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Highlight Review

Heterocyclic Carbene–Metal-catalyzed Csp^2–Csp^2 and Csp–Csp^2 Couplings Using Nonmetallic Substrates

Miguel Yus* and Isidro M. Pastor*

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Abstract

The use of carbene ligands for transition-metal complexes has been developed in the last decades, being of special interest those carbenes derived from a nitrogen-containing heterocyclic system. An interesting variety of carbene–metal complexes has been tested in the Mizoroki–Heck reaction. In comparison, few examples can be found for the Matsuda–Heck version of this coupling reaction. Additionally, the Sonogashira coupling has been also catalyzed with different carbene–metal catalysts.

♦ Introduction

N-Heterocyclic carbenes (NHCs) have emerged in the last years as a new family of ligands with interesting electronic and structural properties.[1] The combination of their strong σ-donor and poor π-acceptor abilities results in good coordination stability and versatility. Consequently, the use of NHC ligands based on imidazolium ions and related heterocycles has appeared as an alternative to phosphanes in the design of new organometallic catalysts.[2] One of the main advantages of employing NHC-based catalysts compared with phosphane-based ones is that they are far less prone to oxidation, allowing their prolonged use, and reuse. Although NHCs were presented as simple tertiary phophane mimics, they have been recognized as much more over the past decade. Therefore, NHC ligands have become an interesting alternative to other types of ligands in different cross-coupling catalytic reactions mediated by transition metals.[3] Moreover, the easy introduction of chiral elements in the corresponding precursors have made chiral NHCs promising chiral ligands in metal-based asymmetric catalysis.[4]

The comparison between phosphane and NHC ligands, from a mechanistic point of view, has been studied, clear differences being found.[5] First, the possibility of carbene ligand dissociation is greatly reduced due to its stronger donor ability; and second, the reactivity of the NHC–metal complex is higher probably caused by the lack of back-donation from the metal to the carbene ligand. Jutand and co-workers studied the reactivity of monocarbene and bis(carbene) Pd(0) complexes toward the oxidative addition of aryl halides, concluding that the electronic and steric properties of the carbene ligand are important factors in this step of the catalytic process.[6]

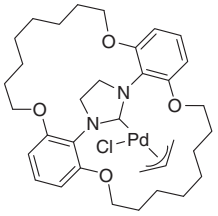
Among the carbon–carbon coupling reactions, the activation of a C–H from an alkene (Mizoroki–Heck reaction) or an alkyne (Sonogashira reaction) are of special interest. This *highlight review* describes the progress on the topic of NHC ligands for transition-metal-catalyzed coupling reactions, employing non-metallic reagents. Thus, both different NHC precursors and NHC–metal complexes with catalytic activity in the Mizoroki–Heck, Matsuda–Heck, and Sonogashira reactions are compiled.

♦ Mizoroki–Heck Reaction

In 1995, Herrmann and co-workers introduced the use of bis(NHC)–Pd complexes as catalysts with long-term stability in the Mizoroki–Heck reaction.[7] Indeed, the carbenes derived from imidazole stabilized the palladium complexes due to their pronounced donor properties, being more stable toward deactivating degradation reactions. Thus, the Mizoroki–Heck reaction employing bromo- and chloroarenes has been satisfactorily catalyzed by the monoNHC Pd(II) complex **1**,[8] bis(NHC) Pd(II) complexes **2**–**22**,[7,9–11] the tetraNHC Pd(II) complex **23**,[12] and Pd(0) complexes **24** and **25** (Chart 1).[7,13] Complexes **2**–**6** adopted a pseudo-square-planar geometry where the NHC ligands were in a *cis*-configuration.[14] The comparison of the catalytic activity between **2**–**6** complexes did not allow to conclude any universal trend, but complex **4** exhibited higher activity than complex **5** what may be attributed to σ- and π-contributions of the substituents in the corresponding NHC-ligand. Interestingly, the palladium(0) complex **25**, which has been prepared by Beller's research group and employed in the Matsuda–Heck reaction (vide infra),[15] catalyzed also the reaction between aryl iodides and enones yielding the Mizoroki–Heck

Prof. Dr. Miguel Yus and Dr. Isidro M. Pastor**
Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain
E-mail: yus@ua.es, ipastor@ua.es

(Photo) Miguel Yus was born in Zaragoza (Spain) in 1947 and received his B.Sc. (1969), M.Sc. (1971), and Ph.D. (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut fuer Kohlenforschung in Muelheim a.d. Ruhr, he returned to Spain to the University of Oviedo where he became associate professor in 1977, being promoted to full professor in 1987 at the same university. In 1988 he moved to a chair in Organic Chemistry at the University of Alicante, where he is currently the head of the newly created Organic Synthesis Institute (ISO).



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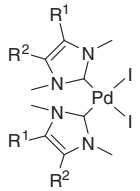
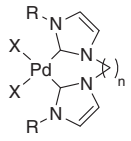
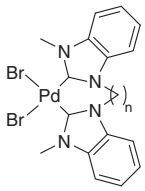


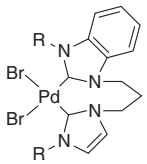
2 [$R^1 = R^2 = H$]
3 [$R^1 = R^2 = Cl$]
4 [$R^1 = CF_3$; $R^2 = H$]
5 [$R^1 = NO_2$; $R^2 = H$]
6 [$R^1 = R^2 = CN$]



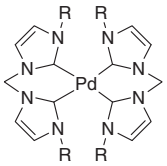
7 [n = 1; X = I; R = Me]
8 [n = 2; X = Br; R = Me]
9 [n = 3; X = Br; R = Me]
10 [n = 1; X = Br; R = $(CH_2)_3OH$]
11 [n = 1; X = I; R = $(CH_2)_2OH$]
12 [n = 1; X = Br; R = Ph]
13 [n = 1; X = Br; R = 4-BrC_6H_4]
14 [n = 1; X = Br; R = 4-$(MeO)C_6H_4$]
15 [n = 1; X = I; R = mesityl]
16 [n = 1; X = NCS; R = mesityl]
17 [n = 1; X = OTf; R = mesityl]



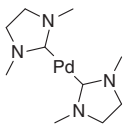
18 [n = 1]
19 [n = 2]
20 [n = 3]



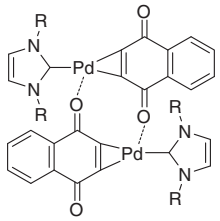
21 [R = Me]
22 [R = CH_2Ph]



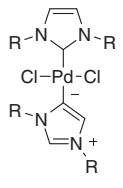
23 [R = *n*-Bu]



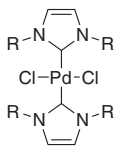
24



25 [R = mesityl]

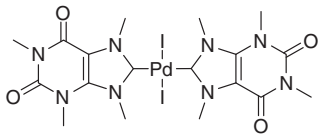


26 [R = mesityl]



27 [R = mesityl]

Chart 1.



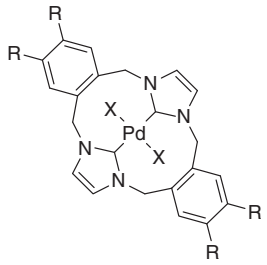
28

Chart 2.

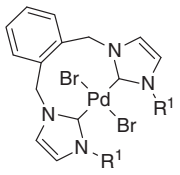
product or the conjugate addition depending on the base employed.[13] The synthesis of complex **26**, which bears NHC ligands in "normal" and "abnormal" binding motifs, has been described by direct metalation of the corresponding imidazolium salt with palladium(II) acetate.[16] Interestingly, this atypical bis(NHC) complex was shown to be a more suitable precursor for the Mizoroki–Heck reaction than the complex **27**, and the in situ generated catalyst.

