Palladium Catalysis

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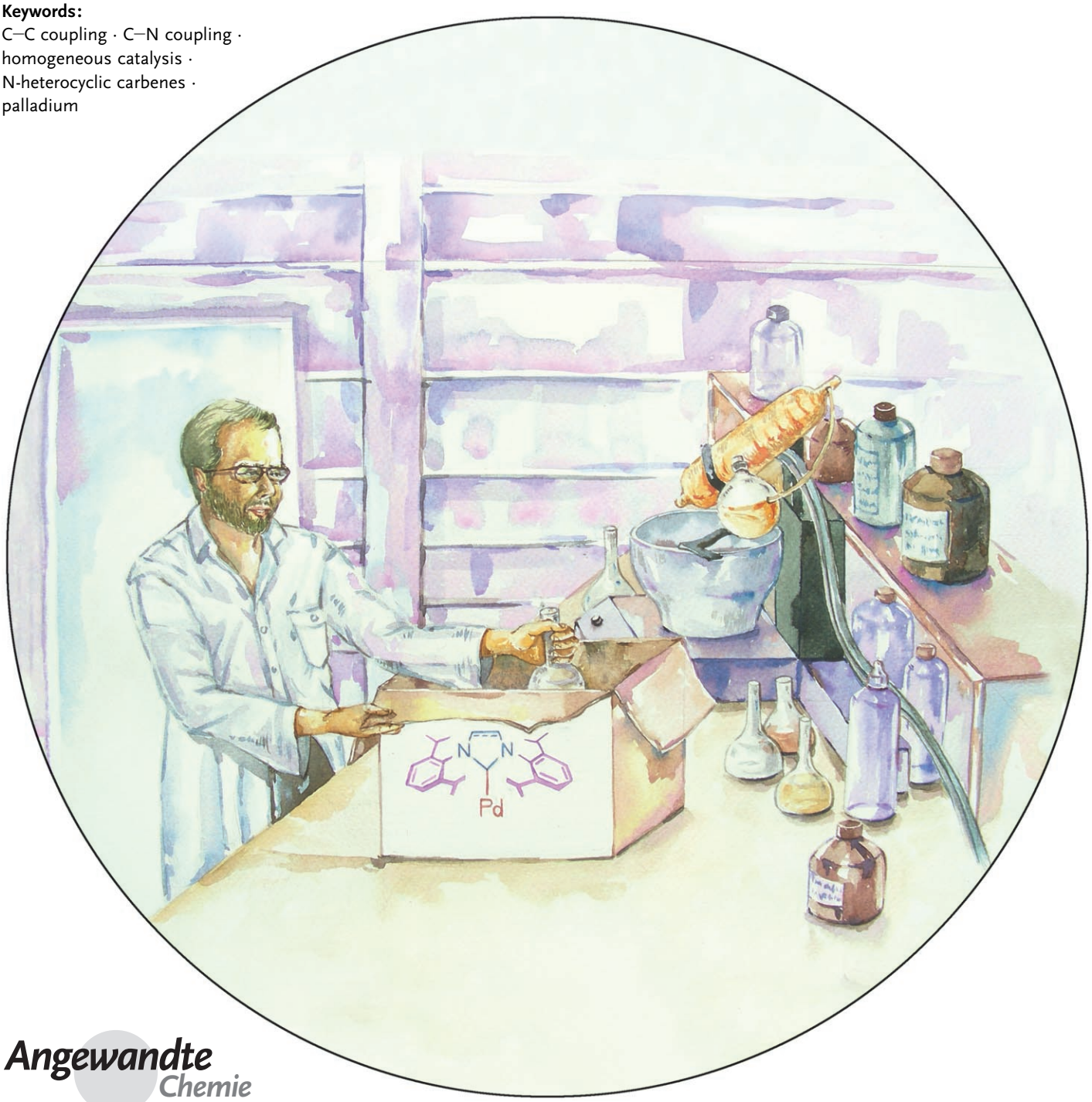
Palladium Complexes of N-Heterocyclic Carbenes as Catalysts for Cross-Coupling Reactions—A Synthetic Chemist's Perspective

*Eric Assen B. Kantchev, Christopher J. O'Brien, and Michael G. Organ**

Keywords:
C–C coupling · C–N coupling · homogeneous catalysis · N-heterocyclic carbenes · palladium

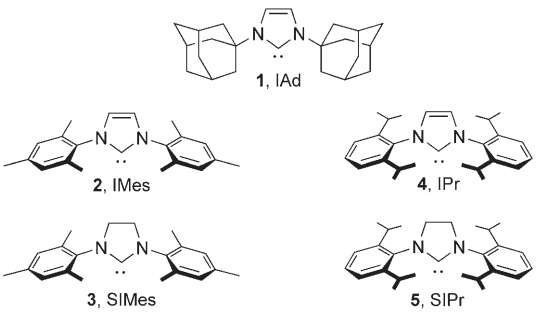


Palladium-catalyzed C–C and C–N bond-forming reactions are among the most versatile and powerful synthetic methods. For the last 15 years, N-heterocyclic carbenes (NHCs) have enjoyed increasing popularity as ligands in Pd-mediated cross-coupling and related transformations because of their superior performance compared to the more traditional tertiary phosphanes. The strong σ-electron-donating ability of NHCs renders oxidative insertion even in challenging substrates facile, while their steric bulk and particular topology is responsible for fast reductive elimination. The strong Pd–NHC bonds contribute to the high stability of the active species, even at low ligand/Pd ratios and high temperatures. With a number of commercially available, stable, user-friendly, and powerful NHC–Pd precatalysts, the goal of a universal cross-coupling catalyst is within reach. This Review discusses the basics of Pd–NHC chemistry to understand the peculiarities of these catalysts and then gives a critical discussion on their application in C–C and C–N cross-coupling as well as carbopalladation reactions.

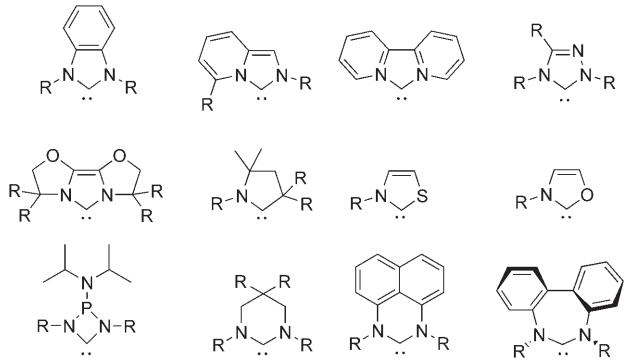
From the Contents

1. Introduction

N-Heterocyclic carbenes (NHCs), first prepared independently by Wanzlick and Schönherr[1] and Öfele[2] in 1968, attracted little interest from the chemical community until 1991, when Arduengo et al. revealed the first stable, crystalline NHC (**1**, IAd).[3] The potential of this class of compounds to serve as spectator ligands in transition-metal complexes



was recognized in 1995 by Herrmann et al.[4] Soon thereafter, the exploitation of the remarkable potential of NHC ligands in catalysis began. The above seminal works led to the development of a variety of other NHC platforms (see right column)[5] and their transition-metal complexes for catalytic applications. However, only NHCs derived from imidazolium or 4,5-dihydroimidazolium salts have found wide-spread use in homogeneous catalysis to date. The most important example is the ruthenium metathesis catalyst developed by Grubbs and co-workers, for which the Nobel Prize was awarded. Replacement of one of the two tricyclohexylphosphane ligands in the generation I Grubbs catalyst with the bulky carbene SIMes (**3**) led to significant improvements in terms of catalyst stability, activity, and substrate range in subsequent generations.[6]



Palladium is another transition metal capable of directing a wide range of useful transformations,[7] in particular C–C and C–heteroatom cross-coupling and carbopalladation reactions.[8] The use of bulky carbenes, in particular IPr (**4**) and SIPr (**5**), as ligands in these transformations has also resulted in significant improvements in catalyst performance compared to the more traditional phosphane ligands. Since these powerful methodologies have now reached the point of adoption by the mainstream synthetic community, this

