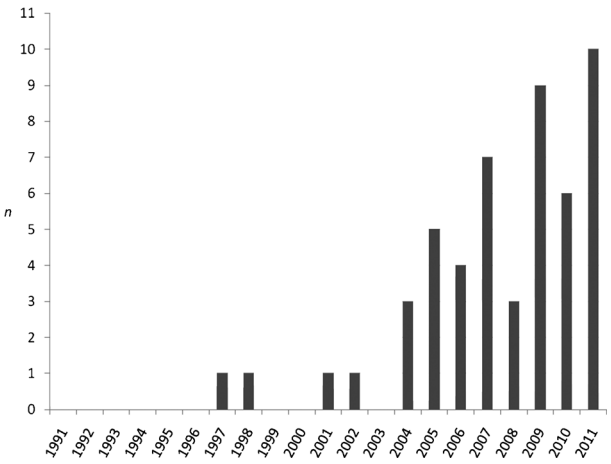


Figure 1. Number of publications (*n*) dealing with transition-metal compounds bound to water-soluble NHCs, 1991–2011.

[*] L.-A. Schaper, S. J. Hock, W. A. Herrmann, F. E. Kühn
Chair of Inorganic Chemistry/Molecular Catalysis, Catalysis Research Centre of the Technische Universität München
Ernst Otto Fischer-Strasse 1
85747 Garching bei München (Germany)
E-mail: wolfgangherrmann@ch.tum.de
fritz.kuehn@ch.tum.de

Reflecting their great industrial importance, a huge variety of Reviews has been dedicated to NHCs.[17] In his 2009 Review, Shaughnessy provided a couple of examples of metal complexes with water-soluble NHCs.[18] Furthermore, some examples were mentioned in Bierenstiel's work dedicated to sulfur-functionalized NHCs or in Youngs' Review about silver carbenes.[19] Yet, no comprehensive Review devoted to the rapidly expanding field of water-soluble NHCs has appeared to date.

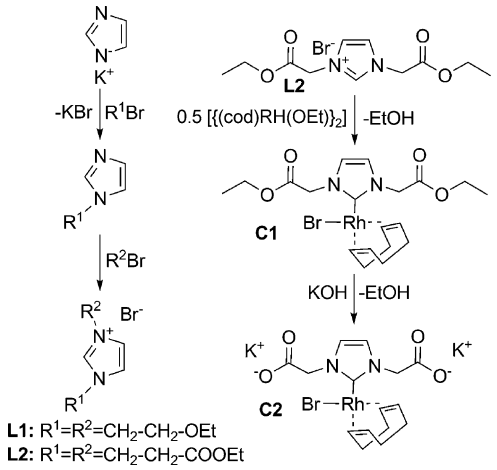
An impressive number of NHC-containing compounds have been reported since the birth of transition-metal NHC chemistry.[20] Only a few years after the initial reports, the first synthesis of a water-soluble NHC compound was described.[21] In most accounts describing water-soluble NHC complexes, however, the water-solubility is not effected by the NHC ligand. Therefore it is important to note, that this Review focuses exclusively on water-soluble NHC complexes, achieving water-solubility through special features on the N-heterocyclic carbene ligands and not through other reasons.

2. Synthesis of Metal Complexes with Potentially Water-Soluble NHCs

Common precursors for NHC complexes are azolium salts, which are in most cases water-soluble. In their ionic form they are applied in organocatalysis,[22] as ionic tags,[23] or as ionic liquids.[24] In case of the ionic liquids, immiscibility with nonpolar solvents is of utmost importance for environmentally benign product separation. Needless to say, that this picture changes as soon as the previously ionic azolium salts are bound to metals in neutral carbene ligand form. Routinely used NHCs feature aliphatic or aromatic substituents, which enhance the hydrophobic properties rather than increase water solubility. Key to hydrophilic behavior, therefore, is an ionic, or at least a strongly polar, functionalization of the NHCs' substituents. The following Sections elucidate all the different paths in ligand design towards water solubility that are known to date. It should be emphasized, that all the ligands presented herein have been reported to be suitable for NHC complex synthesis. However, access to metal complexes of this ligand class has not been reported for all the known routes.[25] For example, free carbenes of this ligand class, although likely to be persistent, have not been isolated and carbene adducts as viable free carbene alternatives have not been synthesized yet.[26]

2.1. Carbonate/Carboxylate or Ester Functionalization

The first NHC complex, in which water solubility was introduced by functionalization of substituents, was described as early as 1997[27] and featured a carbene ligand with two nitrogen-bound methyl carboxylate side chains. Ethoxycarbonyl ethyl ester groups were introduced by conventional quaternization using bromoacetic acid ethyl ester to yield imidazolium salt **L2**. The subsequent reaction with a rhodium precursor, equipped with an internal base, gave water-stable complex **C1** (Scheme 1). This compound's ester group could easily undergo characteristic reactions, such as aminolysis, transesterification, or ester cleavage, as could be shown for water-soluble complex **C2**.[27]



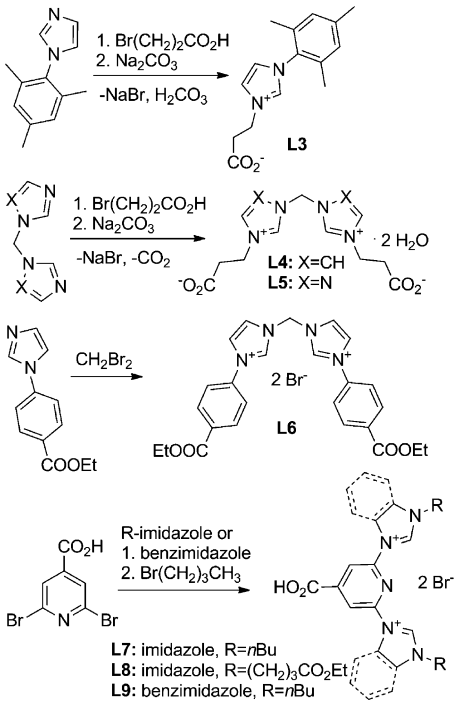
Scheme 1. Ester cleavage yields the first metal complex in which water solubility is induced through ionic N-functionalization of the NHC.[27]

Instead of functionalizing the ligand after metal complexation, other strategies were developed, in which ionic ligands were synthesized prior to metal complexation. Shaughnessy and co-workers presented direct synthesis of zwitterionic imidazolium salts using 3-bromopropanoic acid and sodium

Lars-Arne Schaper was born in 1982 in Hamburg, Germany. He studied chemistry at Universität Hamburg and Technische Universität München (TUM), Germany, where he received his Dipl. Chem. in 2009 under supervision of K. Ruhland and W. A. Herrmann. Currently, he is completing his PhD studies at TUM with F. E. Kühn and W. A. Herrmann, supported by Elite Network of Bavaria: NanoCat. His research interests include synthesis of new ligand systems and substitution patterns in N-heterocyclic carbenes, NHC early-transition-metal complexes and new triazolylidene-based NHC ligands.

Sebastian J. Hock was born 1983 in Munich (Germany). He received his BSc (2006) and MSc in Chemistry (2010) from TUM (Germany) and his MEng degree (2009) in Mining, Metals, and Materials Engineering from McGill University Montréal (Canada). Since 2010 he has been a member of the Elite Network of Bavaria—in the doctorate program "NanoCat: Nanodesign of High Performance Catalysts". Currently he is PhD student under supervision of W. A. Herrmann and F. E. Kühn. His research focuses on rhenium carbene complexes and their application in homogeneous catalysis.

carbonate (Scheme 2, **L3**).[28] Soon, Papini et al.[29] and then Gornitzka, Hemmert et al.[30] followed this route and applied it successfully to bis(imidazoles) (**L4**/**L5**). Another type of carboxylate functionalization was reported by the group of



Scheme 2. Imidazolium-, bis(imidazolium)-, and bis(triazolium)-based betaines **L3**–**L5**; methylene bridged ethyl benzoate-substituted bis(imidazolium) salt **L6**; bis(imidazolium) and bis(benzimidazolium) salts linked by isonicotinic acid **L7**–**L9**.[28–34]

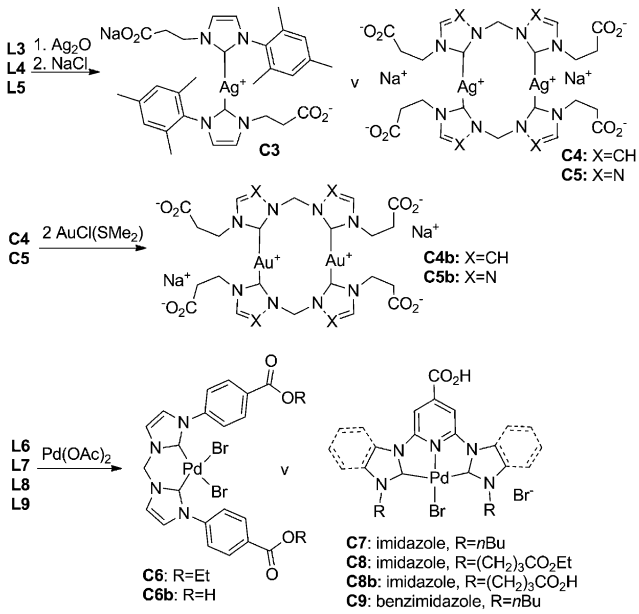
Wang: In this case, 4-ethyl benzoate imidazoles linked by a methylene bridge where described (**L6**).[31] However, water solubility was only induced after metal complexation, following the ester-cleavage route described in Scheme 1.[27]

Another possibility of inducing polarity in NHC ligands is a functionalization of the linker in bis-NHCs. Dibromo-substituted isonicotinic acid is a valuable starting material for this purpose and was applied by Churruca et al. to bridge *n*-butyl substituted imidazoles (Scheme 2, **L7**).[32] This ligand motive was—in terms of water solubility—enhanced by Inés et al. through the use of imidazoles equipped with carboxy ethyl esters (**L8**).[33] Furthermore, Tu and co-workers employed a slightly different procedure to synthesize bis-(benzimidazolium) ligand **L9** as depicted in Scheme 2.[34]