The use of benzimidazole-based ligands has been also reported. Thus, bis(1,3-dimethylbenzimidazol-2-ylidene)- and bis(1,3-diisopropylbenzimidazol-2-ylidene)palladium(II) complexes were studied as catalysts in the reaction between *t*-butyl acrylate and aryl bromides and chlorides producing similar results to the corresponding imidazole derivatives.[17] Regarding benzimidazole derivatives, the influence of electron-donating butoxy substituents has been considered, which increased the solubility of the complexes in organic solvents although without increasing significantly their activity.[18] Additionally, 1,3-dialkylperhydrobenzimidazolium salts have been employed in combination with palladium(II) acetate (in 2:1 ratio) to catalyze the coupling of aryl bromides (i.e., bromobenzene, 4-bromotoluene, 4-bromoanisole, and 4-bromobenzaldehyde) with styrene, giving the corresponding stilbenes in good yields (81–98%).[19] Moreover, quaternization of caffeine with methyl iodide formed the corresponding 1,3,7,9-tetramethylxanthinium salt, which has been employed in the preparation of the bis(NHC) palladium complex **28** (Chart 2).[20] Complex **28**-catalyzed satisfactorily the reaction of iodobenzene and 4-bromoacetophenone with methyl acrylate in water.

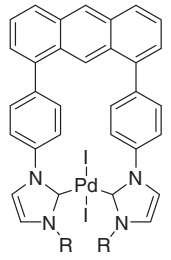
Different bis(NHC) ligands have been described in the literature, which have been employed in the preparation of palladium complexes with potential activity in the Mizoroki–Heck reaction. Thus, bis(carbene) palladium complexes **29**–**37** (Chart 3) derived from imidazole moieties bridged by an *ortho*-xylyl, an anthryl, or a xanthyl linker catalyzed the reaction of methyl and *n*-butyl acrylate with iodoarenes and 4-bromo-1-nitrobenzene.[21] Complexes **38**–**46** (Chart 3) with two imidazol-2-ylidene moieties have been prepared by Cavell and co-workers.[22] The analogous pyridine-bridged bis(benzimidazol-2-ylidene)palladium complexes have been also studied by Tu and co-workers.[23] All complexes **38**–**45** catalyzed the reaction between 4-bromoacetophenone and *n*-butyl acrylate without any significant difference independently of the presence or absence of the methylene spacer group, and the presence of a chloro or a methyl ligand at palladium. Complex **46** produced similar results, as well. Additionally, bidentate *trans*-chelating complexes **47**–**50** (Chart 3) have been successfully tested as precatalyst for the reaction between *t*-butyl acrylate and aryl bromides or chlorides.[24] The in situ generation of the corresponding catalyst using $Pd(OAc)_2$ and the corresponding bis(imidazolium) salts gave activities approximately 33% lower



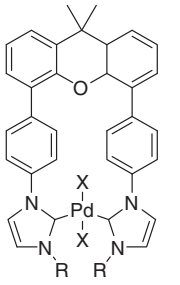
29 [X = I; R = H]
30 [X = Br; R = *n*-C_7H_{15}]



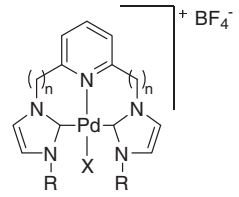
31 [R = Me]
32 [R = CH_2(1-naphthyl)]

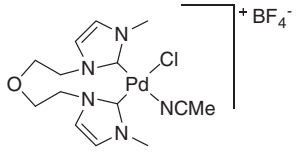


33 [R = *n*-C_8H_{17}]



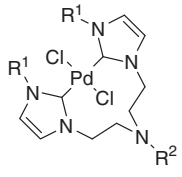
34 [X = I; R = *n*-C_8H_{17}]
35 [X = I; R = Me]
36 [X = I; R = CH_2Ph]
37 [X = Br; R = CH_2Ph]



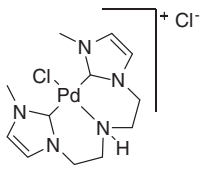


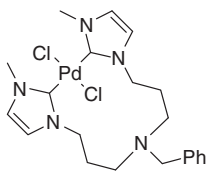
38 [n = 1; X = Me; R = Me]
39 [n = 1; X = Me; R = mesityl]
40 [n = 1; X = Cl; R = mesityl]
41 [n = 1; X = Me; R = *t*-Bu]
42 [n = 1; X = Cl; R = *t*-Bu]
43 [n = 0; X = Me; R = Me]
44 [n = 0; X = Me; R = mesityl]
45 [n = 0; X = Me; R = 2,6-*i*-$Pr_2C_6H_3$]

46



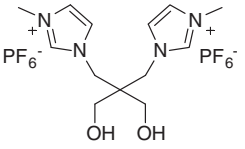
47 [R^1 = *t*-Bu; R^2 = CH_2Ph]
48 [R^1 = mesityl; R^2 = H]



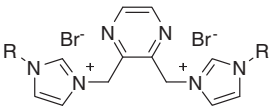


49 **50**

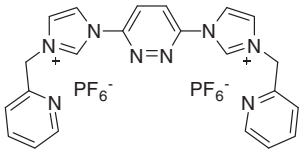
Chart 3.



51



52 [R = Me]
53 [R = *i*-Pr]
54 [R = *n*-Bu]
55 [R = *t*-Bu]
56 [R = 2-MeC_6H_4]
57 [R = mesityl]
58 [R = 2,6-*i*-$Pr_2C_6H_3$]
59 [R = 2-pyridyl]



60

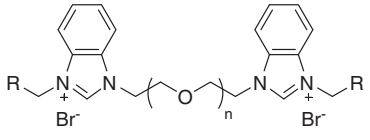
Chart 4.

than the preformed precatalysts. The hydroxy-functionalized bis(imidazolium) salt **51** (Chart 4) has been effectively employed in combination with $PdCl_2$ (in 1:1 ratio) for the coupling between aryl bromides and methyl acrylate.[25] Furthermore, pyrazine-bridged bis(imidazolium) salts **52**–**59** (Chart 4), which have been prepared by double substitution of 2,3-bis(bromomethyl)pyrazine, were used in combination with palladium acetate (in 1:2 ratio) for the reaction of 4-bromobenzaldehyde with styrene and *n*-butyl acrylate.[26] The pyridazine-bridged bis(imidazolium) salt **60** (Chart 4) has been also employed in the synthesis of bis(palladium) complexes, which were active as catalyst for the Mizoroki–Heck coupling.[27]

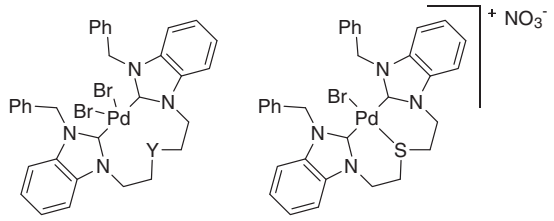
The use of benzimidazole units have been also considered in the preparation of different bis(NHC) precursors. Accordingly, bis(benzimidazolium) bromides **61**–**66** (Chart 5) have been employed in combination with $Pd(OAc)_2$ (in 1:1 ratio) to catalyze the reaction between styrene and bromoarenes.[28] The thioalkyl-bridged bis(benzimidazol-2-ylidene)palladium complexes **67**–**69** (Chart 5) have been prepared and fully characterized.[29] Complexes **67**–**69** were found to be highly active in the coupling of activated aryl bromides and *t*-butyl acrylate, without significantly difference among them.

The research group of Shi has developed a variety of mono- and bis(imidazolium) derivatives based on diamines (i.e., 1,1′-binaphthalene-2,2′-diamine (BINAM), *trans*-cyclohexane-1,2-diamine, and 6,6′-dimethoxybiphenyl-2,2′-diamine), which have been employed in the synthesis of the palladium complexes **70**–**77** (Chart 6).[30] All complexes **70**–**77** were demonstrated to catalyze effectively the reaction of aryl bromides with *n*-butyl acrylate, in each case being necessary to determine the best base in order to perform the reaction. Among them, complexes **75** and **77** showed to be the most active ones, employing only 0.1 mol % of palladium while 0.5–1 mol % were needed with the other related complexes.

Based on the same idea, Wang and co-workers prepared the binaphthyl-bridged bis(benzimidazolium) salt **78** (Chart 7),



61 [n = 1; R = mesityl]
62 [n = 2; R = mesityl]
63 [n = 3; R = mesityl]
64 [n = 1; R = C_6Me_5]
65 [n = 2; R = C_6Me_5]
66 [n = 3; R = C_6Me_5]



67 [Y = S]
68 [Y = SO]

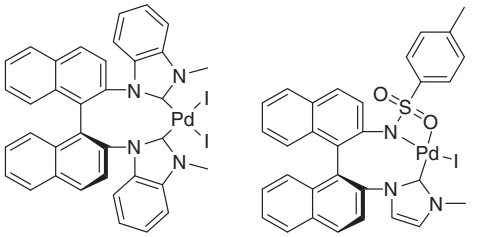
69

Chart 5.