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Review will provide a timely, critical overview of the field specifically from a synthetic viewpoint. Since the general, comprehensive accounts of the chemistry of NHCs by Herrmann and Köcher[9,10] as well as by Bertrand and co-workers,[11] many other reviews dealing with separate aspects of the field, for example, chiral NHCs,[12,13] structure, bonding, and reactivity of free NHCs,[14] as well as NHC complexes with transition metals[15–20] have appeared. The early forays in Pd–NHC chemistry specifically directed towards C–C cross-coupling reactions were summarized by Herrmann et al. in 2003.[21] The aim of this current Review is not to give a comprehensive account of the already very large number of papers available on NHCs and other stable carbenes, their coordination chemistry, and ligand behavior. However, from personal experience we have found that familiarity with this knowledge can greatly assist the chemist in the successful selection, implementation, and adaptation of NHC-based catalytic protocols. Hence, this topic will be covered in the necessary depth in Section 2. The complexation of NHC ligands to palladium is the subject of Section 3, with focus on the preparation of well-defined, singly ligated Pd–NHC complexes for catalytic applications. Sections 4–6 will contain a critical account of the state-of-the art in C–C and C–N cross-coupling and related transformations mediated by Pd–NHC catalysts prepared either in situ or from well-defined complexes. The mechanistic studies pertinent to the nature of the cross-coupling cycle for Pd–NHC catalysts will be presented before applications in the cross-coupling of organometallic Zn, Mg, B, Si, and Sn derivatives, the Sonogashira reaction and acetylene coupling, C–N cross-coupling (Buchwald–Hartwig amination), arylation of enolates, and π-allyl alkylations (the Tsuji–Trost reaction) are discussed. Finally, the Heck–Mizoroki reaction and related carbopalladation methods will be presented. This Review covers literature up to the end of July 2006.

2. Properties of N-Heterocyclic Carbene Ligands

2.1. Fundamentals of NHC Reactions

The idea that substituting the two hydrogen atoms in methylene ($:CH_2$) with σ-electron-withdrawing, π-electron-donating heteroatoms would lead to stabilization of the singlet, nucleophilic state of the carbene and that additional stabilization would be conferred upon incorporation in an aromatic heterocyclic framework first originated in the 1960s (Figure 1a).[22–24] In 1991, the crystal structure of the first stable, "bottle-able" carbene **1** indeed revealed a small N-C-N

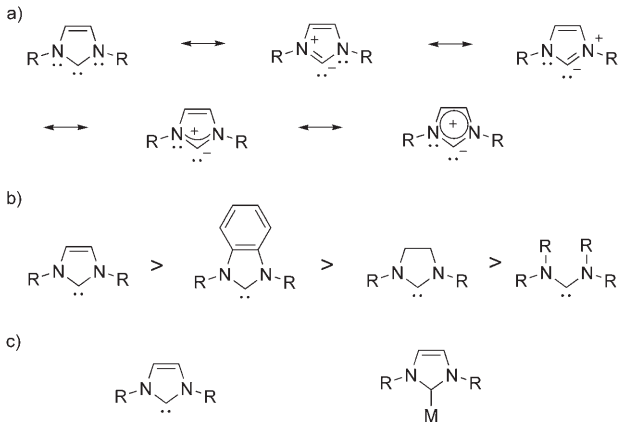

Figure 1. a) Resonance structures of imidazolyl-2-ylidenes. b) Stability trends within the diaminocarbene series. c) Structural formulas of NHCs and their metal complexes.

bond angle (102.2°),[3] characteristic of a singlet carbene, which was later confirmed by calculations.[11,25,26] The bulkiness of the adamantyl residues, however, played only a secondary role in stabilization of the carbene—the *N,N*-dimethyl analogue was also stable.[27] In contrast, bulky substituents on the nitrogen atoms are crucial for the stabilization of thermodynamically less stable carbenes (Figure 1b).[28,29] Accordingly, stable saturated carbenes (such as **3**),[30] acyclic diaminocarbenes,[31] and benzimidazolyl-2-ylidenes[32] were later isolated. Carbenes with less sterically demanding substituents were shown to dimerize readily and reversibly.[24,28,33,34] It is difficult to accurately represent the "true" structure of such carbenes on paper using conventional drawings because of electron delocalization. Therefore, for simplicity, a common idealized representation with single bonds between the carbene carbon atom and the two flanking heteroatoms, with a pair of electrons at the carbene carbon atom and no charges is used (for example, Figure 1c). In depictions of NHC–transition-metal complexes, the electron pair is replaced by a single bond between the metal atom and

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Michael G. Organ is a Professor of Synthetic Organic and Medicinal Chemistry at York University, Toronto, Canada. His synthetic research focuses on improving synthetic efficiency, organometallic chemistry and catalysis, and natural products synthesis. He has published 60 manuscripts, holds 6 patents or patents pending, and has provided 20 ACS short courses worldwide. Recently, he received the Premier's Research Excellence Award for Ontario (Canada) and the SFI Walton Fellowship (Ireland).

the carbene carbon atom (see Section 2.2 for discussion on metal–NHC bonding).

The most versatile method for the generation of NHCs is the treatment of azolium salts with a strong base (Figure 2).[3,27,30] The high proton affinities of NHCs (ca. 250 kcal mol^{-1} in the gas phase) render them as some of

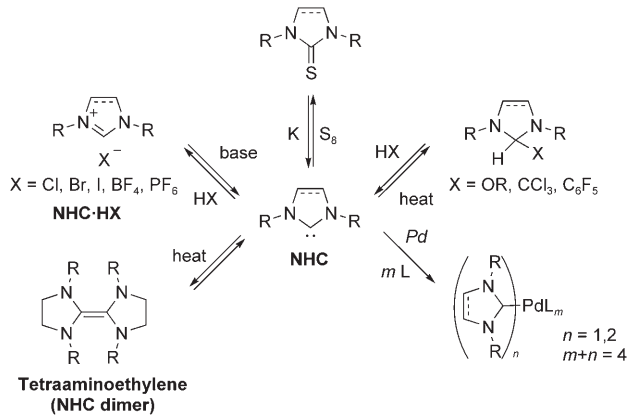
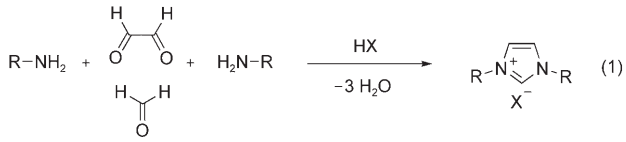


Figure 2. Reactivity patterns of NHCs of importance for palladium catalysis.

the strongest neutral bases known ($pK_a > 23$).[35] To emphasize this base/conjugated acid relationship, the azolium salt precursors are customarily designated as NHC·HX and such designation will be also used in this Review. Isolated NHCs are highly air and moisture sensitive and require handling under strictly inert conditions, in a glovebox, for example. As most palladium-catalyzed cross-coupling protocols involve either a basic organometallic reagent or external base, catalyst generation can be accomplished by simply mixing the NHC precursor and a common palladium source—$PdCl_2$, $Pd(OAc)_2$, $[Pd(dba)_2]$, or $[Pd_2(dba)_3]$—in the reaction flask before or during addition of the coupling partners. This approach avoids the cumbersome preparation and handling of isolated NHC ligands altogether. The saturated carbenes can also be prepared by 1,1-elimination of alcohols,[6,36] chloroform,[24,37] or pentafluorobenzene[37] as well as reduction of cyclic thioureas with molten potassium.[29] Since the dimerization of diaminocarbenes and saturated NHCs is reversible, the tetraaminoethylene derivatives (carbene dimers) can be used as carbene sources upon heating.[38,39]

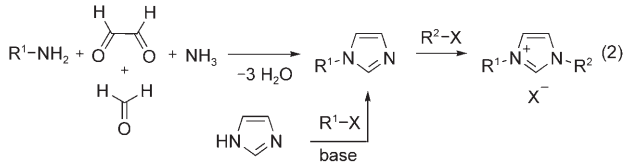
Christopher J. O'Brien obtained a BSc (UMIST, Manchester, UK) and a PhD (University of Sheffield) in organic chemistry. After working at Peakdale Molecular (UK), he undertook postdoctoral training at University of Glasgow. He is currently a senior postdoctoral fellow in the laboratory of Prof. M. G. Organ at York University. His research interests encompass transition-metal and organocatalysis, molecular design, materials, and target-oriented synthesis.