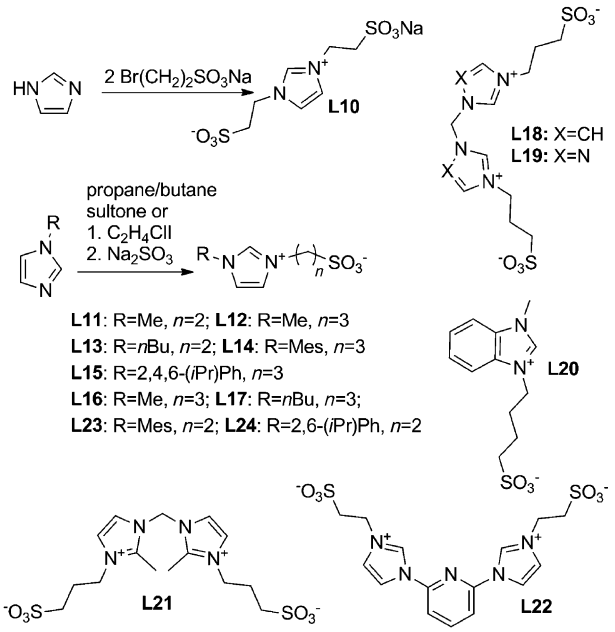
As exemplified in compounds **C1** and **C2** (Scheme 1), metal complexation of carboxylate-functionalized NHCs is carried out using imidazolium salts and metal precursors equipped with internal bases, such as $[\{Rh(cod)OEt\}_2]$ (cod = cyclooctadienyl), Ag_2O, or $Pd(OAc)_2$. To date, no synthesis via free carbene intermediates has been described. One possible reason might be that by application of internal bases nucleophilic attack on the carbonyl carbon atom is prevented. Based on the established route of Wang and Lin[35] and Young's initial report of the first synthesis of a silver carbene compound in neat water,[36] Shaugnessy and co-workers synthesized silver carbene **C3**, using water as the reaction medium.[28] NaCl was added to avoid cationic coordination of silver to the carboxylate and to prevent formation of polymeric structures. Bis(imidazolylidene) and 1,2,4-triazolylidene silver complexes were synthesized by Santini's group, applying a very similar procedure (Scheme 3, **C4**/**C5**).[29] Cure et al. later reproduced these complexes and used them in transmetalation to isolate the corresponding gold compounds. Following Youngs' report of a carbene transfer in H_2O as the reaction medium,[37] the carbene transfer was performed in deoxygenated water. Although formation of purple gold nanoparticles was observed, **C4b** could be isolated in good yields (Scheme 3).[30] To allow synthesis of a variety of potential precatalysts, $Pd(OAc)_2$ was employed as ideal starting material (**C7**–**C9**). Dominguez and co-workers reported *n*-butyl substituted isonicotinic acid bridged palladium complex **C7**.[32] Later, solubility was further enhanced through ethyl carboxylate ethyl ester substituted **C8** and subsequent ester hydrolysis (**C8b**), similar to the route described by our group in 1997.[27,33] Li et al. also followed this route to generate water-soluble catalyst precursor **C6b**.[31] Typically for NHC coordination to Pd, DMSO is utilized as the reaction medium and high temperatures as well as long reaction times (> 12 h) are necessary to complete reactions. However, Tu and co-workers developed a microwave-based synthesis to yield bis(benzimidazolylidene) complex **C9** within two hours overall reaction time.[34] Certainly, their

Wolfgang A. Herrmann studied chemistry at the TU München (TUM) and obtained his diploma degree in the group of E. O. Fischer. He received his PhD in 1973 at the University of Regensburg under the direction of H. Brunner. After postdoctoral research with P. S. Skell (Pennsylvania State University), he completed his Habilitation in Regensburg, where he was appointed Associate Professor in 1979. He received a full professorship in Frankfurt/Main in 1982 and moved to the TUM in 1985 as successor to E. O. Fischer. He has been president of the TU München since 1995.

Fritz E. Kühn studied chemistry at the TU München (TUM), Germany, and received his PhD with W. A. Herrmann in 1994. After postdoctoral research with F. A. Cotton (Texas A&M University, 1995/96), he completed his Habilitation in Munich and became "Privatdozent" in 2000. From June 2005 to March 2006 he was Deputy Chair of Inorganic Chemistry at TUM. In April 2006 he was appointed Principal Researcher at the Instituto Técnológico e Nuclear (ITN) in Sacavém, Portugal. In December 2006 he returned to the TUM as Professor of Molecular Catalysis and since October 2007 he has been Acting Chair of Inorganic Chemistry.



Scheme 3. Synthesis of transition-metal complexes with carboxylate-functionalized NHCs. Structures of corresponding ligands **LX** can be found in Scheme 2.[28–34]



Scheme 4. Mono- and bis-NHC precursors with alkyl sulfonate functionalization.[28–29, 40–41, 43, 46]

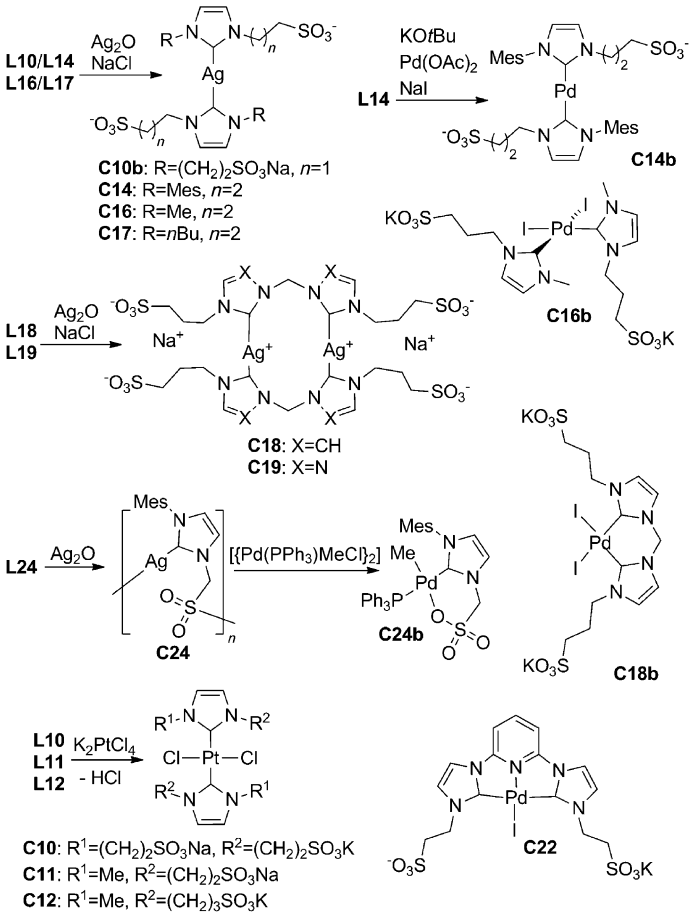
route should be taken into consideration when planning future work in this area.

2.2. Sulfonate Functionalization

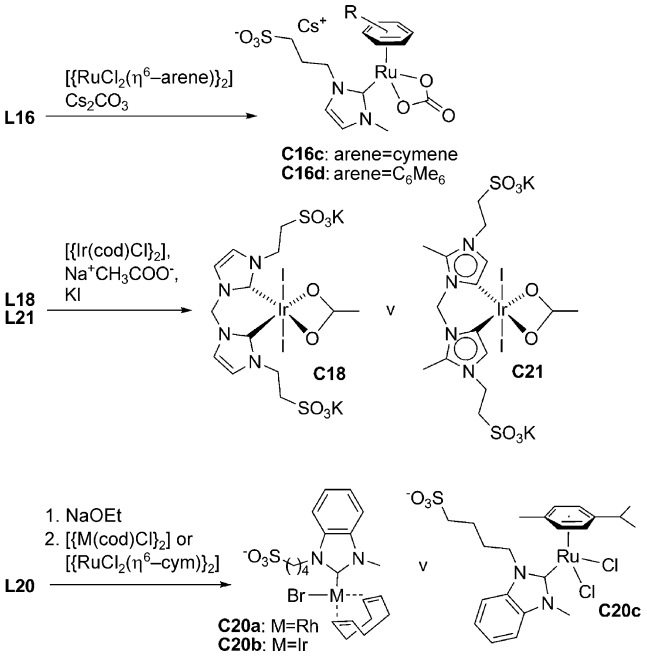
The introduction of water solubility in NHC ligand design through sulfonates is extremely common. Used in detergents and surfactants for more than 70 years,[38] sulfonate groups are known for excellent water solubility arising from their high acidity. As described for imidazolium carbonates, attachment of sulfonates to imidazolium yields zwitterionic compounds, often used in ionic liquids.[39] Almost 40% of all reports retrieved in preparation for this Review, describe NHC ligands equipped with sulfonate groups to enhance the metal complexes' hydrophilic properties. Apart from their ionic character, sulfonate groups are often preferred by virtue of their non-coordinating behavior; at least in most cases.[28,40] Two types of sulfonate functionalization have been described, namely alkylsulfonates and arylsulfonates bound to NHCs.

Alkylsulfonates bound to N-heterocyclic carbene ligands were first described in a patent filed by our group in 1995.[41] Two ways of generating sulfonate-substituted imidazolium salts were described: either through reaction of imidazoles with sodium 2-bromoalkylsulfonate (Scheme 4, **L10**/**L11**) or through cleavage of sultones (**L12**). These routes were soon employed in ionic-liquid synthesis.[42] Over ten years later, the group of Shaughnessy was the first to utilize these routes to generate new ligands for transition-metal coordination, by reaction of variously substituted imidazoles with sodium 2-bromoethanesulfonate or propanesultone (**L13**–**L15**).[28] The propanesultone route became sort of a standard route: sultones were already used to generate mono- and bis(imidazolium), bis(triazolium) or benzimidazolium salts (**L16**–**L20**).[29,43] Furthermore, this route was utilized by Azua et al. to synthesize the first imidazolium precursor for abnormal bis-NHCs (**L21**).[44] In addition, Godoy et al. prepared the first example of a pyridinyl-bridged tridentate imidazolium salt with sulfonate functionalization (**L22**).[43d] But recent examples show, that access to such substituted NHC precursors is not limited to the two described routes. Almassy et al. showed, that a conventional condensation procedure, often applied for symmetrically substituted NHCs,[45] can be applied for dialkylsulfonato NHCs using taurine (**L10**).[43c] Nozaki's group reported ethyl sulfonate functionalization of arylimidazoles through reaction with 1-chloro-2-iodoethane and subsequent anion exchange by addition of sodium sulfite (Scheme 4, **L23**/**L24**).[40]