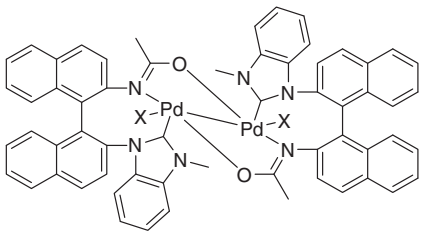
which in combination with $Pd(OAc)_2$ (1 mol %) showed catalytic activity in the Mizoroki–Heck reaction of bromoarenes with ethyl acrylate, acrylonitrile, and acrylamide.[31] Additionally, bis(benzimidazolium) bromides **79**–**100** (Chart 7) have been used in combination with $Pd(OAc)_2$ (3 mol % of Pd) to catalyze the reaction between *n*-butyl acrylate and bromoarenes (i.e., bromobenzene, 4-bromoacetophenone, and 4-bromoanisole), the best results being obtained for the catalytic systems employing monobridged ligands derived from salts **79**–**94**.[32] For this type of ligand, the influence of butoxy substituents on the benzo-fused ring has been studied, but lower catalytic activity was obtained in comparison with the unsubstituted NHC ligands.[33] Furthermore, bis(benzimidazolium) salts **101**–**106** (Chart 7) bearing furfuryl or thienyl moieties in combination with $Pd(OAc)_2$ (1 mol %, in 1:1 ratio) have shown high activity in the reaction of 4-bromoanisole and activated or deactivated aryl chlorides with styrene under microwave irradiation producing the expected stilbenes in fair yields (50–99%) in only five minutes.[34]

In some cases, the use of bis(NHC) ligands produced the formation of dinuclear palladium complexes, which were shown to be active in the Mizoroki–Heck reaction. Thus, two 1-substituted imidazole units were bridged with different chain lengths forming the corresponding bis(imidazolium) salts, which were then employed in the preparation of palladium complexes **107**–**117** (Chart 8).[35] This type of dipalladium complex catalyzed satisfactorily reactions of bromoarenes with styrene, employing 0.5 mol % of Pd. Moreover, dinuclear complexes **118**–**120** (Chart 8) were prepared bridging the imidazole moieties with a 2,7-bis(methylene)naphtalene unit.[36]

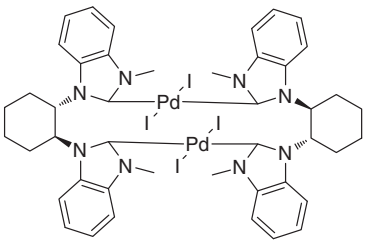
An NHC based on 1,10-phenanthroline has been employed in the preparation of bis(NHC) complex **121** (Chart 9), which was shown to be active in the Mizoroki–Heck reaction catalyzing (with 2 mol % of **121**) the coupling of 4-bromoanisole with *n*-butyl acrylate in 90% yield.[37] The preparation of complex the **122** (Chart 9) bearing two NHC-tetracyclic rings



70 **71**



72 [X = I]
73 [X = OAc]



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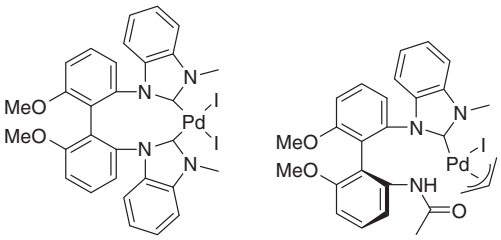
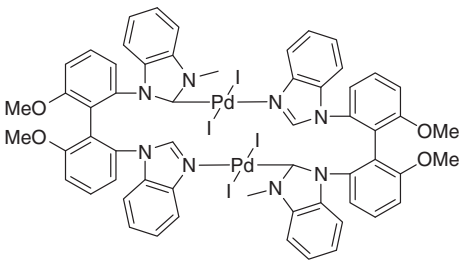


75 **76**

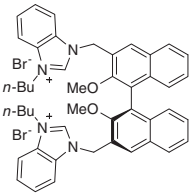


77

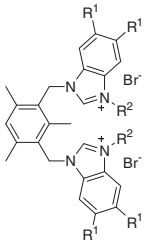
Chart 6.

has been also reported, and its catalytic activity in the Mizoroki–Heck reaction has been tested with similar results.[38]

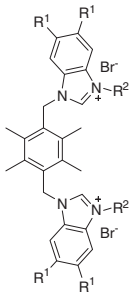
Palladium complexes with benzothiazole carbene ligands, such as **123**–**128** (Chart 10), which have been isolated and fully characterized by X-ray structures, showed to be active in the



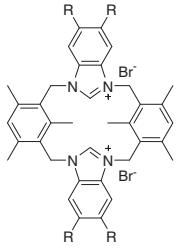
78



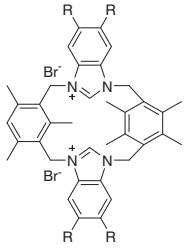
79 [R^1 = H; R^2 = CH_2CH_2OH]
80 [R^1 = H; R^2 = CH_2-mesityl]
81 [R^1 = H; R^2 = CH_2-(2,3,5,6-Me_4C_6H)]
82 [R^1 = H; R^2 = $CH_2C_6Me_5$]
83 [R^1 = Me; R^2 = CH_2CH_2OH]
84 [R^1 = Me; R^2 = CH_2-mesityl]
85 [R^1 = Me; R^2 = CH_2-(2,3,5,6-Me_4C_6H)]
86 [R^1 = Me; R^2 = $CH_2C_6Me_5$]



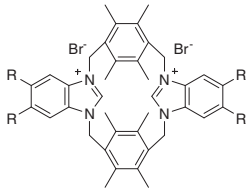
87 [R^1 = H; R^2 = CH_2CH_2OH]
88 [R^1 = H; R^2 = CH_2-mesityl]
89 [R^1 = H; R^2 = CH_2-(2,3,5,6-Me_4C_6H)]
90 [R^1 = H; R^2 = $CH_2C_6Me_5$]
91 [R^1 = Me; R^2 = CH_2CH_2OH]
92 [R^1 = Me; R^2 = CH_2-mesityl]
93 [R^1 = Me; R^2 = CH_2-(2,3,5,6-Me_4C_6H)]
94 [R^1 = Me; R^2 = $CH_2C_6Me_5$]



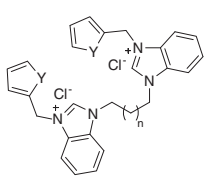
95 [R = H]
96 [R = Me]



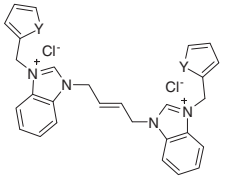
97 [R = H]
98 [R = Me]



99 [R = H]
100 [R = Me]

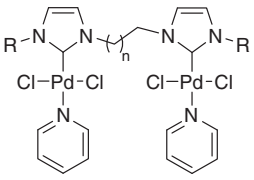


101 [n = 1; Y = O]
102 [n = 1; Y = S]
103 [n = 2; Y = O]
104 [n = 2; Y = S]

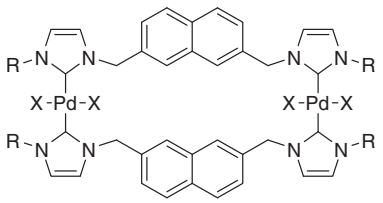


105 [Y = O]
106 [Y = S]

Chart 7.