Imidazolium salts are readily available from the corresponding amine, glyoxal, and formaldehyde (or formaldehyde equivalent) in the presence of strong acid, which also provides the inorganic counterion (Scheme 1).[40–42] This synthetic



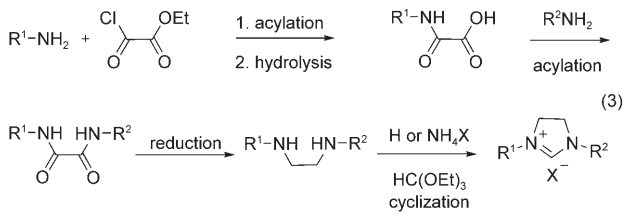
Scheme 1. R = alkyl, aryl.

approach leads to only symmetrically substituted *N*,*N*′-diaryl or *N*,*N*′-dialkyl imidazolium salts being available. However, unsymmetrical imidazolium salts can be prepared by alkylation of *N*-aryl or *N*-alkyl imidazoles (Scheme 2).[43–52] This

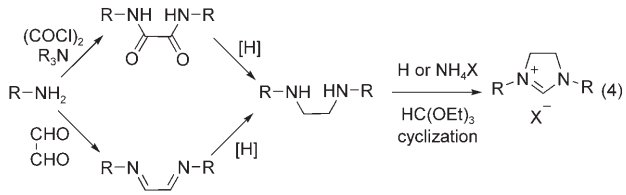


Scheme 2. R^1 = alkyl, aryl; R^2 = alkyl.

approach has been widely used for the preparation of chelating or side chain functionalized NHC precursors. 4,5-Dihydroimidazolium salts are especially well suited for the preparation of multiple analogues because the aryl substituents on the two nitrogen atoms can be varied independently when the mixed oxalamide route is employed, something that is difficult to achieve in the case of the unsaturated ligands (Scheme 3).[53–55] The shorter routes via symmetrical oxalamides[56] or diazabutadienes,[57] however, only allow the preparation of symmetrical products (Scheme 4).



Scheme 3. R^1,R^2 = alkyl, aryl.



Scheme 4. R = alkyl, aryl.

2.2. A Comparison of NHCs with Tertiary Phosphanes as Ligands

A wide variety of NHC complexes with main-group and transition metals in high and low oxidation states have been synthesized.[9] In the palladium complexes, as with most other transition metals, the NHCs act as powerful, neutral two-electron donors to form a single bond to the metal atom.[9,16,18] Whereas the π-acceptor properties of phosphanes are well-established,[58,59] there is a consensus that π-back donation from Pd to the NHC π* orbital is negligible.[60,61] However, some recent computational and experimental studies challenge such views[62]—the NHCs can use different orbitals for bonding to match the complementary metal orbitals. This bonding versatility is illustrated by the following two examples: Abernety et al. found significant π-back bonding from the chloro ligands in the *cis* position to the NHC in the isolated [(IMes)$VOCl_3$] complex.[63] Nolan and co-workers observed π-donation from I*t*Bu (**64**, Table 3) in a low-coordinate, 14-electron iridium complex.[40]

Thermochemical and computational studies on NHC complexes of ruthenium[64] and nickel[65] have shown that NHCs form considerably stronger bonds to the metal atom than do phosphanes. The concept of NHCs as "phosphane mimics" proved to be extremely fruitful in opening up new avenues for catalyst refinement by simply substituting a phosphane with an NHC.[16,18] However, compared to the extensive studies on the electronic and steric effects of phosphane substituents in transition-metal–phosphane complexes,[66] there is limited data available for NHC.[15] NHCs are stronger σ electron donors than even the most electron-rich phosphanes, as evidenced by the CO stretches in the IR spectra of complexes of the type [$LNi(CO)_2$] or [$LNi(CO)_3$][67] and [$LIr(CO)_2Cl$] or [$LRh(CO)_2Cl$][68] (L = NHC, PR_3). While phosphanes and NHCs have similar electronic structure (Figure 3), there is a very large difference in their topology when coordinated to the metal center. The three substituents of the phosphane project backwards, away from the metal, thereby forming a cone, while the substituents on the NHC nitrogen atoms project forward to form a pocket around the metal center. This arrangement in the latter case allows the topology of the substituents to have a much stronger impact on the metal center.

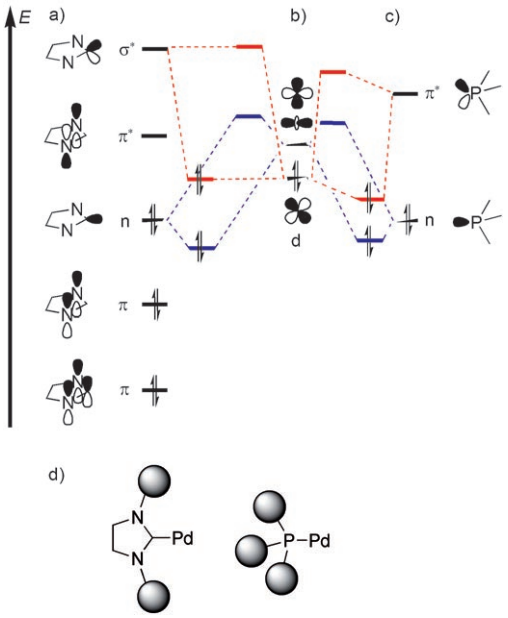


Figure 3. Simplified description of the frontier orbitals of NHCs (a) and tertiary phosphanes (c) and their interaction with the d orbitals of a transition-metal atom (b). The σ bonding from the ligand to the metal is shown in blue, whereas the π backbonding from the metal to the ligand is shown in red (see text for details). d) A comparison of the steric topographies of the two ligand classes. Adapted from Refs. [15, 58, 69].

2.3. Improving the Catalytic Activity of NHC Ligands

Both ligand classes—phosphanes and NHCs—can be tuned by incorporating substituents with predefined steric and electronic properties. In phosphanes these substituents are attached directly to the donor atom and therefore the steric and electronic effects cannot be separated. In contrast, NHCs allow, in principle, their steric and electronic properties to be tuned independently, because the flanking N substituents, which determine the steric bulk of the ligand, are not directly connected to the carbene carbon atom and thus have only a limited effect on the electronic density of this atom.[67,68] The heterocyclic moiety is largely responsible for the electronic properties of the NHC ligand.[69] Direct incorporation of substituents at C4 and C5, has been of limited use because of the lack of versatile synthetic transformations to accomplish the task.[70–73] Fusing an additional benzene ring expands the tunability of the electronic properties of the carbene ligands, as the substituents are not directly attached to the sensitive NHC heterocycle. Moreover, such distal substitution does not lead to perturbation of the steric environment that the ligands create around the Pd center. The preparation of such a library of NHC ligands based on this "orthogonal tuning" approach was recently attempted in our research group (Figure 4a). Unfortunately, as all the intended carbene ligands could not be synthesized,[53] the electronic effects were studied in the Suzuki–Miyaura coupling using only the *N*,*N*-bis(adamantyl) derivatives (Figure 4b).[74] The electron-rich *N*,*N*′-benzimidazolium salt **8** was the best for achieving high conversions with electron-rich and electron-poor reacting partners in various combinations. However, even the electron-poor analogue **6** showed synthetically useful levels of activity. These results confirm the findings that electronic variations by substitution are small. Even complexes of carbenes with electron-withdrawing groups are sufficiently electron rich to readily insert even into deactivated chloroloarenes.