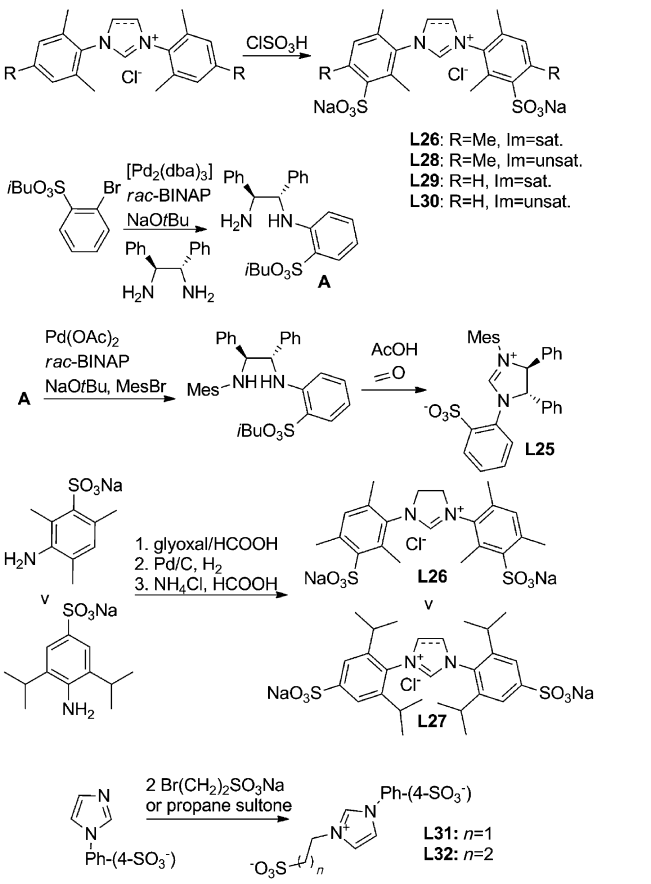
Water-soluble platinum compounds **C10**–**C12** (Scheme 5) are readily available through the reaction of ligand betaines and potassium hexachloroplatinate in water, with concurrent formation of HCl. These compounds exhibit high stability, since even temperatures above 190 °C are tolerated and chromatography with water as eluent is possible.[41] As observed for carboxylate-bound NHCs, silver carbenes functionalized with alkylsulfonates (**C10b**/**C14**/**C16**–**19**) are available through the reaction of ligand precursor salts with silver oxide in water, followed by addition of NaCl.[28,29,43c] Interestingly, the group of Joó reported, that subsequent transfer to Au^I to generate the respective Au compounds gave complex mixtures of the target compounds as well as mono NHC gold chlorides in most cases, although two equivalents of Au precursor were used.[43c] Coordination of alkylsulfonate imidazolylidenes to Pd was described by Moore et al. and performed relatively similarly to the routes described for Pd carboxylate compounds (**C14**). However, due to addition of an equimolar amount of KO*t*Bu, milder reaction conditions were necessary.[28] Indeed, for synthesis of comparable Pd



Scheme 5. Transition-metal complexes of NHC ligands with alkyl sulfonate functionalization. Structures of corresponding ligands **LX** can be found in Scheme 4.[28–29, 40–41, 43, 46]



Scheme 6. Sulfonate-functionalized NHCs bound to various metals by application of different bases. Corresponding ligands **LX** can be found in Scheme 4.[43b, 44, 47]



Scheme 7. Different access routes to various arylsulfonato substituted imidazolium salts.[43c, 48–52] sat. = saturated, unsat. = unsaturated.

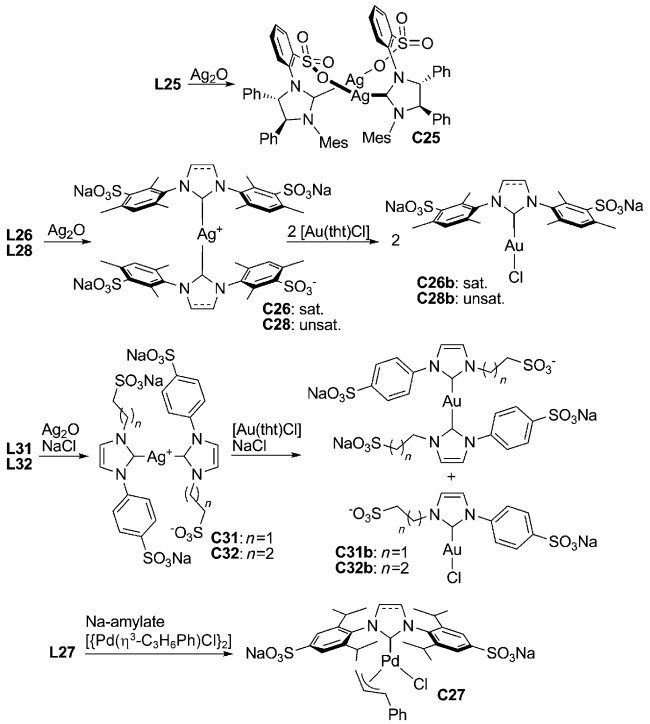
compounds with sulfonate NHCs, Godoy et al. refrained from applying additional bases and hence required more rigorous conditions ($T > 140\,°C$, 12 h, **C16b/C18b/C22**).[43d] Another highly interesting Pd compound was presented by Nagai et al., exhibiting a chelating NHC anchored through its sulfonate group (**C24b**).[40]

The results of Shaughnessy's group exemplify, that bases typically used for carbene generation can be tolerated by sulfonate functionalized NHCs. Indeed, in a very recent publication, Azua et al. used mild bases, such as cesium carbonate or sodium acetate, to synthesize Ru and Ir compounds (Scheme 6, **C16c/C16d/C21/C18**).[44, 47] Furthermore, our group recently demonstrated that sulfonated benzimidazol based NHC complexes can be synthesized by in situ generation of free water-soluble carbenes (**C20**).[43b]

Arylsulfonate-substituted NHCs with excellent solubility in aqueous solvents were presented by many groups, in addition to alkylsulfonate-NHCs. In 2007 Hoveyda's group reported a sophisticated palladium-coupling procedure to yield an unsymmetrical dihydro imidazolium chloride (**L26**) or bis(4-sulfonato-1,3-diisopropylphenyl)imidazo-

lium chloride and the respective dihydroimidazolium chlorides (**L27**) by a conventional condensation route using glyoxal (or the equivalent dioxane-2,3-diol) and triethyl orthoformate.[49] Later, the same group developed an alternative path to generate these and related ligands through direct sulfonation using neat chlorosulfonic acid (**L26**/**L28**–**L30**).[50] Czégéni et al. however showed that oleum can also be applied in this reaction.[51] A different route to arylsulfonate-functionalized NHCs was presented by Almássy et al., who treated the previously described 4-sulfonato-phenylimidazol with 2-bromoethylsulfonate or propansultone (**L31**/**L32**).[43c,52]

Most NHC complexes with arylsulfonate functionalization are synthesized by reaction with Ag_2O in water and subsequent transmetalation. In comparison to the complex mixtures obtained in the transmetalation of **C31** and **C32** to Au^I,[43c] Joó and co-workers were able to isolate solely mono-NHC substituted Au^I compounds in the cases of **C26b** and **C28b** by utilizing two equivalents of [Au(tht)Cl] (tht = tetrahydrothiophene) and switching to MeOH/acetone as reaction medium (Scheme 8).[51] Roy et al. showed, that Pd compounds of this ligand class are also accessible through in situ generation of free carbenes (**C27**).[50]

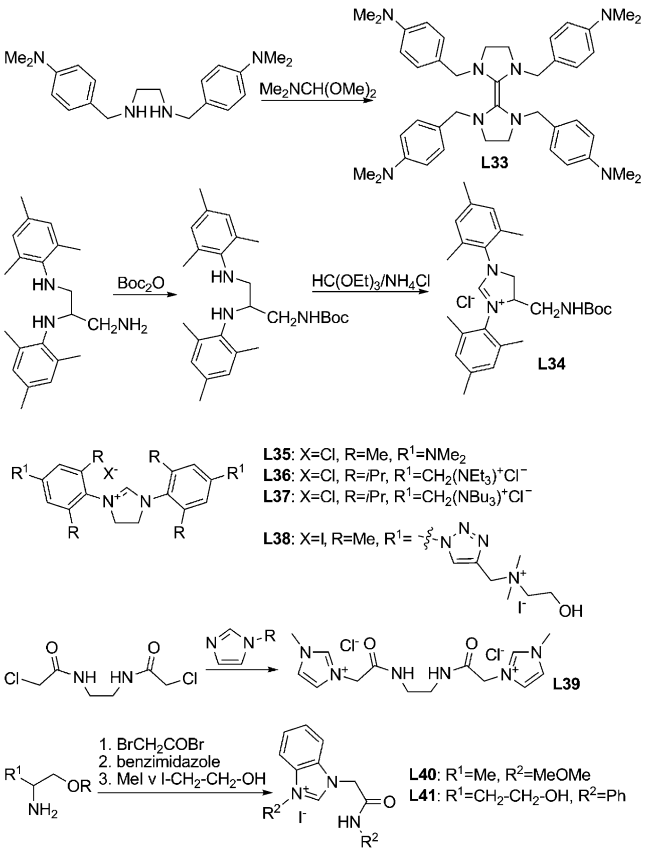


Scheme 8. Group 10 and 11 complexes synthesized from arylsulfonate-functionalized NHC precursors. Structures of respective NHC salts are depicted in Scheme 7.[43c,48–52]

2.3. Amine/Ammonium Functionalization

Another common functionalization of NHCs to obtain water-soluble metal compounds is substitution with amine or ammonium groups. In most cases, amines are quaternized in aqueous environment and the resulting ammonium substituents are expected to improve the hydrophilicity through their polar properties. Another interesting feature of ammonium functionalization is that they often allow pH-sensitive variation of complex solubility. This characteristic can be of vital importance for catalyst/product separation in catalytic applications.

Özdemir et al. were the first to report the synthesis of amine-substituted NHC ligands with the aim of increasing hydrophilicity in the resulting complexes.[53] Interestingly, the ligand precursor employed in this case was not an imidazolium salt but a tetraaminoethene (Scheme 9, **L33**), as

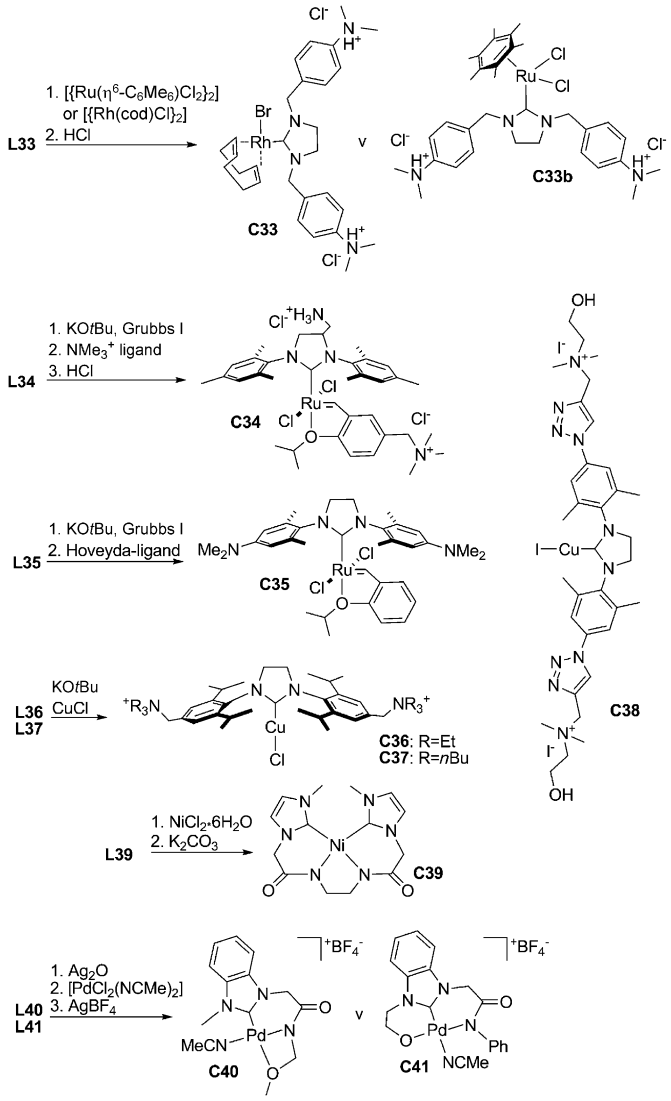


Scheme 9. Various ammonium- and acetamide-functionalized imidazolium salts.[53,55–60]

introduced by Lappert.[54] However, the water solubility of the resulting rhodium and ruthenium complexes was only accomplished after generation of the corresponding ammonium chloride salt. Grubbs and co-workers presented a new approach at solubility enhancement in polar solvents by substituting the NHCs backbone instead of functionalizing N-bound ligands (**L34**).[55] The Boc-protected amine (boc = *tert*-butoxycarbonyl) can be quaternized after carbene coordination to the metal center. This unique method allows electronic and steric fine tuning of the metal center by using unaltered N substituents, while solubility enhancement takes place almost in the outer coordination sphere. Direct substitution of N-aryl substituents was performed by Balof et al. following a conventional condensation route starting from 1,6-dimethyl-4-(dimethylamino)aniline (**L35**).[56] A comparable route was described by Wang et al., who functionalized

diisopropylphenyl substituents with methylene-bridged ammonium chlorides (**L36**/**L37**).[57] By applying a sophisticated click-reaction procedure, Gaulier et al. synthesized triazole-bridged ammonium iodides (**L38**).[58] With synthesis of *N*,*N*′-bis([2-(1-*R*)-imidazolium]acetyl)ethylenediamine (**L39**), Ray et al. reported a new class of precursors for water-soluble bis-NHCs with non-ionic but highly polar ligand design.[59] Simultaneously, Lee et al. presented a related C,N,O-chelating ligand based on benzimidazole and bromo acetamide (Scheme 9, **L40**).[60]