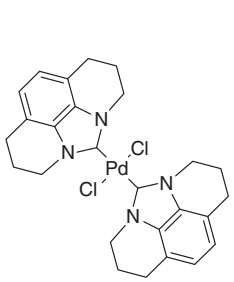


107 [n = 1; R = mesityl]
108 [n = 1; R = 2,6-$Me_2C_6H_3$]
109 [n = 1; R = 2,6-$Et_2C_6H_3$]
110 [n = 1; R = 2,6-i-$Pr_2C_6H_3$]
111 [n = 1; R = Me]
112 [n = 1; R = t-Bu]
113 [n = 2; R = mesityl]
114 [n = 3; R = mesityl]
115 [n = 4; R = mesityl]
116 [n = 5; R = mesityl]
117 [n = 9; R = mesityl]

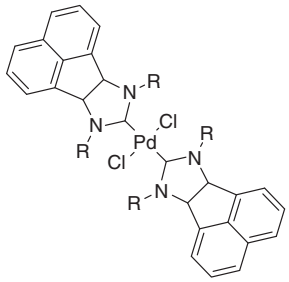


118 [X = Cl; R = 2,6-i-$Pr_2C_6H_3$]
119 [X = Cl; R = c-C_6H_{11}]
120 [X = I; R = n-C_4H_9]

Chart 8.

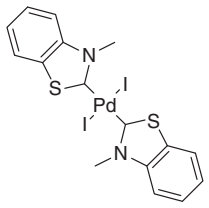


121

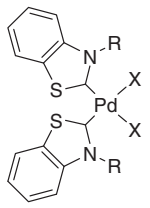


122 [R = mesityl]

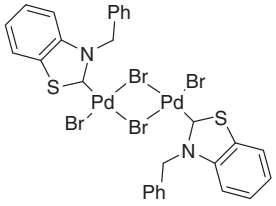
Chart 9.



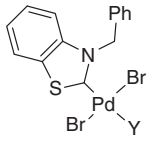
123



124 [X = I; R = Me]
125 [X = Br; R = CH_2Ph]

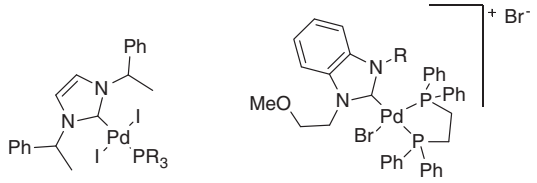


126



127 [Y = MeCN]
128 [Y = DMF]

Chart 10.



129 [R = Ph]
130 [R = 2-MeC$_6$H$_4$]
131 [R = CH$_2$-(2,3,5,6-Me$_4$C$_6$H)]
132 [R = CH$_2$-C$_6$Me$_5$]

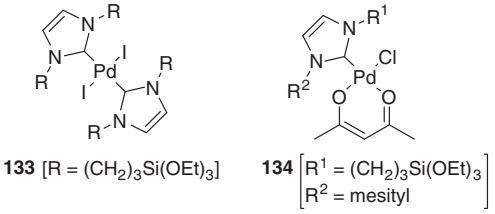
Chart 11.

olefination of styrene, *n*-butyl and *t*-butyl acrylates with aryl iodides and bromides.[39] The complex **123** resulted in greater activity performing the reactions in DMF as solvent and with a 0.001 mol % of catalyst. Additionally, similar results were obtained with complexes **125** and **128**, under the same reaction conditions, but employing 1 mol % of catalyst.

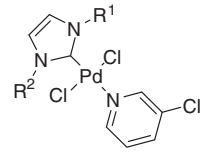
Complexes of palladium(II) having NHC and phosphane ligands, such as **129**–**132** (Chart 11), were prepared and tested in the Mizoroki–Heck reaction, showing slight superiority in the coupling of aryl bromides compared with the bis(NHC) complexes.[40] Moreover, the preparation of a bis[(tridecafluorooctyl)imidazol-2-ylidene]palladium complex with a pyridine ligand,[41] and its use in the Mizoroki–Heck reaction of 4-iodotoluene and 1-octene have been described.[42]

New polymeric materials containing imidazolium moieties have been synthesized via a modification of commercially available Merrifield resin,[43] or polyisobutylene (PIB) oligomers[44] by reaction with imidazole derivatives. These functionalized polymers have been employed in the preparation of NHC–palladium-supported materials, which effectively catalyzed the Mizoroki–Heck reaction. Thus, the complexes **10** and **11** were immobilized on a functionalized polystyrene support through one of the oxygen atoms. These heterogeneous catalysts catalyzed efficiently the reaction of aryl bromides with styrene and *n*-butyl acrylate.[9] Yields were similar to those obtained with the analogous homogeneous catalysts, and they could be recycled up to 15 times without detectable loss of activity. Moreover, poly(norbornene)-supported NHC ligands have been prepared by ring-opening metathesis polymerization of the corresponding norbornyl-functionalized NHC–Pd monomer.[45] Additionally, the sol–gel condensation allowed the preparation of hybrid silica-based catalysts from Pd–NHC complexes. Thus, the bis(imidazol-2-ylidene) complex **133**[46] and imidazol-2-ylidene complexes **134** and **135** (Chart 12),[47] with substituents bearing triethoxysilyl moieties, have been employed in the preparation of the corresponding silica-supported palladium complexes by the mentioned sol–gel methodology. The catalytic activity of **133** (using 0.037 mol % of Pd) has been tested in the reaction of aryl iodides and activated aryl bromides with styrene and methyl acrylate, under microwave irradiation, producing the expected products with good yields. Whereas, the complexes **134** and **135** have been employed and reused (up to 5 cycles) in the coupling of 4-bromoacetophenone and *n*-butyl acrylate, under conventional heating (150 °C) with a 0.2 mol % of Pd loading, producing the expected cinnamate with almost quantitative yield in all five cycles.

Carbene ligands prepared from other 5-membered nitrogen heterocycles, such as pyrazole, have been described. Thus, (pyrazolin-4-ylidene)palladium(II) complexes **136**–**139** (Chart 13)

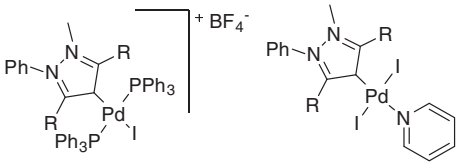


133 [R = (CH$_2$)$_3$Si(OEt)$_3$]
134 [R^1 = (CH$_2$)$_3$Si(OEt)$_3$, R^2 = mesityl]



135 [R^1 = (CH$_2$)$_3$Si(OEt)$_3$, R^2 = mesityl]

Chart 12.



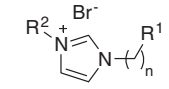
136 [R = Me]
137 [R = Ph]
138 [R = Me]
139 [R = Ph]

Chart 13.

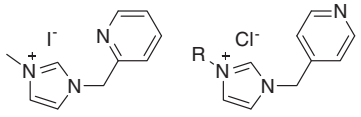
were prepared from the corresponding 4-iodopyrazolium tetrafluoroborates, and tested in the coupling of 4-bromoarenes to *t*-butyl acrylate. The phosphane complexes **136** and **137** showed higher activity than their pyridine analogous, the bulkier complex **137** with phenyl substituents being the best of this type.[48]

Differently functionalized imidazolium salts have been employed in the preparation of different mono- and bis(NHC)–Pd(II) complexes. Functionalized imidazolium salts **140**–**151** (Chart 14) have been prepared and used in the synthesis of active palladium complexes for the Mizoroki–Heck reaction.[49,50] The use of a pyrrolidine-functionalized imidazolium salt gave the dinuclear palladium complex **152** (Chart 15).[51] Among the different complexes prepared with these imidazolium salts, bis(carbene) complex **153** (Chart 15) gave the greatest turnover (1700000, with a 5×10^{-5} mol % palladium loading) in the coupling of 4-bromoacetophenone with *n*-butyl acrylate, using tetrapropylammonium bromide as additive, with a final conversion of 85%. In comparison, mono(carbene) complexes **154**–**156** (Chart 15) showed to be less active in the reaction of aryl bromides,[49,52] as well as the pyridazine-functionalized complex **157** (Chart 15).[53] Furthermore, amido-functionalized NHC ligands have been designed and employed in the preparation of different palladium complexes, such as **158**–**160** (Chart 15), which catalyzed effectively the Mizoroki–Heck reaction of aryl bromides and chlorides with styrene and *n*-butyl acrylate.[54] Palladium(II) complexes **159** and **160** were more active, although higher temperature (up to 140 °C) was needed in order to get the reaction to work.