Thus, varying the steric bulk of the substituents surrounding the metal center offers a more promising avenue for tuning the NHC ligands. Table 1 shows a comparison of a range of imidazolium and 4,5-dihydroimidazolium NHC precursors in the context of a number of Pd-mediated reactions (Schemes 5–14): aryl–aryl Suzuki–Miyaura coupling,[75] alkyl–alkyl Negishi coupling,[54] Heck–Mizoroki reactions,[76] Sonogashira coupling with aryl[77] and alkyl bromides[78] and Buchwald–Hartwig amination[57] reactions,

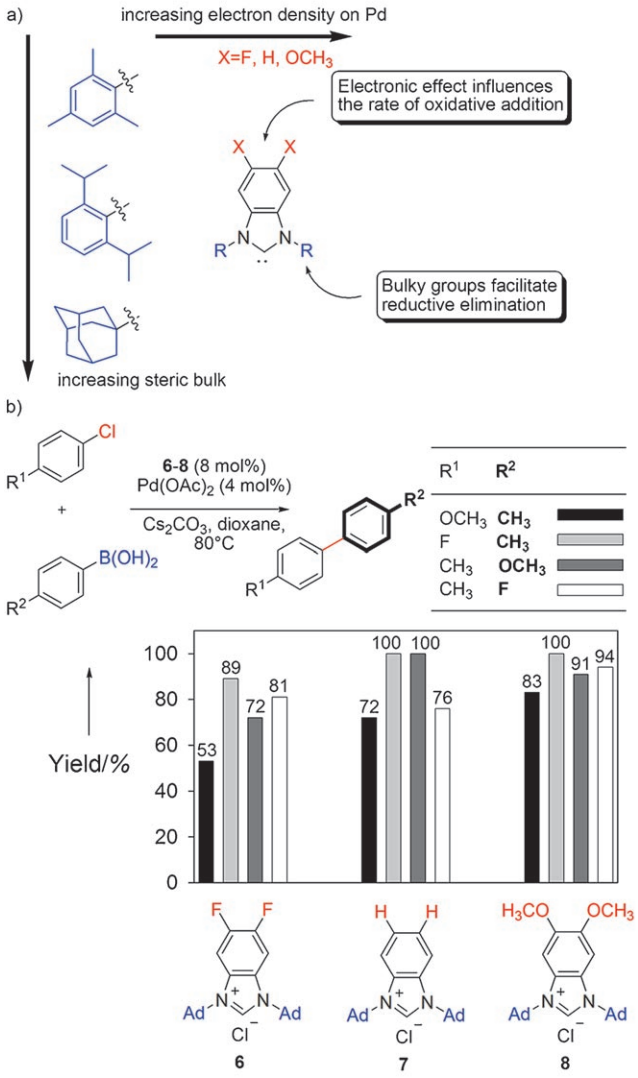
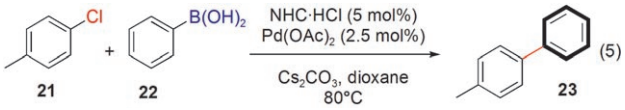
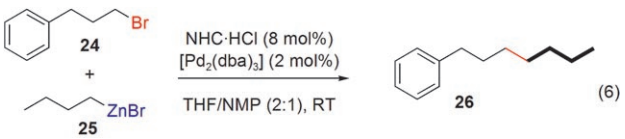


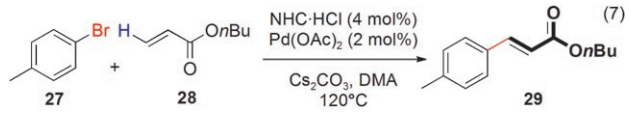
Figure 4. a) Orthogonally tunable benzimidazolyl-2-ylidenes. b) Ligand activity of *N*,*N*′-bis(adamantyl)benzimidazolium salts **6**–**8** in the Suzuki–Miyaura coupling.[53,70]



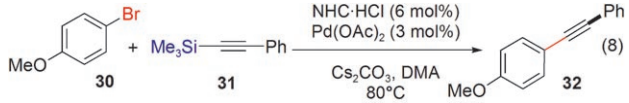
Scheme 5.



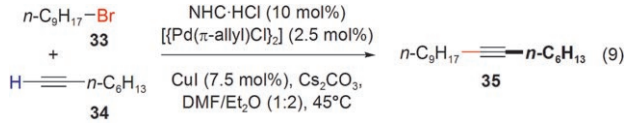
Scheme 6.



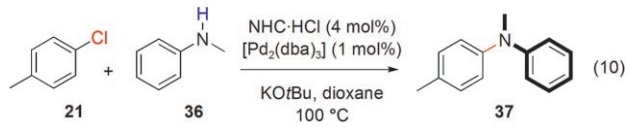
Scheme 7.



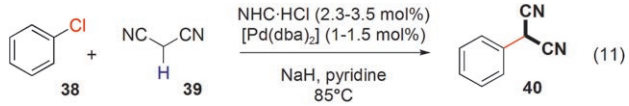
Scheme 8.



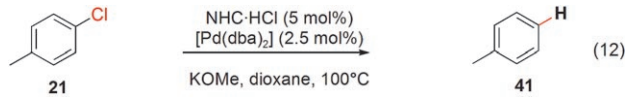
Scheme 9.



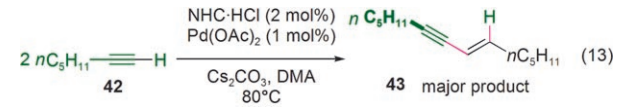
Scheme 10.



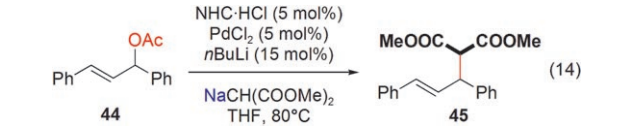
Scheme 11.



Scheme 12.



Scheme 13.

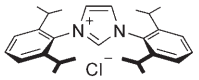


Scheme 14.

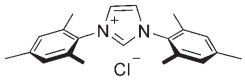
arylation of malononitrile,[79] dehalogenation of arenes,[80] dimerization of alkynes,[81] and π-allyl alkylation (Tsuji–Trost reaction).[82] The most bulky *N*,*N*′-diaryl ligand precursors IPr·HCl (**9**) and SIPr·HCl (**13**) showed overall the best performance in almost all cases. Therefore, IPr and SIPr are the best choice for the preparation of Pd–NHC catalysts of high activity and broad applicability. In particular, these ligands are indispensable for the activation of alkyl reaction partners (Schemes 6, 9, and 14). In general, less sterically hindered IMes·HCl (**11**) and SIMes·HCl (**17**) were effective

Table 1: Yields [%] in reactions with Pd–NHC catalysts derived from salts **9**–**20** (Schemes 5–14).

N,N'-diarylimidazolium salts

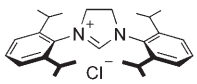


9, IPr·HCl

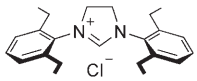


11, IMes·HCl

N,N'-diaryl-4,5-dihydroimidazolium salts

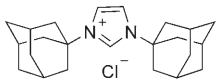


13, SIPr·HCl

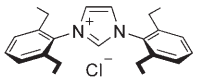


16, SIEt·HCl

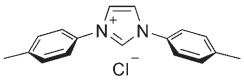
N,N'-dialklylimidazolium salts



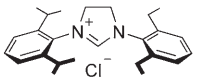
18, IAd·HCl



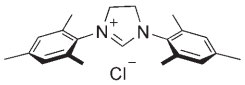
10, IEt·HCl



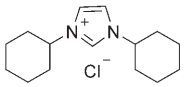
12, ITol·HCl



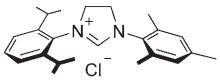
14, SIPr-Et·HCl



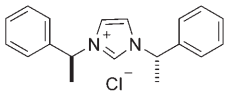
17, SIMes·HCl



19, ICy·HCl



15, SIPr-Mes·HCl



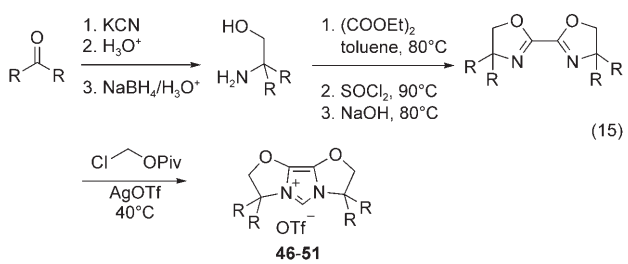
20, IPhEt·HCl

Scheme	9	10	11	12	13	14	15	16	17	18	19	20
5[75]	95[a]	–	99	5	–	–	–	–	–	44	14	–
6[54]	76[b]	17	2.8	–	85	47	23	11	1.2	0.6	–	–
7[76]	66	–	94	13	19[c]	–	–	–	64	2	90	–
8[77]	80	–	87	62	60	–	–	–	66	56	–	–
9[78]	67	–	–	–	58[d]	–	–	–	<58[d]	80	–	–
10[57]	98	–	22	<5	–	–	–	–	–	–	–	–
11[79]	70[e]	73[e]	75	<5	–	–	–	–	–	–	–	–
12[80]	45	–	46	–	56	–	–	–	96[f]	49	30	–
13[81]	76	–	97	34	14	–	–	–	88	45	34	–
14[82]	77	–	25	–	–	–	–	–	–	–	0[g]	13