Following the route of Lappert, Ru and Rh compounds were readily synthesized by cleavage of tetraaminoethene. However, Özdemir et al. obtained water solubility only after quaternization with HCl and generated **C33** and **C33b** (Scheme 10).[53] Metathesis precatalysts **C34** and **C35** were isolated after in situ generation of the corresponding free carbene from the respective ligand precursors **L34** and **L35**, a subsequent phosphane exchange reaction at the Grubbs I precursor, and final benzylidene ligand exchange.[55,56] In the case of **C34**, Grubbs and co-workers added a Hoveyda-type ligand with ammonium chloride substitution to increase water solubility. However, the stability of the complex in water is described as being low in this case. As observable in the latter cases, the use of mild and stronger bases for the generation of free carbene intermediates is quite common for amine-substituted NHCs, as demonstrated in the syntheses of Ni and Cu compounds (Scheme 10, **C36**–**C39**).[57–59] Yet, for tridentate NHC ligands bound to Pd, a common Ag_2O carbene transfer method was applied by Lee et al (Scheme 10, **C40**/**C41**).[60]



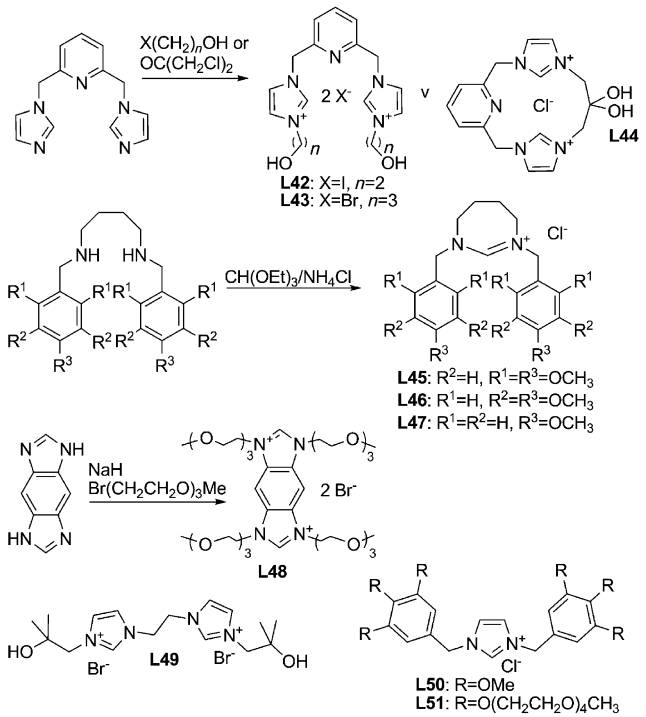
Scheme 10. Various transition-metal complexes synthesized from ammonium- or acetamide-functionalized NHC precursors.[53,55–60]

2.4. Alcohol/Ether Functionalization

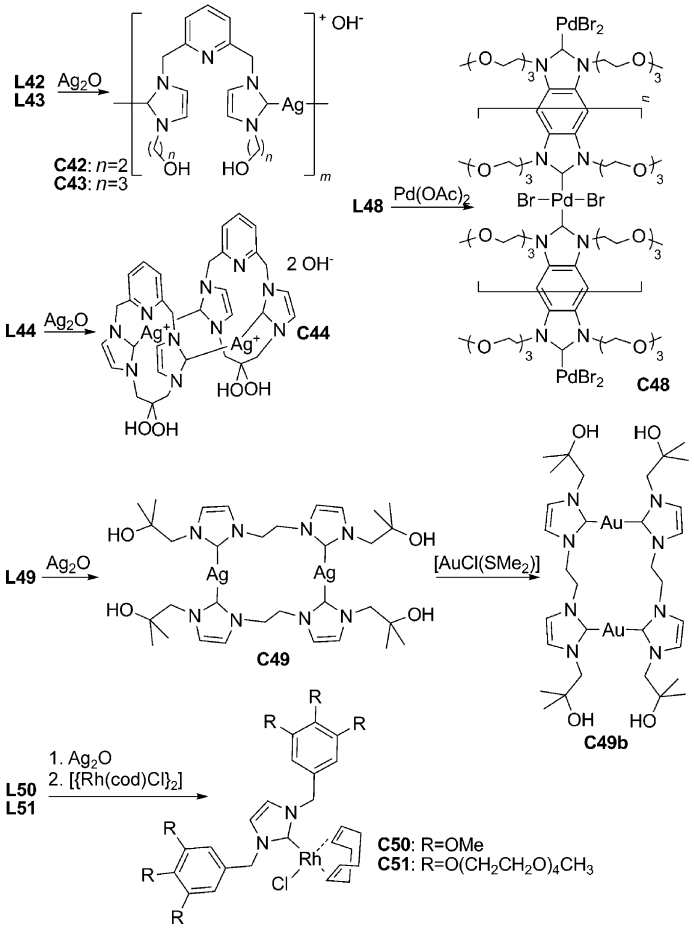
Apart from ionic functionalization as a method for enhancing water solubility, many research groups reported using NHC ligands with strongly polar substituents to enhance the hydrophilicity of their compounds. Even glycol or ether substituents strongly enhance compound polarity, to the extent that the water solubility of the corresponding complexes is accomplished. Although less common than sulfonate or carboxylate functionalized ligands, a variety of compounds with alcohol or ether substituents bound to NHCs has been described.

Youngs and co-workers were the first to report a carbene precursor with such characteristics. By reaction of a pyridinyl-bridged bis(imidazole) with 2-iodoethanol or 3-bromopropanol, alcohol-substituted bis(imidazolium) salts **L42** and **L43** could be obtained.[61] Later, the same group described a related cyclic carbene precursor, which was synthesized through the reaction of previously mentioned bis(imidazole) and 1,3-dichloroacetone (Scheme 11, **L44**).[62] In a typical ring-closing reaction, Özdemir et al. synthesized tetrahydrodiazepinium ligands from variously substituted dibenzylbutane-1,4-diamines (**L45**–**L47**).[63] A ligand motive reminiscent of the these ligands was synthesized by Tsuji and co-workers. However, apart from simple methoxy groups at the benzyl ligands, also tetraethyleneglycol monomethyl ether groups were employed (**L50**/**L51**).[64] Karimi et al. used triethyleneglycol to functionalize their Janus-type ligand (**L48**).[65]

Given the observed behavior of free carbenes to form alcohol adducts,[26a] it is not surprising that no metal complex synthesis via free intermediates has been reported in this area. In all the cases described to date, metal compounds are formed through the reaction of carbene precursor salt and metal precursors equipped with internal base, such as Ag_2O or $Pd(OAc)_2$. Through this route, Youngs and co-workers isolated polymeric silver carbene compounds with ethoxy or propoxy substituents (Scheme 12, **C42**/**C43**).[61] As soon as the employed ligand precursors were replaced with a cyclic alternative (**L44**), only a dimeric congener was produced from the reaction with silver oxide in water (**C44**).[62] Cure et al. also synthesized dimeric silver carbenes without polymer generation. As reported by the same group for carboxylate NHC gold compound **C4b**, transmetalation in deoxygenated water was also possible in the case of **C49b**, although formation of Au nanoparticles can be observed.[30] Another polymeric structure was presented by Karimi et al., who



Scheme 11. Alcohol-, ether-, and polyether-functionalized imidazolium salts.[30,61–64,65b]



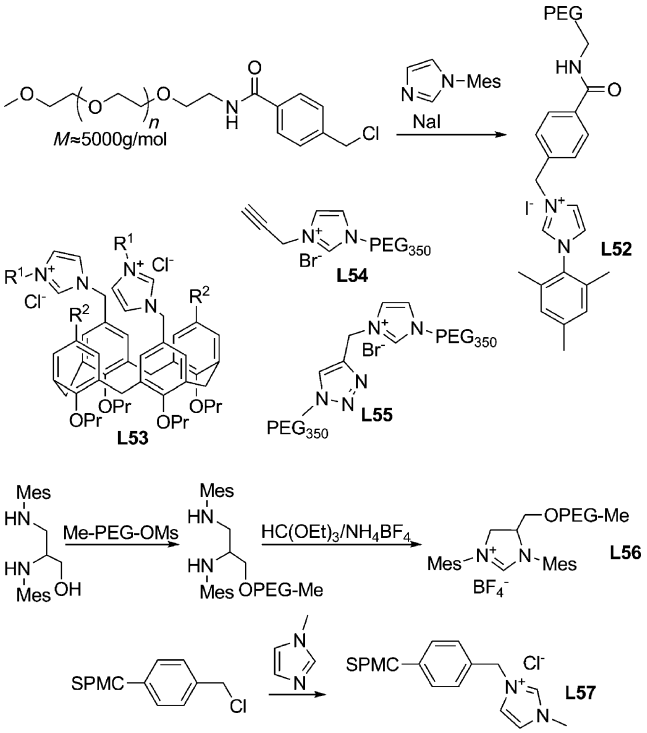
Scheme 12. Metal complexes incorporating alcohol- or ether-functionalized NHC ligands. Corresponding ligands are depicted in Scheme 11.[30,61–64,65b]

synthesized a centipede-like water-soluble Pd compound in the reaction of Janus-type ligand **L48** and $Pd(OAc)_2$.[65b]