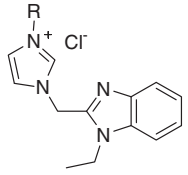
The coupling reaction of 4-bromoacetophenone and styrene has been also studied employing the in situ formed carbene complexes from palladium(II) acetate and functionalized benz-



140 [n = 1; R^1 = COPh; R^2 = Me]
141 [n = 1; R^1 = CO_2Me; R^2 = Me]
142 [n = 1; R^1 = CN; R^2 = mesityl]
143 [n = 2; R^1 = CN; R^2 = mesityl]
144 [n = 3; R^1 = CN; R^2 = mesityl]
145 [n = 1; R^1 = CO_2Me; R^2 = mesityl]
146 [n = 2; R^1 = CO_2Me; R^2 = mesityl]
147 [n = 3; R^1 = CO_2Me; R^2 = mesityl]



148 **149** [R = *i*-Pr] **150** [R = mesityl]



151 [R = mesityl]

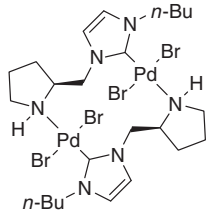
Chart 14.

imidazolium salts **161**–**169** (in 1:2 ratio) (Chart 16), producing the expected product with good yield.[28,55] The complex **170** with a pyridyl-functionalized benzimidazol-2-ylidene ligand has been successfully employed in the regioselective reaction of aryl halides with 3,4-dihydro-2*H*-pyran (Table 1).[56]

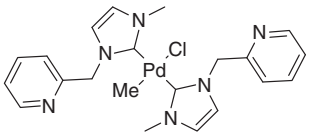
The phosphinoalkyl-functionalized imidazolium bromide **171** (Chart 17) has been prepared by Nolan's research group. The catalytic system formed with [Pd(dba)$_2$] (0.5 mol %) and **171** (0.5 mol %) proved to be highly efficient in the reaction of bromoarenes with *n*-butyl acrylate.[57] In relation to that, complexes **172** and **173** (Chart 17) were prepared and tested under similar reaction conditions, but the catalytic activity was moderately lower than that with the in situ formed catalyst.[58] Additionally, the corresponding NHC ligand bearing a diphenylphosphinoethyl substituent at both nitrogen atoms has been also considered, and it has been employed in the synthesis of the cationic palladium(II) complexes **174** and **175** (Chart 17).[59] Both complexes **174** and **175** catalyzed effectively the reaction between bromoarenes and olefins (i.e., styrene and *n*-butyl acrylate). Regarding activity, **175** was found to be better, catalyzing the coupling between phenyl iodide and styrene with a turnover number (TON) of 56000000 (employing 1.25×10^{-6} mol % of palladium).

Phosphanyl–benzimidazolium salt **176** (Chart 18) bearing an alkyne-bridged dicobalt complex as nitrogen substituent has been prepared, and employed in the synthesis of the corresponding palladium complex [Pd(NHC)$_2$Br$_2$]. This complex was shown to be active in the coupling between 4-bromoanisole and styrene.[60]

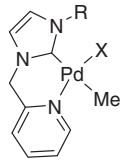
Phospha- and aza-palladacycles with an NHC ligand, such as **177**–**179** (Chart 19), have been reported as well-defined



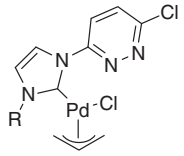
152



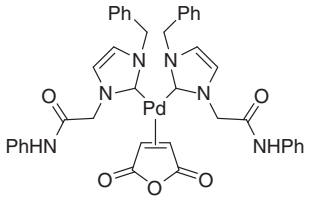
153



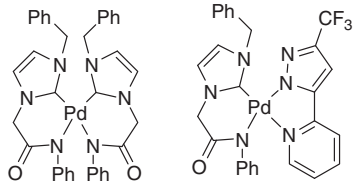
154 [X = Cl; R = Me]
155 [X = Br; R = *t*-Bu]
156 [X = Br; R = mesityl]



157 [R = 2,6-$Me_2C_6H_3$]



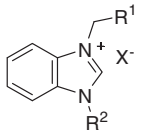
158



159 **160**

Chart 15.

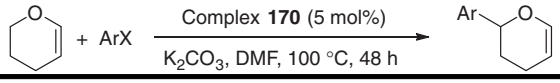
catalysts for the Mizoroki–Heck olefination of haloarenes.[61] The palladacycle **179** showed lower activity than the phospha-palladacycles **177** and **178** for the coupling of different bromoarenes and chloroacetophenone with styrene employing Cs_2CO_3 as base and tetrabutylammonium bromide as additive. On the contrary, complex **179** was really superior to other NHC-palladacycles when Ca(OH)$_2$ was added, being the only catalysts that coupled a chloroarene in quantitative yield. Regarding stability of the complexes, palladium black was formed during catalysis with **179**, but it was not the case employing phospha-palladacycle-NHC complexes. Furthermore, the group of Ying has reported the one-pot three-component synthesis of NHC-palladacycle **180** (Chart 19), which was obtained in excellent yield performing the reaction in large scale (90%, 95 g). This complex catalyzed the coupling between *t*-butyl acrylate and 4-bromoanisole even with a TON of 522000 at a loading of 1×10^{-5} mol %.[62] Interestingly, aryl halides were satisfactorily



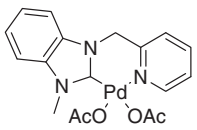
161 [X = Cl; R^1 = 1-naphthyl; R^2 = $(CH_2)_2OMe$]
162 [X = Cl; R^1 = 1-naphthyl; R^2 = $(CH_2)_2NEt_2$]
163 [X = Cl; R^1 = 1-naphthyl; R^2 = $(CH_2)_2N(CH_2CH_2)_2CH_2$]
164 [X = Cl; R^1 = 1-naphthyl; R^2 = $(CH_2)_2N(CH_2CH_2)_2O$]
165 [X = Br; R^1 = mesityl; R^2 = CH_2CH_2OMe]
166 [X = Br; R^1 = mesityl; R^2 = $(CH_2CH_2O)_2Me$]
167 [X = Br; R^1 = C_6Me_5; R^2 = CH_2CH_2OMe]
168 [X = Br; R^1 = C_6Me_5; R^2 = $(CH_2CH_2O)_2Me$]
169 [X = Br; R^1 = C_6Me_5; R^2 = $(CH_2CH_2O)_3Me$]

Chart 16.

Table 1. Coupling reactions of aryl halides with 3,4-dihydro-2*H*-pyran catalyzed by complex **170**



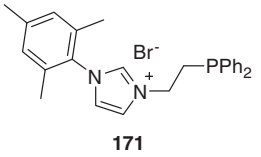
X	Ar	Yield/%
I	Ph	51
I	2-MeC_6H_4	71
I	3-MeC_6H_4	75
I	2-$(MeO)C_6H_4$	62
I	4-$(MeO)C_6H_4$	80
I	4-$(CF_3)C_6H_4$	15
I	2,6-$(Me)_2C_6H_3$	55
I	3-Pyridyl	61
Br	Ph	35
Br	4-$(MeO)C_6H_4$	21



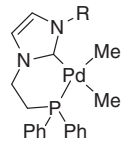
170

coupled with *t*-butyl acrylate, *N*-isopropylacrylamide, acrylonitrile, or styrene derivatives employing this catalyst **180** (2 mol %, Table 2).

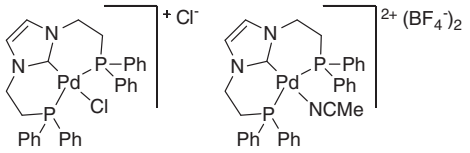
Six-membered NHC–palladium complexes have been prepared and successfully employed in the reaction of aryl bromides and chlorides with styrene and *n*-butyl acrylate. Thus, (3,4,5,6-tetrahydropyrimidin-2-ylidene)palladium(II) complexes **181** and **182** (Chart 20) have been synthesized from the corresponding bis(NHC)–silver(I) complexes by transmetalation with $[PdCl_2(CH_3CN)_2]$, and fully characterized.[63] High TONs were observed with complex **181** (up to 2000000), but complex **182**, though less active, catalyzed the coupling of a broader variety of aryl halides without formation of palladium black. More recently, these types of NHC ligand have been supported on commercially available polymer supports (i.e., polystyrene–divinylbenzene, and Merrifield polymer), and the obtained supported catalysts worked with similar TONs in the reaction of aryl bromides with styrene and *n*-butyl acrylate but with longer



171

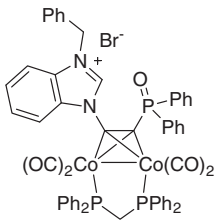


172 [R = 2,6-*i*-$Pr_2C_6H_3$]
173 [R = mesityl]



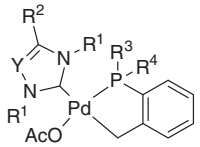
174 **175**

Chart 17.