[a] Using 1 mol% $[Pd_2(dba)_3]$; the standard conditions resulted in only 53% yield. [b] Other Pd sources used (4 mol%): $Pd(OAc)_2$ 75%; $PdBr_2$ 74%; $Pd(OOCCF_3)_2$ 40%; $PdCl_2$ 19%; $[\{(\pi\text{-allyl})PdCl\}_2]$ 6%. [c] Using 2 mol% $[Pd(dba)_2]$ 4% yield. [d] The corresponding BF_4 salts were used. [e] The corresponding 2,4,6-trisubstituted imidazolium chlorides were used. Surprisingly, **9** and **10** led to <5% yield. Such a discrepancy in the yield is probably due to failure to form the active catalyst rather than intrinsic low catalytic activity. *para* Substitution is unlikely to introduce gross perturbation in the ligand properties (see text). [f] At 2 mol%, $[PdCl_2(PhCN)_2]$ 16%; $Pd(OAc)_2$ 2%. [g] *N,N*-diisopropylimidazolium chloride.

only if haloarenes were used. ITol·HCl (**12**), which lacks any *ortho* substituents, was shown to be inferior to IPr and IMes in all cases. Among *N,N'*-dialkylimidazolium salts, IAd·HCl (**18**) provides good to excellent results in some reactions (Schemes 8 and 9), but seldom outperforming IPr. The less bulky ligand precursors ICy·HCl (**19**) and IPhEt·HCl (**20**) were not studied in detail, but their performance seems to be generally unsatisfactory. The saturated 4,5-dihydroimidazolyl-2-ylidenes were much less reliable than their unsaturated counterparts. This is attributed to the higher stability of the aromatic, unsaturated ligands. The use of more stable ligands affects the amount of active catalyst produced initially, its stability, and its lifetime, especially at the high temperatures required for some cross-coupling protocols. The nature of the transformation itself is also important when ligands are to be compared: the more challenging the coupling, the higher the differences in the ligand activity observed. Almost all the ligands tested were shown to be quite effective for the trivial Heck reaction of *para*-bromotoluene (**27**) and *n*-butyl acrylate (**28**, Scheme 7); indeed, $Pd(OAc)_2$ alone led to 38% yield. For comparison, the very challenging alkyl–alkyl Negishi coupling (Scheme 6) poses a very stringent requirement for the steric environment created by the ligand. While SIPr·HCl (**13**) led to an 85% yield of the cross-coupling product, the yield dropped almost by half when one of the 2,6-diisopropylphenyl substituents was changed to 2,6-diethylphenyl (SIPr-Et·HCl, **14**); another halving of the yield occurred when a mesityl substituent was introduced in its place (SIPr-Mes·HCl, **15**).

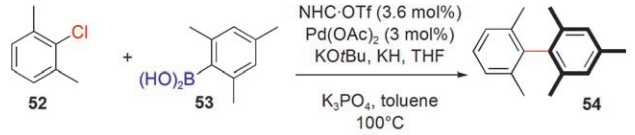
The concept of steric tuning was further refined by Glorius and co-workers, who prepared a range of pentacyclic NHC precursors (**46**–**51**) bearing conformationally flexible cyclic rings in proximity to the Pd center (Scheme 15).[83,84] These NHCs proved to be slightly less σ donating than the monocyclic imidazolium derivatives as a result of the electron-withdrawing effect of the oxygen atoms at the distal carbon atoms of the imidazolium ring. The size of the cycloalkyl substituents did not affect the electronic properties of the ligands, again confirming the idea of independent steric and electronic tuning. The effect of the ligand size was probed by using a very challenging Suzuki–Miyaura cross-coupling reaction to give a tetra-*ortho*-substituted biphenyl as the



Scheme 15. Synthesis of ligand precursors **46**–**51** with flexible steric bulk.

product (Table 2). It was proposed that the conformational flexibility ("flexible steric bulk") of the medium-sized spirocyclooctyl and spirocyclododecyl substituents is primarily responsible for the exceptionally high activity of ligands **50** and **51**. These ligands are able to adapt to the differing steric requirements of the catalyst during the different stages of the catalytic cycle. In contrast, IMes·HOTf and IAd·HOTf proved to be completely ineffective in this reaction. The exceptional elegance of this ligand system is, unfortunately, marred by the lengthy ligand synthesis (seven steps from commercially available cycloalkanones, Scheme 15) and the use of alkali cyanide during the preparation of the required β-aminoalcohol intermediates.

Table 2: Activity of pentacyclic NHC ligands (**46**–**51**, Scheme 15) in the Suzuki–Miyaura cross-coupling reaction.[83]

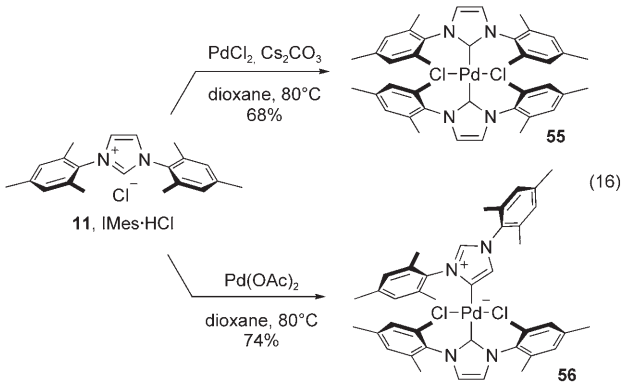


Entry	NHC·OTf	R,R	Name	Yield [%]
1	**46**	Me_2	$IBioxMe_4$	12
2	**47**	$-(CH_2)_4-$	IBiox5	19
3	**48**	$-(CH_2)_5-$	IBiox6	18
4	**49**	$-(CH_2)_6-$	IBiox7	64
5	**50**	$-(CH_2)_7-$	IBiox8	82
6	**51**	$-(CH_2)_{11}-$	IBiox12	96

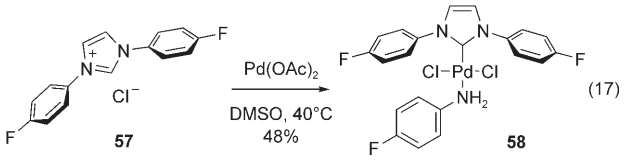
3. Pd–NHC Complexes in Homogeneous Catalysis

3.1. Complexation of NHCs to Pd—Implications for Catalysis

The source of the Pd used in the reaction was found to create large variations in the performance of Pd–NHC catalysts generated in situ (Table 1).[54,75,76,80] Furthermore, only low to moderate yields were often achieved when Pd–NHC complexes were synthesized under conditions similar to the conditions of the cross-coupling reactions.[50,83,85,86] In addition, coordination of NHCs through the backbone carbon atoms (with formation of "unusual" NHC complexes, Scheme 16)[87] and even incorporation of degradation products from the NHC precursor in the coordination sphere of Pd atom (Scheme 17)[88] were occasionally reported. The yields of the cross-coupling product observed when utilizing catalyst prepared in situ are cumulative of two distinct events: 1) the formation of a certain amount of active catalyst; 2) the intrinsic activity of this catalyst in the reaction of interest. However, the contributions of these two events cannot be measured separately. In most of the cross-coupling reactions shown in Schemes 3–15 a NHC/Pd ratio of 2:1 was used, since it was assumed that a $[(NHC)_2Pd]$ species was formed. Comparative studies utilizing precatalysts of different composition question this assumption. For the alkyl–alkyl Negishi cross-coupling reaction, when IPr/Pd ratio was varied from 1:1 to 3:1, our research group found little change in the yield,

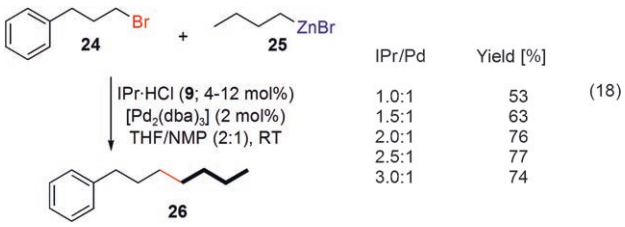


Scheme 16.