2.5. Water-Soluble Macrocycle/Polymer Functionalization

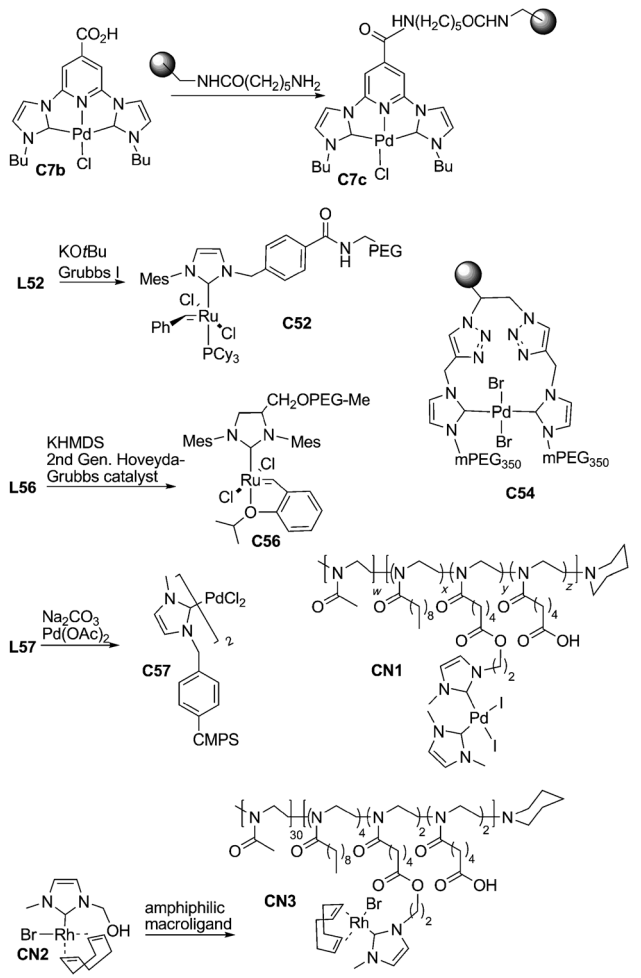
Although this Review does not focus on immobilized ligand systems, NHC metal complexes bound to water-soluble polymers should be discussed.[66] However, these polymeric-support-based NHC complexes are active catalysts in the homogeneous phase, so they must be viewed in contrast to heterogeneous systems, such as silica or zeolite anchored catalysts.[67]

In terms of synthesis, two routes are generally followed. In some examples, NHC precursor salts equipped with a polymer are synthesized before coordination to the transition metal (Scheme 13). The alternative route is to isolate functionalized



Scheme 13. Polymer- or macrocycle-bound imidazolium salts.[68]

NHC complexes first and connect these to polymers through their functional groups in the subsequent steps. Weberskirch and co-workers followed the latter route and synthesized a Rh complex with alcohol-functionalized NHC (Scheme 14, **CN2**; "**CN**" denotes complexes equipped with potentially water-soluble ligands not described or depicted earlier in the Review). Subsequently, a poly(2-oxazoline), which has amphiphilic characteristics, was bound to the metal complex through the NHC's ethoxy group yielding polymer precatalyst **CN3**.[68a] Concurrently, the same research groups reported the related palladium-Pd based polymer catalyst **CN1**. However, in this case, first the corresponding Pd compound with oxazoline functionalized side chain was isolated, and then, the polymer-bound compound was obtained by polymeri-

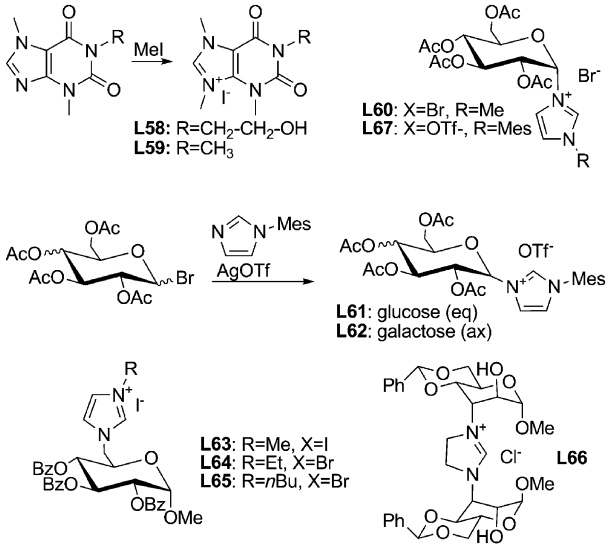


Scheme 14. NHC complexes anchored to water-soluble polymers. Structures of corresponding NHC precursor salts LX can be found in Scheme 13.[68]

zation of 2-methyl-2-oxazoline and the oxazoline NHC Pd complex.[68e] Steel and co-workers connected isonicotinic acid derived **C7b** to an amino-terminated polymer resin (**C7c**).[68j] Gallivan et al. followed a different route to access a polymer-bound NHC complex. Initially, poly(ethylene glycol) N-functionalized ligand precursor **L52** was prepared. After deprotonation using KO*t*Bu, the free carbene intermediate replaces PCy_3 in the Grubbs I complex, to yield **C52**.[68g] The same research group also described another metathesis precatalyst, in which the NHC moiety is functionalized at the ligand backbone with a poly(ethylene glycol) polymer (**C56**), comparable to ammonium functionalized **C34** (Scheme 10).[68c] Again, this type of design is advantageous, since full functionality of the NHC's N-substituents can be preserved. Brendgen et al. synthesized a variety of macrocyclic calix[4]arene based NHC ligands (Scheme 13, **L53**) for application in aqueous catalysis, however they did not isolate a metal-bound example.[68h] Meise et al. also incorporated a macrocycle in their ligand design and isolated poly(ethylene glycol) bound Pd compounds, such as **C54**.[68b] Finally, Byun et al. were able to synthesize a polymer-substituted Pd complex by reaction of precursor salt **L57** with $Pd(OAc)_2$ and Na_2CO_3 in water/DMF (Scheme 14, **C57**).[69]

2.6. Natural-Product-Based Functionalization

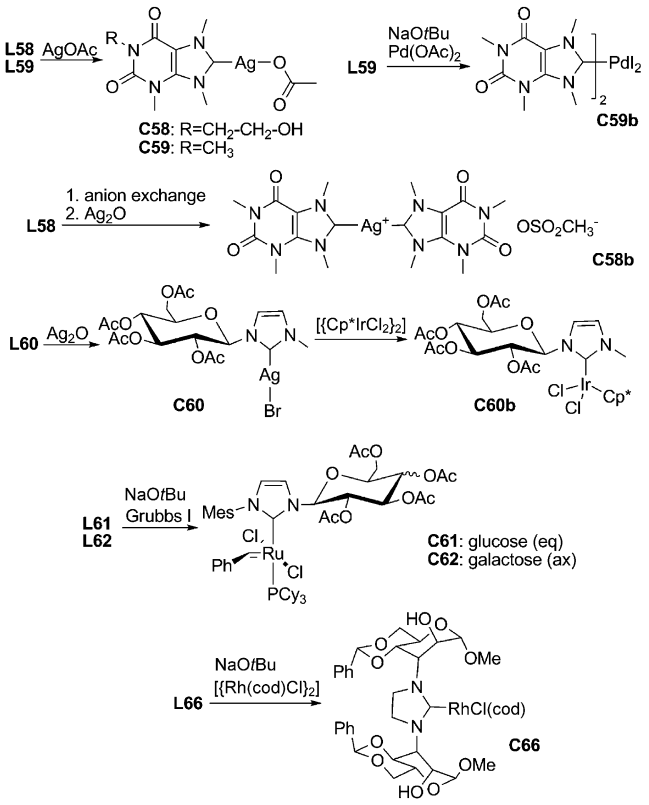
Clearly, natural products very often exhibit excellent water solubility. For example, an equilibrated mixture between alpha and beta glucose exhibits solubility of 51 wt% at 25 °C,[70] and also caffeine is highly soluble in boiling water (66 g/100 mL).[71] Therefore, it seems only consistent to induce water solubility of transition-metal complexes through ligand functionalization with natural products, such as sugar or caffeine derivatives. Although a variety of carbohydrate-containing metal compounds has been synthesized,[72] NHC functionalization with carbohydrates is relatively scarce. The same is true for caffeine-based NHCs, although this ligand class is quite easily available through methylation of the purine heterocycle (Scheme 15, **L59**).[73]



Scheme 15. Natural-product-based imidazolium salts as precursors for water-soluble NHC compounds.[26b,74]

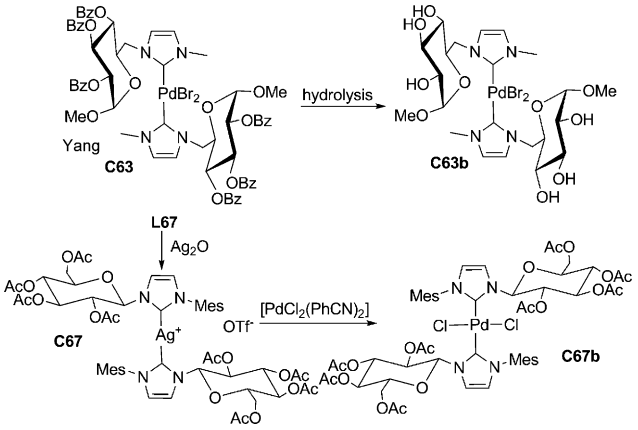
Water-soluble caffeine-based NHC complexes were first reported by the group of Youngs.[74a] After N-methylation (Scheme 15, **L59**), the NHC precursor was treated with Ag_2O in water to give the respective Ag compound **C59** (Scheme 16).[74b] Later, the same research group further varied this ligand class by ethoxy substitution of theobromine to yield ligand **L58**. Following a reaction with AgOAc, metal complex **C58** was isolated.[74c] Luo et al., however, synthesized Pd compound **C59b** by using $Pd(OAc)_2$ as the metal precursor in combination with NaO*t*Bu.[74d]

Early reports of sugar-incorporated NHC ligands bound to transition-metal complexes came from Nishioka and Kinoshita, Glorius and Shi. Nishioka and co-workers produced ligand **L60** by using methylimidazole and 2,3,4,6-tetra-*O*-acetyl-(*R*)-D-glucopyranosyl bromide as starting materials



Scheme 16. Transition-metal complexes synthesized from natural-product-based imidazolium salts.[26b,74]

(Scheme 15). The corresponding silver complex **C60** was readily prepared from **L60** and silver oxide in acetone. This compound could be employed as transfer reagent to give the respective iridium compound **C60b** (Scheme 16).[74e] Shi et al. incorporated glycopyranoside moieties at both N substituents of a saturated NHC (**L66**). Subsequent deprotonation in the presence of [{Rh(cod)Cl}$_2$] yielded Rh compound **C66**.[74f] In addition to the metal complex, they were able to isolate the related H_2O adduct of **L66** as a side product. The yield of this side product strongly depended on the dryness of **L66**. Yet, adducts of sterically crowded alcohols have been observed for saturated NHCs.[26b] Hence, generation of free saturated NHCs in the presence of alcohol-containing carbohydrates is probably less effective and the conventional carbene-transfer methods might be preferable.[26b] However, Grubbs and co-workers exchanged PCy_3 in the Grubbs I precatalyst for a glucose- or galactose-functionalized NHC through in situ generation of free carbenes (**C61**/**C62**).[75] Glorius and co-workers followed a more conventional Ag_2O route to prepare **C67** in excellent yield (Scheme 17). By carbene transfer, a bis-NHC Pd compound was isolated (**C67b**).[76] Interestingly, Yang et al. gave water solubility to their complexes through ligand hydrolysis after metal complexation—comparable to the route presented by our group in 1997 (Scheme 1, **C2**, Scheme 17, **C63b**).[27,77] In their report, the benzoyl-substituted glucopyranoside moiety was hydrolyzed by addition of NaOMe in MeOH and then HBr to give a water-soluble precatalyst for Suzuki coupling.