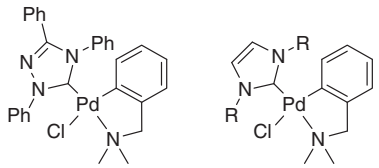


176

Chart 18.



177 [Y = N; R^1 = Ph; R^2 = Ph; R^3 = R^4 = 2-MeC_6H_4]
178 [Y = CH; R^1 = mesityl; R^2 = H; R^3 = *t*-Bu; R^4 = 2-MeC_6H_4]

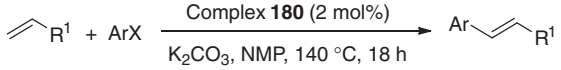


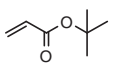
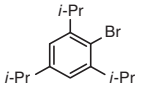
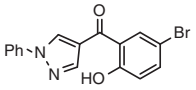
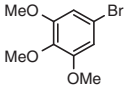
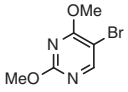
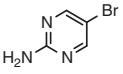
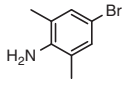
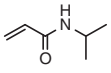
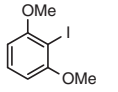
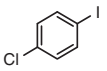
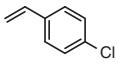
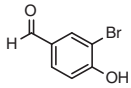
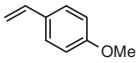
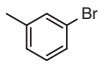
179 **180** [R = mesityl]

Chart 19.

reaction times.[64] A ferrocene-based NHC ligand, which formally contains a six-membered heterocyclic ring, has been employed in the preparation of complex **183** (Chart 20), and its activity in the Mizoroki–Heck reaction was poor compared with the complex **182**.[65] Moreover, other tetrahydropyrimidinium salts, such as **184**–**205** (Chart 21), have been prepared and tested as precursors of NHC ligands in the palladium-catalyzed reaction of styrene with bromoarenes.[66] The presence of methoxy groups on the benzyl substituent of the ligand precursor was found to

Table 2. Mizoroki–Heck reaction of functionalized aryl and heteroaryl bromides and iodides mediated by complex **180**



Alkene	Aryl halide	Yield/%
		72
		77
		92
		84
		63
		82
		83
		88
		59
		92
		88
		78
		79
		92

enhance the catalytic activity. Moreover, the synthesis of a series of 6- and 7-membered NHC–palladium(0) complexes, such as **206**–**212** (Chart 22), and their application in the coupling of 4-bromoacetophenone with *n*-butyl acrylate has been reported.[67]

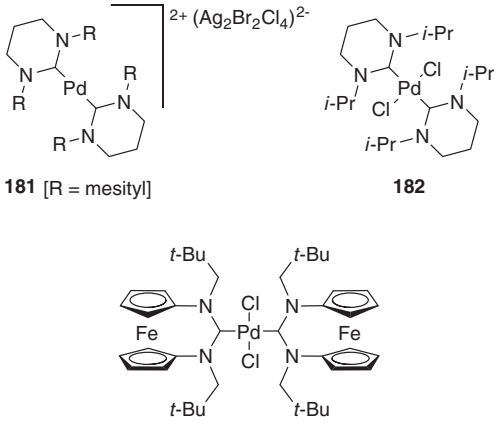
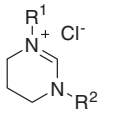
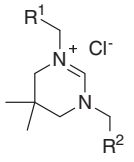


Chart 20.



184 [$R^1 = R^2 = CH_2$-(2,4,6-$Me_3C_6H_2$)]
185 {$R^1 = R^2 = CH_2$-[2,4,6-$(MeO)_3C_6H_2$]}
186 {$R^1 = R^2 = CH_2$-[3,4,5-$(MeO)_3C_6H_2$]}
187 {$R^1 = R^2 = CH_2$-[3-$(PhO)C_6H_4$]}
188 [$R^1 = R^2 = CH_2$-(4-*t*-BuC_6H_4)]
189 {$R^1 = R^2 = CH_2$-[4-(EtO)-3-$(MeO)C_6H_3$]}
190 {$R^1 = R^2 = CH_2$-[4-$(EtO)C_6H_4$]}
191 {$R^1 = R^2 = CH_2$-[2-$(EtO)C_6H_4$]}
192 [$R^1 = R^2 = CH_2$-(2-ethoxy-1-naphthyl)]
193 [$R^1 = n$-C_6H_{11}; $R^2 = CH_2$-(2,4,6-$Me_3C_6H_2$)]
194 [$R^1 = (CH_2)_2OMe$; $R^2 = CH_2$-(2,4,6-$Me_3C_6H_2$)]

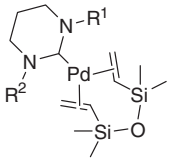


195 [$R^1 = R^2$ = mesityl]
196 [$R^1 = R^2$ = 4-$(MeO)C_6H_4$]
197 [$R^1 = R^2$ = 4-MeC_6H_4]
198 [$R^1 = R^2$ = 4-*t*-BuC_6H_4]
199 [$R^1 = R^2$ = 3,4,5-$(MeO)_3C_6H_2$]
200 [$R^1 = CH_2OMe$; = R^2 = mesityl]
201 [$R^1 = CH_2OMe$; = R^2 = 2,3,5,6-Me_4C_6H]
202 [$R^1 = CH_2OMe$; = R^2 = 2,3,4,5,6-Me_5C_6]
203 [$R^1 = CH_2OEt$; = R^2 = mesityl]
204 [$R^1 = CH_2OEt$; = R^2 = 2,3,5,6-Me_4C_6H]
205 [$R^1 = CH_2OEt$; = R^2 = 2,3,4,5,6-Me_5C_6]

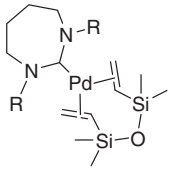
Chart 21.

Perimidine constitutes an interesting heterocyclic core in order to obtain six-membered NHC derivatives. Indeed, the bis(perimidinium) salt **213** (Chart 23) was synthesized in quantitative yield from readily available starting materials, and it has been employed in combination with palladium acetate as efficient precatalyst for reaction of iodo- and bromoarenes with *n*-butyl acrylate.[68] The σ-donor ability of NHC ligand generated from bis(perimidinium) salt is higher than the analogous NHC ligands starting from bis(imidazolium) and bis(benzimidazolium) that improves the efficiency of the palladium catalyst formed in situ. The reaction of 4-bromotoluene produced the expected product with 77% yield employing 0.0002 mol % of palladium (with a TON of 385000).

Decarbonylative reaction of a benzoyl chloride with a 4-substituted styrene has been reported in the preparation of different analogs of resveratrol. This type of Mizoroki–Heck

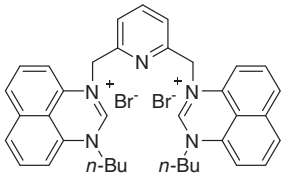


206 [$R^1 = R^2$ = mesityl]
207 [$R^1 = R^2$ = 2,6-$Me_2C_6H_3$]
208 [$R^1 = R^2$ = 2-MeC_6H_4]
209 [R^1 = mesityl; R^2 = 2-(MeO)C_6H_4]



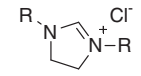
210 [R = mesityl]
211 [R = 2,6-$Me_2C_6H_3$]
212 [R = 2-MeC_6H_4]

Chart 22.

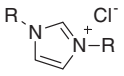


213

Chart 23.