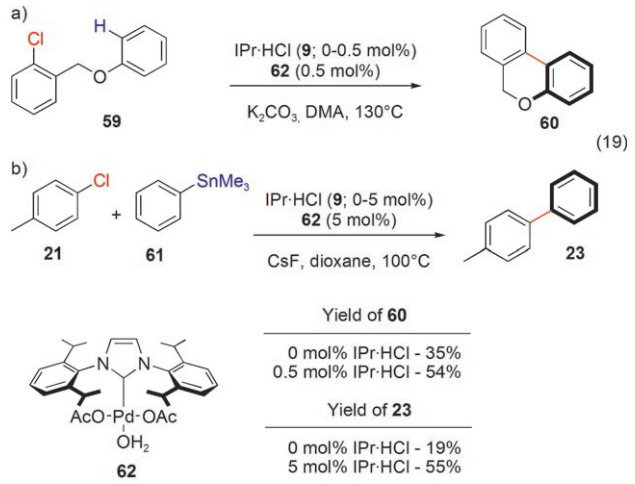


Scheme 17.

thus indicating that one and the same catalytically active species, which was proposed to be a singly ligated [(IPr)Pd] complex, was formed in different amounts (Scheme 18).[54] Similarly, Fagnou and co-workers[89] reported that the addition of excess IPr·HCl (**9**) to the catalytically active, preformed IPr–Pd complex **62** led to increased turnover and prevention of the formation of palladium-black during the course of the intramolecular arylation (Scheme 19a) and Stille reactions (Scheme 19b). Presumably, the excess of ligand precursor helped recruit inactivated Pd back into the catalytic cycle; it was shown that the addition of IPr·HCl (**9**, Table 1) to Pd/C also produced an active catalyst. These results imply that the active species in these cases was a singly ligated IPr–Pd complex regardless of the nominal IPr/Pd ratio. Therefore, generation of the catalyst in situ allows no control over the chemical composition and amount of active catalyst produced. The formation of a number of complexes under these conditions, each having different catalytic activity, is possible. Consequently, the necessary quantitative studies of catalyst performance for rigorous mechanistic interpretation of results are not possible and a large proportion of the total amounts of precious metal and ligand precursor are wasted. The use of well-defined Pd–



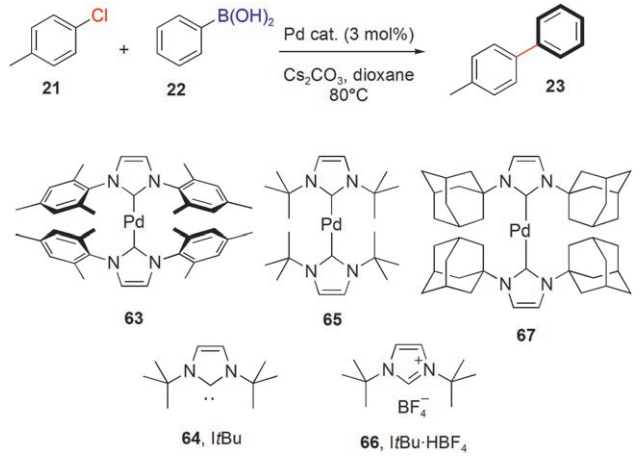
Scheme 18.



Scheme 19.

NHC complexes could potentially alleviate the problems associated with the generation of the catalyst in situ—provided that such complexes can be activated upon submission to the reaction conditions, which is not often the case. Even though the catalysts prepared from IMes·HCl (**11**, Table 1) and $[Pd_2(dba)_3]$ showed high and comparable activity when NHC/Pd was either 1:1[90] or 2:1,[75] the corresponding isolated $[(IMes)_2Pd]$ (**63**) complex was completely inactive (Table 3, entries 1–3).[90] However, the I*t*Bu ligand (**64**) gave the opposite result—$[(I\mathit{t}Bu)_2Pd]$ (**65**) led to 68% yield, whereas the catalyst produced from I*t*Bu·HBF_4 (**66**) and $[Pd_2(dba)_3]$ (1:1) was completely inactive (Table 3, entries 4 and 5).[90] The even bulkier $[(IAd)_2Pd]$ (**67**) was highly active

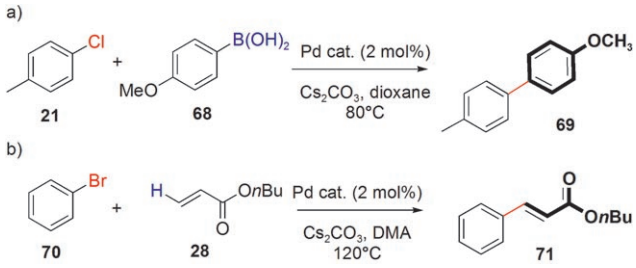
Table 3: Comparison of $[(NHC)_2Pd^0]$ precatalysts and in situ generated catalysts in the Suzuki–Miyaura cross-coupling reaction.[75,90,91]



Entry	NHC	Pd cat.	Yield [%]
1	IMes (**2**)	$[(IMes)_2Pd]$ (**63**)	0
2	IMes·HCl (**11**) +	$[Pd_2(dba)_3]$ (1:1)	93
3	IMes·HCl (**11**) +	$[Pd_2(dba)_3]$ (2:1)	96
4	I*t*Bu (**64**)	$[(I\mathit{t}Bu)_2Pd]$ (**65**)	68
5	I*t*Bu·HBF_4 (**66**) +	$[Pd_2(dba)_3]$ (1:1)	0
6	IAd (**1**)	$[(IAd)_2Pd]$ (**67**)	96
7	IAd·HCl (**18**) +	$Pd(OAc)_2$ (2:1)	44

in Suzuki–Miyaura cross-coupling reactions of non-activated chloroarenes at room temperature,[91] while the in situ prepared catalyst (IAd/Pd 2:1) was moderately active.[75] Similar results are observed for palladium(II) precatalysts: whereas $[(IMes)_2PdCl_2]$ (**55**) was totally unreactive in Heck–Mizoroki and Suzuki–Miyaura reactions (Table 4),[87] the unusual Pd complex **56** (Scheme 16) bearing one IMes ligand coordinated

Table 4: Comparison of $(NHC)_2Pd^{II}$ precatalysts and in situ generated catalysts in Suzuki–Miyaura cross-coupling (a) and Heck–Mizoroki reactions (b).[87]



Entry	Pd cat.	Yield [%] **69**	**71**
1	$[(IMes)_2PdCl_2]$ (**55**)	0	0
2	$[(IMes)PdCl_2$-(C4-IMes)] (**56**)	44	77
2	IMes·HCl (**11**) + $Pd(OAc)_2$ (1:1)	76	56
3	IMes·HCl (**11**) + $Pd(OAc)_2$ (2:1)	56	66

through C4 and one IMes ligand coordinated through the carbene carbon atom (C1) exhibited activity similar to the catalyst produced by employing the in situ protocol. Presumably, the carbene ligand coordinated in this unusual mode is labile under the reaction conditions and a catalytically active, singly ligated IMes–Pd complex is produced upon its dissociation. The above examples illustrate well an important point: the coordination of Pd with NHCs is not trivial and the preparation of an active catalyst represents a major bottleneck in catalytic applications.