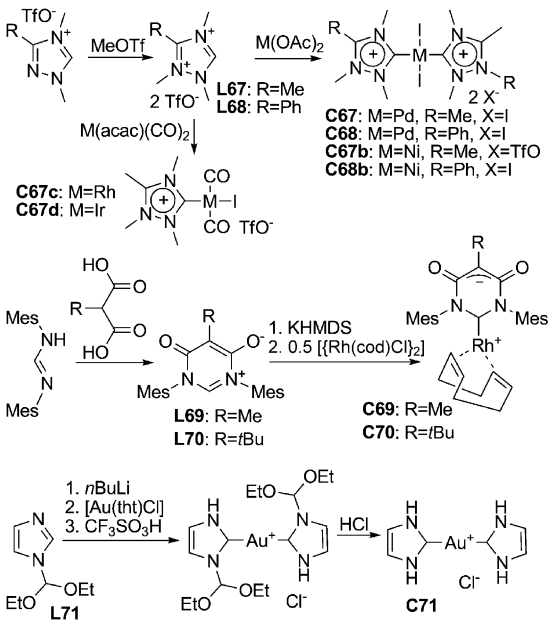


Scheme 17. Sugar-incorporated NHC transition-metal complexes.[76,77]

2.7. Charged Ligands and Proton Functionalization

In all the previously described reports, water solubility of NHC transition-metal complexes was caused by ionic or highly polar substituents bound to the N-heterocycle. Therefore, the following reports are fairly exotic, since two examples describe water solubility that is derived from additional charges located inside the N-heterocycle and one publication describes high water solubility of a proton-N-functionalized NHC. Triazolylidenes could also be described at this point, because these ligands were recently suspected to reveal zwitterionic character under aqueous conditions.[78] However, the following section is limited to complexes with charged NHC ligands, where water solubility is actually mentioned.

Bertrand and co-workers prepared twofold positively charged ligands by additional methylation of a trisubstituted 1,2,4-triazolium salt (Scheme 18, **L67**). Reaction with metal



Scheme 18. Charged or protic NHC ligands and their NHC complexes.[79,80,82]

precursors containing internal bases yielded water-soluble compounds **C67** and **C68**.[79] Although the triazolium-5-ylidene ligands exhibited a positive charge when bound to the metal, their behavior was comparable to conventional NHCs. Crystal structure data and NMR spectroscopy data further supported this observation. The antagonist to positively charged NHCs was prepared by César, Lavigne et al., who prepared pyridinium-based betaines **L69**/**L70** and the corresponding complexes **C69** and **C70**, in which the N heterocycle was negatively charged.[80]

In his early report of a water-soluble complex containing NHCs, Sundberg also envisioned a double proton substituted NHC as an intermediate, responsible for a rapid D_2O exchange.[21] Although Hahn previously reported metal compounds bound to "NHNH" NHCs, solubility in water was not described.[81] Recently, Kunz et al. coordinated such a NHC to Au and were able to isolate the highly water-soluble complex **C71**.[82]

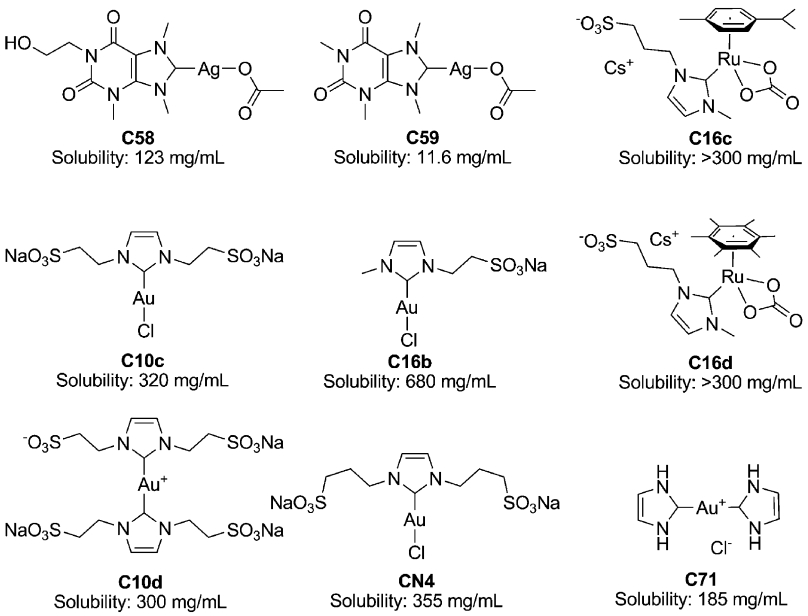


Figure 2. Solubility in neat H_2O of transition-metal complexes with water-soluble NHC ligands.[43c,47,74b,c,82]

3. Properties of Metal Complexes with Water-Soluble NHCs

3.1. Water Solubility

Certainly, water-solubility of NHC complexes is the prime objective of all the described functionalization strategies. In their reports, most research groups describe their compounds as "well soluble" or "highly soluble" in water. Clearly, this information is less useful without direct quantification. Yet, only a few groups reported precise measurements of their metal compounds' solubility properties.

The water solubility of caffeine-derived silver carbene **C59** was reported by Youngs and co-workers to be limited to 11.6 mg mL^{-1} (Figure 2).[74b] Searching for further functionalization to enhance the solubility, the same group soon reported the theobromine derivative **C58**. Through the new ethoxy functionalization at N1, solubility could be raised significantly to a more satisfactory 123 mg mL^{-1}.[74c] Peris and co-workers did not provide exact data of their compounds' solubility properties, however, they described the two Ru compounds **C16c** and **C16d** to exhibit solubilities above 300 mg mL^{-1}.[47] The "NHNH" NHC Au compound **C71**, presented by Kunz et al., was reported to have a solubility of 185 mg mL^{-1}.[82] Finally, Joó and co-workers measured solubility for a variety of Au compounds (**C10c**/**C10d**/**C16b**/**CN4**; "CN denotes complexes equipped with potentially water-soluble ligands not described or depicted earlier).[43c] It is remarkable that the compound exhibiting highest solubility in water was not substituted with two sulfonate groups (as in the other compounds **C10c**/**C10d**/**CN4**), but only had one ethyl sulfonate- and one methyl-substituent (**C16b**).

As a matter of fact, solubilities of transition-metal complexes bound to NHCs with various substitution patterns vary dramatically. Researchers referring to their compounds as "highly soluble" may do so because of earlier, more dissatisfying results. Therefore, future research in this area should always include solubility measurements to present a more complete characterization of a new compound's properties to the reader. The astonishing example from Joó and co-workers (Figure 2, **C10c** vs **C16b**), in which a reduction in sulfonate functionalization leads to higher solubility should be reason enough to include solubility measurements in any experimental part when synthesizing new water-soluble NHC compounds.

3.2. Influence of Functionalization on ^{13}C NMR Resonances

NHC-based catalyst systems can be varied in at least three ways: First of all, the choice of metal dominates catalyst properties and application. In addition, these properties can be further defined through choice of the NHC ligands' donor capacity and steric demand. Furthermore, solubility adds another way to vary the homogeneous catalyst system. In custom-tailored catalyst synthesis, it is imperative to balance these dimensions precisely to leverage the desired characteristics. Accordingly, profound knowledge of the influence of water-soluble substituents on any of these factors is crucial for future work. Fundamental research in this area has yet to be undertaken.

The established method for estimation of the NHC ligands' donor strength is the comparison of IR bands in Ir or Rh complexes, such as [Ir(NHC)(CO)$_2$Cl] or [Rh(NHC)(CO)$_2$I].[13a–c] However, in the case of water-soluble NHC ligands bound to metal complexes, only a few Rh and Ir compounds have been described, let alone the corresponding CO complexes synthesized. Therefore, to date, it is not possible to estimate the influence of water-soluble functionalization on NHCs donor strengths.

Nevertheless, a few compounds have been reported, which are akin to metal complexes without water-soluble

functionalization. On that account, a comparison between ^{13}C NMR resonance signals for the carbene carbon atom of metal complexes bound to NHC substituents with or without improved water-solubility through functionalization is possible (Table 1).

It has to be noted, that differences in ^{13}C NMR carbene chemical shifts are generally not strongly pronounced in Au^{I} NHC complexes, although variation is observable.[87] ^{13}C NMR carbene resonances for dimethyl-substituted ($CDCl_3$: $\delta = 171.8$ ppm; DMSO: $\delta = 169.9$ ppm), diethyl-substituted ($CDCl_3$: $\delta = 169.5$ ppm), dibutyl-substituted ($CDCl_3$: $\delta = 169.9$ ppm), and variously alkylsulfonate-substituted imidazoles (D_2O: $\delta = 166.0$ ppm–168.1 ppm) are nearly identical. Most strikingly, the substitution of one methyl group in **C16b** (Table 1, D_2O: $\delta = 166.9$ ppm) by another propylsulfonate group in **CN4** (D_2O: $\delta = 167.1$ ppm) has a negligible effect on the ^{13}C carbene resonance.[43c]

In conclusion, it may be estimated, that alkylsulfonate- or arylsulfonate-substitution at N-substituents, as well as polymer-functionalization of the backbone, do not have any significant influence on NHC ligands' ^{13}C NMR carbene resonances or on the carbene–metal bond. However, these results are not unexpected, the polar groups of the all ligands examined are electronically insulated from their corresponding carbene carbon atoms.

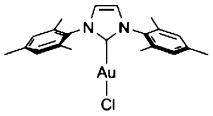
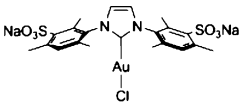
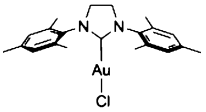
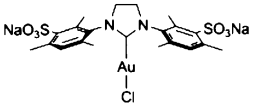
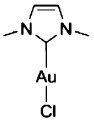
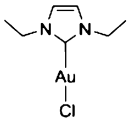
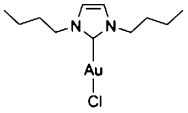
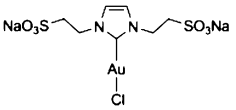
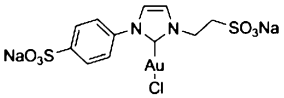
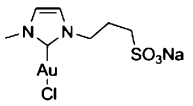
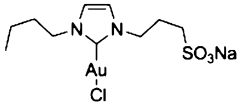
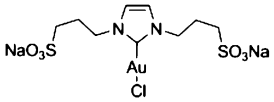
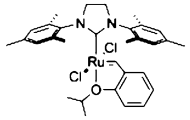
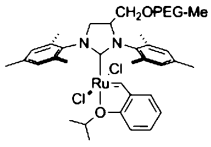
4. Applications of Metal Complexes with Water-Soluble NHCs

The catalytic ability of NHC complexes has been thoroughly examined within the last two decades and great potential was found in hydrosililation,[88] olefin metathesis,[14d,17e,89] hydroformylation,[90] hydrogenation,[91] various C–C coupling reactions,[92] and hydrogen transfer.[93] Therefore, it is only consistent to examine the catalytic abilities of newly synthesized water-soluble NHC compounds.