214 [R = 2,6-*i*-$Pr_2C_6H_3$]



215 [R = mesityl]

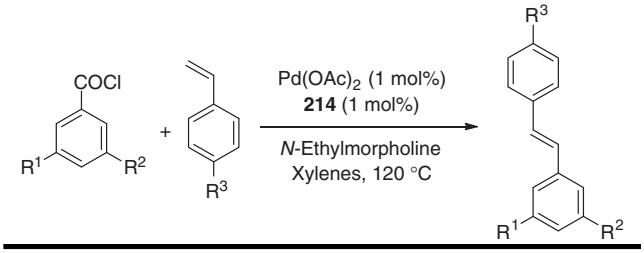
Chart 24.

reaction was catalyzed by 4,5-dihydroimidazolium chloride **214** (Chart 24) and palladium(II) acetate (1 mol %) producing the corresponding stilbene derivatives (Table 3).[69] Moreover, the 1,3-bis(mesityl)imidazolium chloride (**215**) (Chart 24) in combination with palladium(II) acetate (in 2:1 ratio, 5 mol % Pd) catalyzed the one-pot hydroacylation-coupling under mild reaction conditions. Thus, 4-iodobenzaldehyde worked as an acyl donor, allowing then the corresponding coupling with methyl, ethyl, and *t*-butyl acrylates (Table 4).[70]

♦ *Matsuda–Heck Reaction*

In 1977, Matsuda reported the use of diazonium salts as olefin arylation agents, in a palladium-catalyzed process similar to the Mizoroki–Heck reaction.[71] The Matsuda–Heck reaction can be performed in the absence of any external ligand, albeit high amounts of palladium (2–20 mol %) are required. Therefore, the use of a proper ligand can prevent palladium(0) aggregation resulting in a more active catalytic species. The research group of Correia has employed different room-temperature ionic liquids (RTILs) based on imidazole and imidazolidine in combination with palladium(II) acetate in order to perform the coupling between 4-fluorobenzenediazonium tetrafluoroborate and methyl *N*-phenoxycarbonyl-1,2,3,6-tetrahydropyridine-3-carboxylate for the synthesis of an intermediate in the paroxetine synthesis.[72] Thus, the formation of a NHC ligand can be expected in the course of the reaction, which can help in the stabilization of the palladium(0) species.

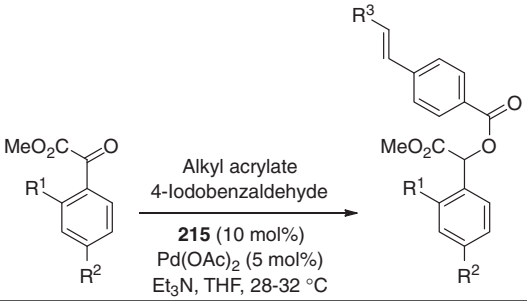
Table 3. Decarbonylative Mizoroki–Heck reaction mediated by the salt **214** and palladium acetate



R^1	R^2	R^3	Yield/%
AcO	AcO	AcO	73
MOMO[a]	MOMO[a]	AcO	56
AcO	AcO	$ClCH_2CO_2$	70
LevO[b]	AcO	AcO	70
LevO[b]	AcO	LevO[b]	72
F	F	F	80
AcO	AcO	F	72

[a]MOMO: methoxymethyloxy ($MeOCH_2O$). [b]LevO: levulinate ($MeCO(CH_2)_2CO_2$).

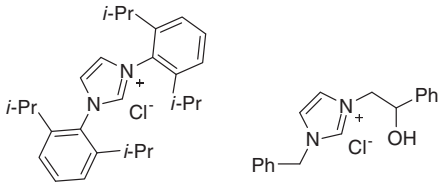
Table 4. Hydroacylation-Mizoroki–Heck coupling mediated by salt **215** and palladium acetate



R^1	R^2	R^3	Time/h	Yield/%
H	Br	CO_2Me	15	65
H	Br	CO_2Et	14	71
H	Br	CO_2t-Bu	14	64
Cl	H	CO_2Me	14	70
Cl	H	CO_2Et	10	65
Cl	H	CO_2t-Bu	12	74

The use of 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (**216**) (Chart 25) as precursor of NHC ligand has been reported by the research group of Andrus.[73] The reaction between diazonium salts and alkenes (i.e., styrenes, acrylonitrile, and methyl acrylate) was performed employing palladium(II) acetate (2 mol %) and **216** (2 mol %) in THF at room temperature, giving the final products in 80–90% yield. Beller and co-workers have obtained similar good results employing a monocarbene palladium(0) complex, such as **25**, performing the reaction in MeOH at 50–65 °C.[15]

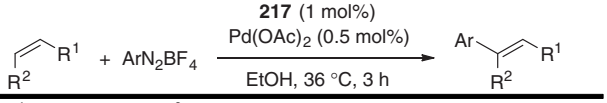
The catalytic system formed in situ from palladium(II) acetate and the hydroxy-functionalized imidazolium salt **217** (in a 1:2 ratio) has been employed in the Matsuda–Heck reaction of



216 **217**

Chart 25.

Table 5. Matsuda–Heck coupling mediated with salt **217** and palladium acetate



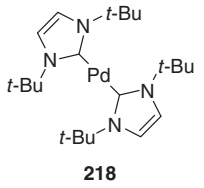
R^1	R^2	Ar	Yield/%
CO_2Et	H	Ph	98
CO_2Et	H	4-(MeO)C_6H_4	92
CO_2Et	H	2-MeC_6H_4	93
CO_2Et	H	4-IC_6H_4	94
CO_2Et	H	4-(CN)-2-EtC_6H_3	81
CO_2t-Bu	H	Ph	96
CO_2t-Bu	H	2-MeC_6H_4	90
$CONH_2$	H	Ph	82
$CONH_2$	H	2-MeC_6H_4	78
$-(CH_2)_4-$		Ph	82
$-(CH_2)_4-$		4-(NO_2)C_6H_4	88

different olefins (i.e., methyl and *t*-butyl acrylates, styrene, acrylamide, and cyclohexene) and arenediazonium tetrafluoroborates.[74] The reactions were performed with low catalyst loadings (0.5 mol % of Pd) in EtOH at 36 °C (Table 5). Interestingly, the reaction with cyclohexene produced the corresponding 1-arylcyclohexene as a single regioisomer.

♦ *Sonogashira Reaction*

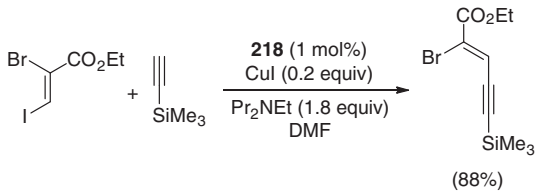
The coupling reaction of terminal alkynes with different aryl or vinyl halides is a well-established protocol for the bond formation between a C(sp) and a C(sp^2).[75] In 1998, Herrmann and co-workers showed that NHC–Pd complexes are suitable catalysts for the Sonogashira coupling.[9] Hence, the palladium(II) complex **7** (1 mol %) catalyzed the reaction between phenylacetylene and 4-bromoacetophenone or 1-bromo-4-fluorobenzene in the absence of copper, yielding the corresponding alkyne with 76 and 71% yield respectively. Caddick, Cloke, and co-workers reported, for the first time, the use of a bis(NHC)–Pd(0) complex in the Sonogashira reaction.[76] Thus, ethyl 2-bromo-3-iodopropenoate was coupled satisfactorily with trimethylsilylacetylene employing the palladium complex **218** (Chart 26), the yield being comparable with the reaction catalyzed by [$Pd(PPh_3)_4$] (Scheme 1).

Ghosh and co-workers have prepared different palladium(II) complexes with NHC ligands, which have been tested in coupling reactions.[77] Regarding the Sonogashira coupling, complexes **219**–**228** (Chart 27) were suitable catalysts (using 2–4 mol %) for the reaction of aryl bromides and iodides with



218

Chart 26.

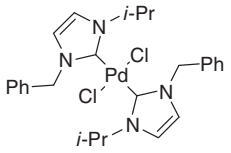


Scheme 1. Sonogashira type coupling using Pd(0) complex **218**.