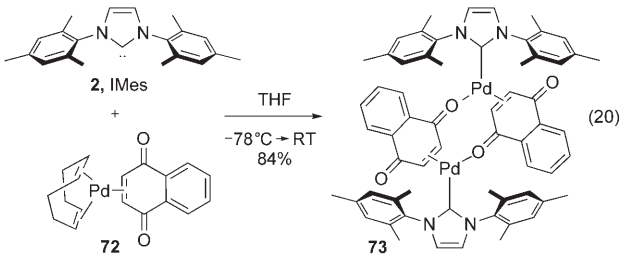
In summary, doubly ligated homoleptic Pd^{II}–NHC complexes have much lower activity than their Pd^0 counterparts, presumably because of the higher stability of $(NHC)_2Pd^{II}$ species. Calculations have shown that NHC ligands have higher affinity to Pd^{II} than to Pd^0.[53] The results in Table 4 demonstrate that Pd^{II} precatalysts are much more active when another ligand more labile than a second NHC ligand is present. Palladium complexes with chelating and pincer carbenes[20] are even more stable then their monodentate counterparts.[4] In general, they have proven to be of limited use in cross-coupling reactions, even though in selected cases[92–94] very high TOFs and TONs have been observed at high temperatures. Since chelating NHCs require higher synthetic investment, the development of general, synthetically useful catalysts has focused exclusively on monodentate carbenes.

3.2. General Synthetic Methods for Pd–NHC Complexes

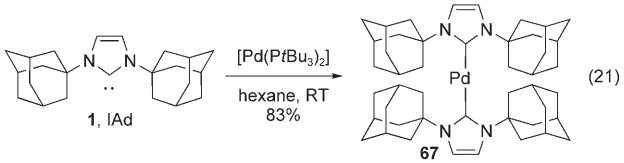
The synthesis of well-defined Pd–NHC complexes has been the subject of extensive studies. The aim of this section is

to briefly present the general synthetic routes available. Selected examples will be used to demonstrate each method.

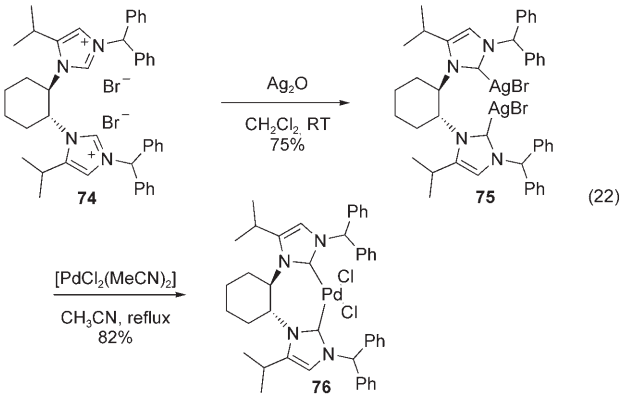
Most NHCs form either singly or doubly ligated complexes with both Pd^0 and Pd^{II} centers; higher coordination numbers are observed only for the smallest NHCs, and are rare.[95–98] The strength of the Pd–NHC bonds renders ligand exchange (Schemes 20–25) an excellent general route to



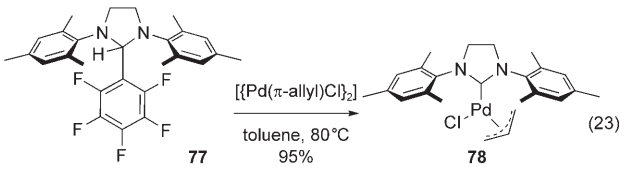
Scheme 20.



Scheme 21.

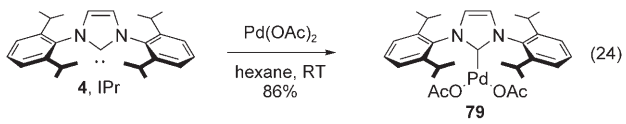


Scheme 22.



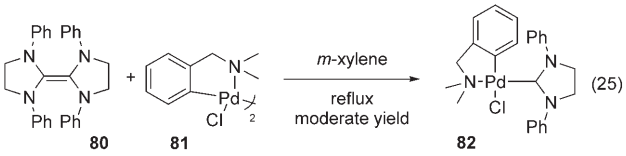
Scheme 23.

Pd–NHC complexes starting from the preformed carbene and Pd^{II} or Pd^0 complexes with alkenes,[99] phosphanes,[91] nitrogen ligands,[45] or bridging chloride[37,100] or acetate ligands.[101] Pure, isolated carbenes (Schemes 20, 21, and 24), or carbene transfer agents such as silver halide complexes (Scheme 22), pentafluorobenzene adducts (Scheme 23), or carbene dimers



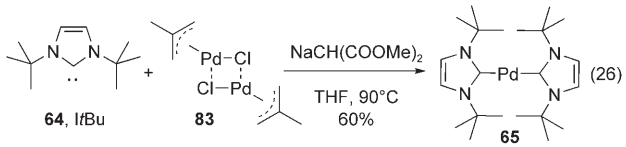
Scheme 24.

(Scheme 25) are suitable. Under certain conditions, reduction of Pd^{II} to Pd^0 can be carried out simultaneously with the



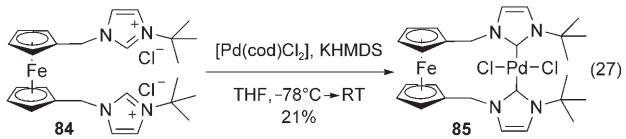
Scheme 25.

complexation of the NHC (Scheme 26).[102] Another approach is to use an azolium salt precursor in the presence of a base to

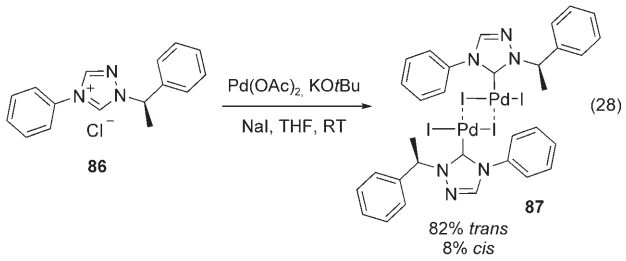


Scheme 26.

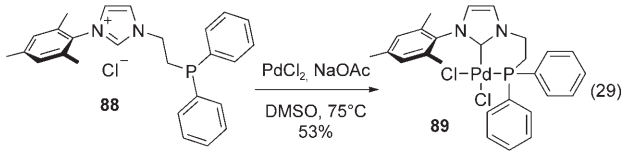
form in situ the NHC, which is captured by Pd (Schemes 16 and 27–29). Even though strong bases such as KHMDS[43] and KO*t*Bu[103] are effective, more often, weak bases such as



Scheme 27.

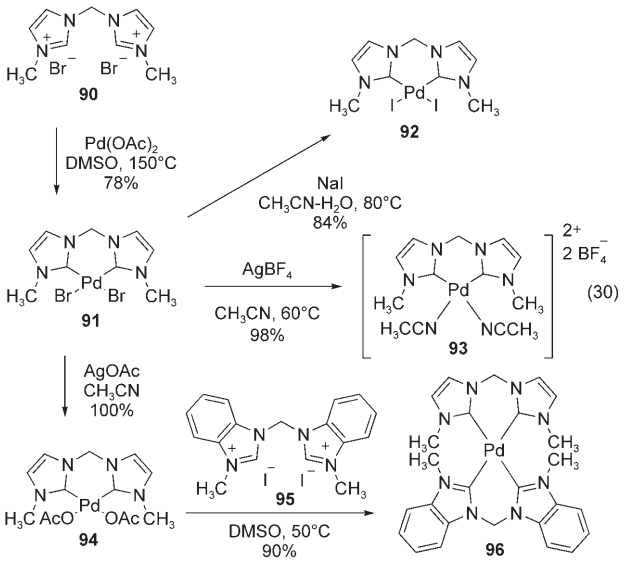


Scheme 28.



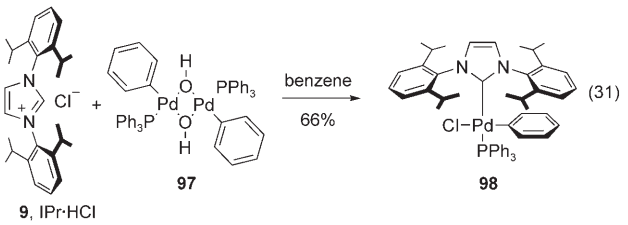
Scheme 29.