Indeed, most publications covered in this Review describe catalytic or medicinal studies of the transition-metal NHC complexes, since the advantages of water-soluble metal complexes for these applications are evident. For catalytic application, easy product–catalyst separation represents the main benefit of water-soluble transition-metal complexes: While the catalyst is highly soluble in water or ionic liquids, reaction products can be obtained by extraction using another, less-polar solvent.[94] This research area has seen dramatic growth throughout the last decade, certainly initiated through Ruhrchemie/Rhône–Poulenc's oxo process.[95]

While medicinal application of silver complexes equipped with water-soluble NHC ligands (i.e. their antimicrobial activities and cytotoxicity) has been described in Youngs extensive Review,[19b] the following Sections thus describe advances in catalytic applications of transition-metal complexes with water-soluble NHCs.

Table 1: Comparison of ^{13}C NMR resonances of various metal compounds, with or without water-soluble groups.

Compound		^{13}C NMR, (NCN)	Ref.
	[Au(IMes)Cl]	173.4 ($CDCl_3$)	[83]
	**C28b**	172.8 (MeOH/D_2O)	[51]
	[Au(SIMes)Cl]	195.0 ($CDCl_3$)	[83]
	**C26b**	194.9 (H_2O/D_2O)	[51]
	[Au(Me_2Im)Cl]	171.8 ($CDCl_3$), 169.9 (DMSO)	[84]
	[Au(Et_2Im)Cl]	169.5 ($CDCl_3$)	[85]
	[Au(nBu$_2$Im)Cl]	169.9 ($CDCl_3$)	[84a]
	**C10C**	168.1 (D_2O)	[43c]
	**C31b**	166.0 (D_2O)	[43c]
	**C16b**	166.9 (D_2O)	[43c]
	**C17b**	166.9 (D_2O)	[43c]
	**CN4**	167.1 (D_2O)	[43c]
	**CN5**	Alkylidene: 296.8 NHC: 211.1 ($CDCl_3$)	[86]
	**C56**	Alkylidene: 296.5 NHC: 213.3 (CD_2Cl_2)	[68c]

4.1. Suzuki Coupling

Almost without exception, all reports presenting new Pd compounds with water-soluble NHCs test the catalytic abilities of their complexes in Suzuki–Miyaura coupling of organic halides and organoboron reagents. Developed by Nobel Prize laureate Akira Suzuki, this type of reaction is certainly one of the most powerful synthetic tools for the C–C coupling of biaryls.[96] However, testing of new Pd catalysts in Suzuki reactions is generally not considered to be a useful benchmark, as it was found, that even ligand-free Pd salts catalyze the reaction between arylbromides and phenylboronic acid in water.[97] Furthermore, even traces of Pd (for example 20–50 ppb of Pd can be found in "ultrapure" Na_2CO_3) can catalyze this reaction under tolerable conditions (150 °C).[98] For these reasons, results must be treated with caution, unless less-reactive substrates, such as arylchlorides are used.[99] Recently, a NHC-based catalyst that is highly active under non-aqueous conditions was reported by Nolan's group. In the room-temperature catalyzed coupling reaction between 4-chlorotoluene and phenylboronic acid, [{Pd(μ-Cl)Cl(NHC)}$_2$] gave yields of up to 99% within 0.5 h at catalyst loadings of 1 mol%.[100]

One palladium-catalyzed reaction tested in almost all articles, was the substrate combination of 4-halidoanisole and phenylboronic acid. Therefore, Table 2 provides an overview of catalysts able to catalyze this reaction, the corresponding reaction conditions, and yields.

More than one third of the catalysts tested were reported to catalyze reactions between less-activated arylchlorides and phenylboronic acid in water or solvent mixtures. Depending on the catalyst, reaction temperatures and reaction times varied significantly. Full conversion was only observed by Fleckenstein et al. after 12 h at 100 °C. Yet, in this case tolylboronic acid was utilized as coupling reagent (Table 2, entry 4).[49] Probably the most intriguing result was presented by Karimi et al., who reported a yield of 74% for this reaction after 30 h at room temperature in neat water. Just 0.1 mol% of their triethylene glycol legged, "centipede-like" Pd catalyst **C48** was sufficient. Even more significant, the catalyst could be recycled 17 times without any observable loss in activity.[65b] Türkmen et al. used catalyst **CN6** (Figure 3), to obtain

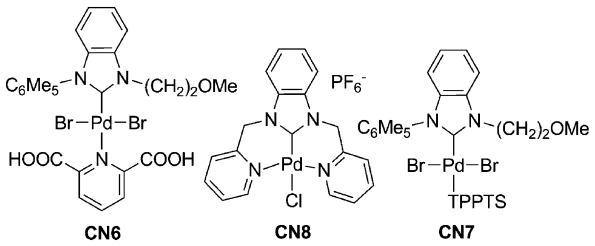
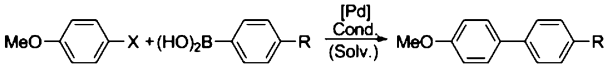


Figure 3. Pd catalysts utilized in aqueous Suzuki coupling.[101–103]

a GC yield of 89% in the reaction between 4-chloroanisole and phenylboronic acid after 4 h at 100 °C in water (Table 2, entry 2).[102] This result is interesting, as it is comparable to the result obtained the same research group using catalyst **CN7** (Figure 3), equipped with TPPTS (TPPTS = 3,3′,3″-phosphinidynetris(benzenesulfonic acid) trisodium salt). Although water solubility should be further improved by the TPPTS ligand, no improvement in yields can be detected (Table 2, entry 1).[101] As previously mentioned, the results for the catalyzed coupling reaction between arylboronic acids and arylbromides (Table 2, entries 8–17) provide less-conclusive results. As a matter of fact, conditions vary significantly: Catalyst loadings between 1.0 mol% and 0.005 mol% were

Table 2: Overview of Suzuki coupling reactions carried out using water-soluble NHC catalysts.



Entry	Catalyst	X	R	Solv.	Conditions	Yield [%]	Ref.
1	**CN7**	Cl	H	H_2O	1 mol% [Pd], K_2CO_3, 100 °C, 4 h	88[b]	[101]
2	**CN6**	Cl	H	H_2O	1 mol% [Pd], KOH, 100 °C, 4 h	89[b]	[102]
3	**C48**	Cl	H	H_2O	0.1 mol% [Pd], K_2CO_3, RT, 30 h	74[a]	[65b]
4	**L26** + Na_2PdCl_4	Cl	Me	H_2O	1 mol% [Pd], KOH, 100 °C, 12 h	99[b]	[49]
5	**L45** + 0.5 $Pd(OAc)_2$	Cl	H	H_2O/DMF 1:1	1 mol% [Pd], K_2CO_3, 60 °C, 0.5 h	77[a]	[63]
6	**C16b**	Cl	H	H_2O/*i*PrOH 1:1	1 mol% [Pd], K_2CO_3, 110 °C, 12 h	35[b]	[43d]
7	**C27**	Cl	Me	H_2O/*n*BuOH 1:1	0.1 mol% [Pd], KOH, 100 °C, 12 h	80[a]	[50]
8	**C6b**	Br	H	H_2O	0.1 mol% [Pd], K_2CO_3, 100 °C, 6 h	95[a]	[31]
9	**CN1**	Br	H	H_2O	0.1 mol% [Pd], KOH, 110 °C, 0.5 h	90[b]	[68f]
10	**C8b**	Br	H	H_2O	0.01 mol% [Pd], K_2CO_3, 100 °C, 2 h	87[c]	[33]
11	**CN8**	Br	H	H_2O	0.1 mol% [Pd], Cs_2CO_3, 100 °C, 2 h	96[b]	[103]
12	**C48**	Br	H	H_2O	0.05 mol% [Pd], K_2CO_3, RT, 18 h	88[a]	[65b]
13	**C7**	Br	H	H_2O	0.1 mol% [Pd], K_2CO_3, 100 °C, 2 h	99[c]	[32]
14	**L51** + [{Pd(η^3-C_3H_5)Cl}$_2$]	Br	H	THF	1 mol% [Pd], KO*t*Bu, KF, 65 °C, 15 h	53[a]	[64]
15	**C57**	Br	H	H_2O/DMF 1:1	0.01 mol% [Pd], Na_2CO_3, 50 °C, 12 h	69[a]	[69]
16	**C16b**	Br	H	H_2O/*i*PrOH 1:1	1 mol% [Pd], K_2CO_3, 110 °C, 4 h	86[b]	[43d]
17	**C9**	Br	H	H_2O/MeOH 1:1	0.005 mol% [Pd], K_2CO_3, 100 °C, 3 h	99[a]	[34]

[a] Yield of isolated product. [b] GC yield. [c] Yield determined by NMR spectroscopy. [d] Catalyst deprotonated and dehalogenated in pyridine, TBAB (TBAB = Tetra-*n*-butylammonium bromide) added.

applied with temperatures between room temperature and 110 °C.

4.2. Other C–C Coupling Reactions

Apart from *S*uzuki–Miyaura, other powerful palladium-catalyzed C–C coupling methods were tested with water-soluble NHC complexes, namely the Heck[104] and the Sonogashira reaction.[105] Schönfelder et al. examined the reaction, originated from recent Nobel Prize awardee Richard Heck, utilizing a congener of Pd NHC based polymer **CN1** (Scheme 14). As substrates, iodobenzene and styrene were employed. *trans*-Stilbene could be obtained in yields above 93% within 1.5 h at 90 °C, leading to turnover frequencies (TOFs) of 570 h^{-1}. Recycling experiments were conducted and minor loss in activity could be observed.[68e] Later, the same group described application of **CN1** and related compounds in Heck reactions with a more advanced substrate library. At catalyst loadings of 0.7 mol%, yields over 93% could be obtained within 1.5 h at 90 °C.[68f] Applying caffeine-derived water-soluble catalyst **C58c**, Luo et al. examined the reaction between 4-bromoacetophenone and methyl acrylate in neat water. Using catalyst loadings of 2 mol%, satisfactory yields of up to 92% were obtained after 12 h at 90 °C.[74d] However, other known homogeneous catalyst systems operating under non-aqueous conditions have been reported to show high activities, even with arylchlorides as substrates. For comparison, one of the most active NHC-based systems was recently described by Lee et al. Their amido-functionalized complex allows the reaction between 4-chloroacetophenone and styrene to be conducted at 120 °C, giving yields of 40% in DMA (DMA = dimethylacetamide) or 99% in an ionic liquid within 2 h.[106] However, effective utilization of arylchlorides as substrates in the Heck reaction at room temperature is to date limited to phosphane-based systems.[107]