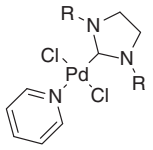
phenylacetylenes. Significantly higher conversions of the coupling product were observed in the case of bis(NHC) complex **219**[78] in comparison with the complexes bearing a pyridine ligand **220**–**224**.[79] The [$Pd(NHC)_2X_2$] complexes have more electron-rich metal centers, and presumably makes more active catalysts by facilitating the oxidative addition step. Following the same idea, palladium complexes **225**–**228**, bearing a more σ-donating imidazo[1,2-*a*]pyridine based on a abnormal NHC ligand, exhibited superior activity than the previously reported complexes based on the normal NHC ligands.[80] Furthermore, Shi and co-workers have prepared the NHC–Pd–pyridine complex **229** (Chart 27), which catalyzed the reaction of aryl bromides with phenylacetylene and hex-1-yne.[81] Additionally, NHC–Pd–pyridine complexes **230**–**232** (Chart 27) were easily prepared from the corresponding azolium salts. Complexes **230**–**232** have been employed in a sequential Sonogashira-hydroalkoxylation coupling for the synthesis of benzofurans, being **231** the most active catalyst.[82] Thus, 2-halophenylmethanols reacted with phenylacetylene in the presence of a complex (**230**–**232**: 1 mol % of palladium) providing the expected (*Z*)-1-benzylidene-1,3-dihydroisobenzofuran (Table 6). Similarly, the reaction of 2-iodophenol with phenylacetylene formed the 2-phenylbenzofuran under the same reaction conditions.

Andrus and co-workers studied the use of bulky substituted dihydroimidazolium salts, such as **214** and **233**–**235** (Chart 28), as NHC ligand precursors in the Sonogashira coupling.[83] The catalyst prepared in situ from the bulky imidazolium salt **235** and [$Pd(PPh_3)_2Cl_2$] promoted the coupling of different iodo- and bromo-substituted arenes with terminal acetylenes. Surprisingly, the salt **214** showed only moderate activity.

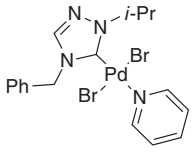
Functionalized NHC–palladium complexes have been also tested in the Sonogashira coupling. Thus, complexes **153** and **154** catalyzed the coupling between 4-bromoacetophenone and phenylacetylene, the monocarbene ligand **154** being superior in terms of activity.[49a] Furthermore, complex **28**, which was prepared from caffeine, catalyzed the coupling between the 1-bromo-4-nitrobenzene and phenylacetylene in water, being necessary the use of Brij 30 as nonionic surfactant.[20] Batey and co-workers reported the use of the functionalized NHC–palladium complex **236** (Chart 29) in the Sonogashira reaction



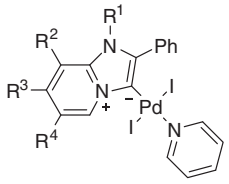
219



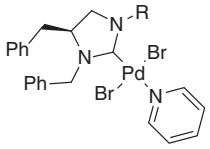
220 [R = mesityl]
221 [R = 2,6-$Me_2C_6H_3$]
222 [R = 2,6-$Et_2C_6H_3$]
223 [R = 2,6-*i*-$Pr_2C_6H_3$]



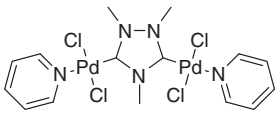
224



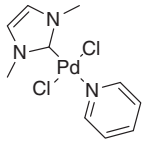
225 [R^1 = Me; R^2 = R^3 = R^4 = H]
226 [R^1 = R^2 = Me; R^3 = R^4 = H]
227 [R^1 = Et; R^2 = H; R^3 = Me; R^4 = H]
228 [R^1 = Et; R^2 = R^3 = H; R^4 = Me]



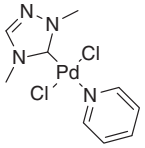
229 [R = 2,6-*i*-$Pr_2C_6H_3$]



230



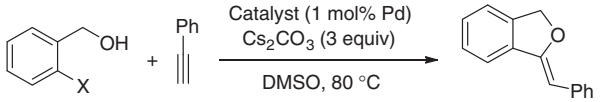
231



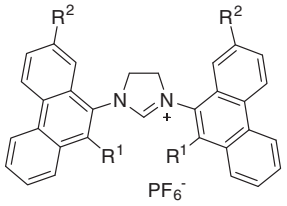
232

Chart 27.

Table 6. Sonogashira-cyclic hydroalkoxylation reaction

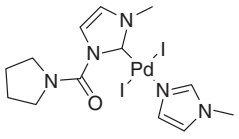


X	Catalyst	Time/h	Yield/%
I	**230**	1	99
I	**231**	1	98
I	**232**	1	98
Br	**230**	12	43
Br	**231**	12	77
Br	**232**	12	45

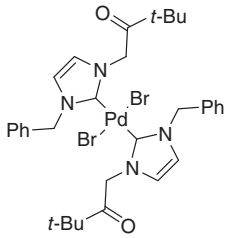


233 [R^1 = R^2 = H]
234 [R^1 = *n*-C_6H_{11}; R^2 = H]
235 [R^1 = R^2 = *n*-C_6H_{11}]

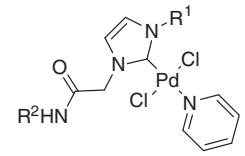
Chart 28.

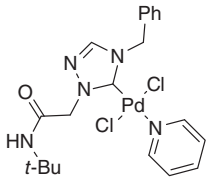


236



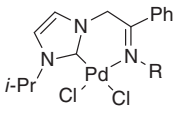
237





238 [R^1 = mesityl; R^2 = Ph]
239 [R^1 = *i*-Pr; R^2 = 2,6-*i*-$Pr_2C_6H_3$]

240

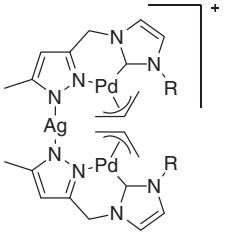


241 [R = 2,6-*i*-$Pr_2C_6H_3$]

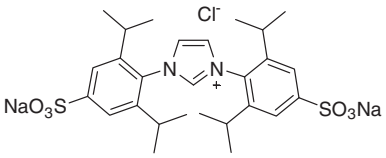
Chart 29.

of simple bromo- and iodoarenes with terminal acetylenes in the presence of CuI (2 mol %) and PPh_3 as coligand.[84] Moreover, the functionalized bis(NHC) complex **237** (Chart 29) and the monoNHC complexes **238**–**241** (Chart 29) have been prepared and tested by Ghosh and co-workers.[77–79,85] The activity of these catalysts showed to be very similar to other PEPPSI-themed complexes.

A pyrazole-functionalized imidazolium salt has been employed as the corresponding NHC ligand precursor in the preparation of the mixed palladium–silver complex **242** (Chart 30).[86] A variety of aryl bromides were coupled with phenylacetylene, hex-1-yne and oct-1-yne using 1 mol % of complex **242**, albeit the activation of the catalyst was achieved by the addition of PPh_3 (1 mol %). Sulfonated NHC ligands were designed in order to catalyze Sonogashira reactions in aqueous solvents. Accordingly, imidazolium salt **243** (Chart 30) formed in situ the corresponding NHC ligand in the presence of $Na_2[PdCl_4]$ and KOH in water/isopropanol, giving a very active



242 [R = mesityl]



243

Chart 30.

catalytic system for the alkynylation of aryl and heteroaryl halides.[87] Actually, the conversion data for the Sonogashira reactions involving heterocyclic substrates is very remarkable.

Polymeric materials containing NHC–palladium complexes have been also considered as catalysts in the Sonogashira coupling.[43,88] Poly(norbornene)-supported catalyst showed high activity comparable to the nonsupported analogues.[45] Moreover, the silylated Pd–NHC complexes **134** and **135** were immobilized on hybrid silicas, producing recyclable catalysts, which have been tested in the copper-free Sonogashira reaction between 4-bromoacetophenone and phenylacetylene with a 0.2 mol % of palladium loading. The supported catalysts were recycled up to 5 times with a loss of activity, longer reaction times being required.[47]

The one-pot hydroacylation-Sonogashira coupling was reported employing imidazolium salt **215** as NHC ligand precursor, following the same methodology as for the hydroacylation-Mizoroki–Heck reaction (vide supra). Thus, different alkynes underwent coupling with the iodo derivative resulting in the first reaction between a methyl 2-aryl-2-oxoacetate and 4-iodobenzaldehyde.[70]

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