Luo et al. also reported the examination of catalyst **C58b** in Sonogashira coupling. Again, a catalyst loading of 2 mol% was used in the reaction between 4-bromonitrobenzene and phenylacetylene. With potassium hydroxide as the base, product could be isolated in yields of up to 96%.[74d] Furthermore, Plenio and co-workers reported the application of an arylsulfonate functionalized ligand **L27** in combination with sodium tetrachloropalladate for a Sonogashira coupling. A variety of substrates were tested.[50] With a catalyst loading of only 0.25%, significant results could be obtained in the reaction between 2-chloropyridine and different alkynes, superior to previous reports.[108] For example, Yang et al. were able to isolate product in a yield of 29% in the reaction between 2-chloropyridine and phenylacetylene within 24 h at 80 °C in DMA, employing 1 mol% of Pd catalyst, while Plenio and co-workers obtained a yield of 94% within 12 h at 90 °C in the same reaction using a solvent mixture of H_2O/*i*PrOH 1:1.[50]

4.3. Hydrosilylation

A few research groups also reported application of their water-soluble platinum- or rhodium-based NHC catalysts in hydrosilylation.[109] For the hydrosilylation of cyclohexanone, Ohta et al. used **C51** as catalyst, in which a triethyleneglycol functionalized NHC is bound to Rh. In various solvents, yields of up to 61% could be obtained at room temperature in 3 h, using diphenylsilane and a catalyst loading of 0.5 mol%.[64] Under nearly the same conditions, Virboul et al. reported 72% yield in 3 h in methylene chloride as the solvent, utilizing catalyst **CN11**.[110] However, both reports did not test the hydrosilylation reaction in water, in contrast to Flores and Jesús' report. In this case, two Karstedt-type catalysts with sulfonate functionalized NHCs were prepared (Figure 4, **CN9**/**CN10**). Hydrosilylation was carried out at 30 °C in neat water, using 1-octyne and various silanes at catalyst loadings between 0.5 mol% and 0.1 mol%. Yields of up to 94% could be isolated within 6 h at 30 °C. In comparison to other homogeneous NHC systems operating under water-free conditions, these results are notable. For example, Markó's group reported for their closely related IPr-NHC based Pt catalyst yields of 93% for the reaction between 1-octyne and dimethylphenylsilane within 0.1 h at 60 °C and a catalyst loading of 0.1 mol%.[111] However, even more significant in Flores and Jesús' report is the observed catalyst stability. **CN9** and **CN10** were tested in recycling experiments, together with the original Karstedt's catalyst. While significant losses in Karstedt catalyst's reactivity were observed, the two NHC-Pt species showed far higher stability.[46]

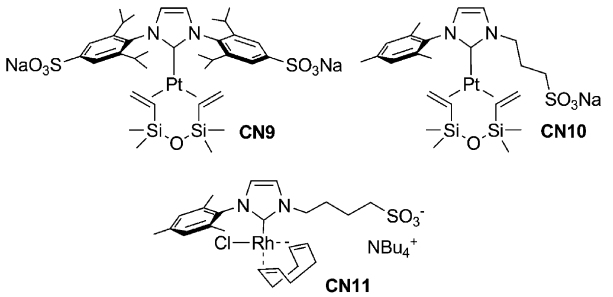


Figure 4. Hydrosilylation catalysts prepared by Silbestri et al.[46,110]

4.4. Hydrogenation

Yet another possible application of water-soluble Ru NHC complexes is for hydrogenation in aqueous solvents.[112] Our group recently reported results for the aqueous hydrogenation of acetophenone catalyzed by Ru compound **C20c** (Scheme 6). At room temperature and under a hydrogen pressure of 40 bar, good yields of up to 87% could be obtained after 21 h with a catalyst loading of 2.5 mol%.[43b] Csabai et al. also reported hydrogenation of acetophenone in water, using a water-soluble NHC catalyst without NHC functionalization to improve solubility. With a catalyst loading of only 0.7 mol%, up to 46% conversion is reached.

However, it must be emphasized, that H_2 pressure was as low as only 10 bar.[113]

Recently, Peris and co-workers reported reduction of CO_2 to potassium formate in neat water, catalyzed through sulfonate-functionalized Ir catalysts **C18** and **C21** (Scheme 6). Additionally, the *n*Bu-substituted congener of **C18** and **C21** was tested in comparative studies. At a pressure of 60 bar (H_2:CO_2, 1:1) and 80 °C, the *n*Bu-substituted compound gave a TON of 243, while for **C18** (TON: 1247) and abnormal NHC substituted **C21** (TON: 1663) far higher values could be observed. From these observations it can be concluded, that in these reactions water solubility is vital to prevent catalyst deactivation.[44] Under more rigorous conditions, enormous TONs of up to 190000 could be reached (200 °C, 75 h, a "background" concentration of formate formed without catalyst has been subtracted from the values obtained), which are among the best values reported in this area.[114]

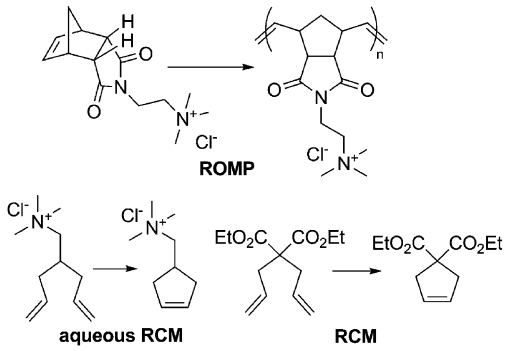
4.5. Olefin Metathesis

The metathesis reaction between olefins is one of the most interesting transition-metal-catalyzed reactions for the chemical industry. Clearly for water-based applications, ruthenium-based catalyst systems are preferred because of their high stability.[115] Water-soluble catalyst systems are convenient for metathesis between polar substrates. In addition hydrophilic systems are beneficial for easy catalyst removal from non-polar reaction solutions. Research groups working in this area have developed a whole variety of NHC-based water-soluble catalysts to benefit from both advantages.

Gallivan et al. tested the poly(ethylene glycol) N-anchored catalyst **C52** (Scheme 14) in a ring-opening metathesis polymerization (ROMP) reaction in D_2O, using a sterically hindered *endo*-norbornene with ionic substituents as substrate (Scheme 19, ROMP). Activity was high compared to a water-soluble bis(phosphane) congener. Under acidic conditions (necessary to inhibit re-association of the phosphane ligand), 95% conversion within 24 h at 45 °C could be observed.[68g] Hong et al. reported considerably higher activities for the same reaction, catalyzed by backbone-anchored poly(ethylene glycol) functionalized **C56** (Scheme 14). Owing to its phosphane-free catalyst design, no HCl was necessary to improve activities, and at 45 °C complete conversion could be observed within the first three minutes, employing a catalyst loading of 5 mol%.[68c] Furthermore, Jordan et al. examined ROMP using the same substrate with ammonium-functionalized catalyst **C34** (Scheme 10). For comparison, **C52** and **C56** were also tested, at catalyst loadings of 3.3 mol%. Activities observed did not differ between these three catalysts and complete conversion could be observed within three minutes.[55] The results show, however, that small-molecule-based Ru catalysts can be as effective as polymer-based compounds.

Another reaction examined was ring-closing metathesis (RCM). Gallivan et al. tested the RCM of diethyl diallyl malonate at 45 °C in methanol and compared activities to water-soluble Grubbs I based phosphane derivatives. Although at 5 mol% catalyst loading only conversions of 40% were reached, **C52** showed significantly higher activities than the phosphane derivatives.[68g] Hong et al. showed, that in this reaction, carried out in CH_2Cl_2, backbone-functionalized **C56** basically showed identical activities (1 mol% of Ru catalyst, 30 °C, 99% conversion in 35 min) to the classical Grubbs II or Grubbs–Hoveyda catalysts. However, the efficiency of removing catalyst **C56** from the reaction solution was superior to that of its more hydrophobic predecessors.[68d] In addition, Balof et al. tested the same RCM reaction, utilizing amine-substituted catalyst **C35** (Scheme 10) in benzene, benchmarking it against the Grubbs II or Grubbs–Hoveyda catalysts. Activities of both Grubbs–Hoveyda type catalysts were higher than those of the examined phosphane congeners (at a catalyst loading of 0.5 mol%, conversion of almost 70% could be observed for a Grubbs–Hoveyda second-generation catalyst within 1 h at room temperature, while under the same conditions conversion of 60% could be detected for water-soluble catalyst **C35** and a conversion of only 45% could be evidenced for a Grubbs II catalyst). Yet, a very efficient method of catalyst removal was presented: After quenching the reaction, HCl was added (roughly 10 equivalents based on catalyst), to immediately precipitate the dicationic analogue of **C35**. Separation gave filtrates with significantly reduced content of Ru.[56] Carbohydrate-substituted catalysts **C61**/**C62** (Scheme 16) were also tested in exactly the same reaction, carried out in CH_2Cl_2. The conversions obtained were mediocre compared to those with the Grubbs II catalyst. Reproducibly, the glucose-substituted complex **C61** was less reactive than the galactose functionalized **C62**.[75]

Finally, aqueous RCM was also tested for **C56** and **C34** (5 mol% catalyst loading), using a water-soluble diene and water as reaction medium (Scheme 19). Applying catalyst **C56**, over 95% conversion were reached after 12 h at room temperature. In contrast, small-molecule-based **C34** reached over 95% conversion within 30 min at 30 °C.[55,68c] It must be noted, that in contrast to RCM of diethyl diallyl malonate, this type of reaction could not be carried out by traditional Ru metathesis catalyst systems.



Scheme 19. Various metathesis reactions tested with water-soluble catalysts.

5. Conclusion

The preceding Sections gave an overview on the state-of-the-art of transition-metal complexes formed with water-soluble NHC ligands. All known paths to introducing water-solubility through ligand design were elucidated. It is quite clear that some of these paths appear to be rather exotic, while other routes have become common practice through the last decade, for example, sulfonate-functionalization. As the enhanced hydrophilicity of catalysts offers a great number of advantages for industrial application, it is not surprising that the majority of publications in this area report catalytic studies of new transition-metal compounds with water-soluble NHCs. To date, activity studies of aqueous C–C coupling reactions dominate the field, but recent reports show a variety of other uses. Notably, new water-soluble compounds applied in metathesis and hydrogenation reactions are among the best performing catalysts known. Nevertheless, whole catalytic areas still remain to be investigated. For example, oxidation catalysis in aqueous media or ionic liquids represents a field perfectly suited for this type of ligand.

However, ongoing fundamental research is certainly essential to further complete the picture. Only a few publications describe compound stability in water. In addition, academic literature lacks information about the influence of functionalization on the ligand's donor strength and buried volume and data has not been generated in a consistent manner to date. Furthermore, until now only a few transition metals have been bound to water-soluble NHCs. A quantitative description of the solubility in water is, unfortunately, very often lacking and toxicity examinations—important when applying such compounds as catalysts in larger amounts in industry—are extremely rare if not completely absent.

There is no serious doubt that this field of research will increase significantly in the future, hopefully making another step towards more environmentally friendly and energy/resources saving processes.

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