Cs_2CO_3[87] or even NaOAc[44] are used. However, the mechanism of the generation and transfer of the carbene in the presence of such weak bases is unclear. $Pd(OAc)_2$ as both the Pd source and base is especially attractive from an atom economical point of view (Schemes 17 and 30);[88,98,104,105] a



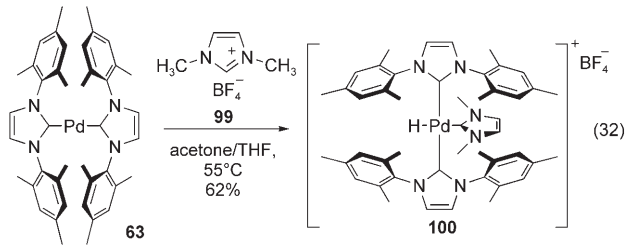
Scheme 30.

related methodology involves the use of Pd-μ-hydroxide (Scheme 31).[106] Halides introduced either as the counterion to the azolium salt or from an additive are incorporated in the

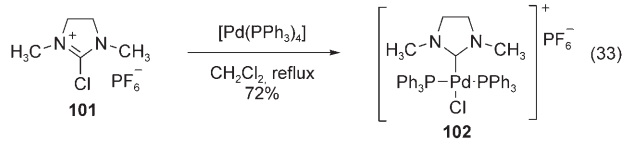


Scheme 31.

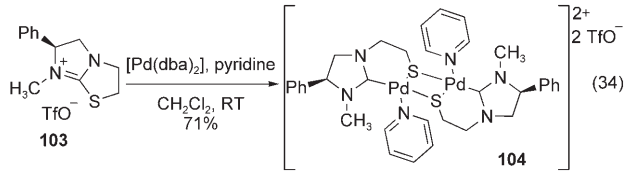
coordination sphere of the Pd atom, thereby resulting in the formation of NHC–palladium halide complexes (Schemes 16, 17, 28, 30, and 31). The Pd-bound halides are labile and subject to anion exchange in the presence of Ag or alkali-metal salts of ions with high coordinating affinity in suitable solvents. The use of salts of noncoordinating anions such as BF_4^- or PF_6^- in acetonitrile leads to the preparation of cationic palladium–acetonitrile complexes which can be isolated as the corresponding BF_4 or PF_6 salts (Scheme 30).[98,104] Finally, Pd^0 species oxidatively insert into C–H,[95] C–Cl,[107] and C–S[108] bonds at the carbene carbon atom (Schemes 32–34) to form Pd^{II}–NHC complexes.



Scheme 32.



Scheme 33.

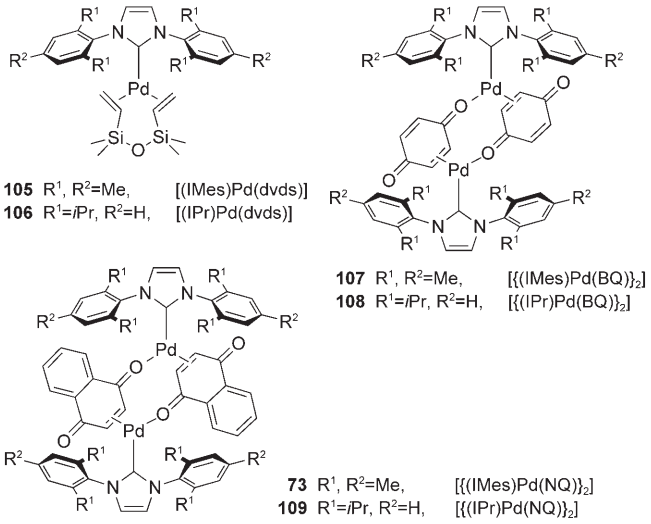


Scheme 34.

3.3. Development of Well-Defined, Highly Active Singly Ligated Pd–NHC Precatalysts

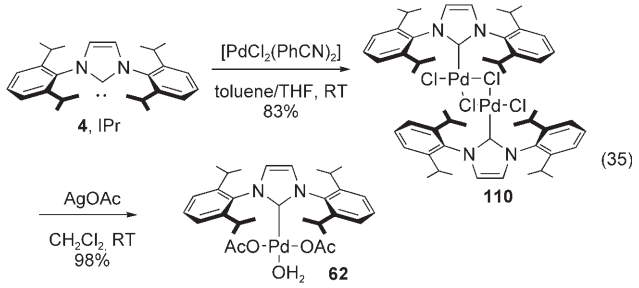
Stable, coordinatively saturated 18- or 16-electron complexes are formed when four vacant coordination sites around the Pd atom (oxidation states 0 or +II, respectively) are filled. The ligand-screening studies presented in Section 2.3 have shown that the bulky carbenes IPr (**4**) and SIPr (**5**), and—to a lesser extent—IMes (**2**) and SIMes (**3**), are the most active and versatile ligands for Pd–NHC-catalyzed reactions. These carbenes are especially favorable for the stabilization of coordinatively unsaturated, singly ligated Pd–NHC species. Analogous singly ligated complexes of Pd and bulky phosphanes have been shown to have excellent activity in cross-coupling reactions.[109] Therefore, a single bulky NHC ligand is sufficient for high catalyst activity. This leaves up to three coordination sites to be filled with appropriate replaceable ligands. The nature of the replaceable ligands determines the ease of activation of the Pd–NHC precatalyst, and this is a crucial factor for the success of the attempted catalytic transformation. Finally, the oxidation state of the palladium center and, to a lesser extent, the nature of the replaceable ligands determines the stability of the complex.

The inadequate stability of Pd^0–NHC complexes to oxygen and storage as well as the limited, unattractive synthetic routes—all of which require handling the moisture- and air-sensitive free carbene—handicap their use as precatalysts. The research group of Beller developed a number of singly ligated Pd^0 complexes of IPr and IMes with *para*-quinone (**73**, **107**–**109**) or dvds ligands (**105** and **106**) by substitution of the cycloocta-1,5-diene (cod) ligands in



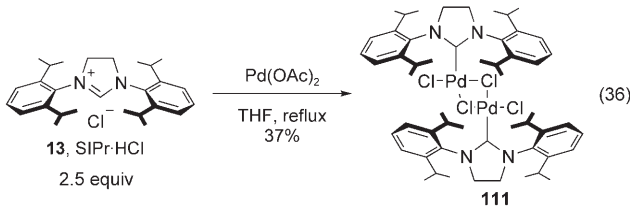
commercially unavailable [Pd(cod)(alkene)] complexes (for example, **72**, Scheme 20).[99,110,111]

Pd^{II}–NHC complexes are more attractive as precatalysts because of their stability to air, moisture, and heating and also have an excellent long-term storage profile. IPr adducts of simple Pd salts, for example, $Pd(OAc)_2$ and $PdCl_2$, are known. Monomeric IPr complexes of $Pd(OAc)_2$ and $Pd(OOCCF_3)_2$ were prepared by treatment of the Pd salt with the free carbene **4** under anhydrous conditions (for example, **79**, Scheme 24).[101,112] In contrast, a similar reaction with $[PdCl_2(RCN)_2]$ (R = Me, Ph) resulted in the formation of the dimeric IPr–$PdCl_2$ adduct **110** (Scheme 35).[113] Further anion



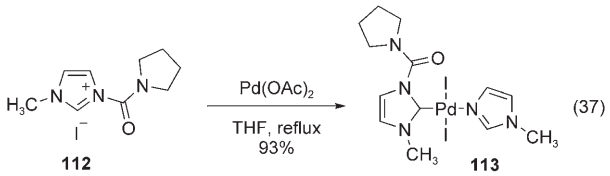
Scheme 35.

exchange of **110** with AgOAc leads to **62**, the hydrated analogue of complex **79**.[89,114] Similar complexes can be prepared directly from the imidazolium salts, thus by-passing the cumbersome handling of free carbene: Andrus and co-workers prepared the SIPr–$PdCl_2$ dimer (**111**) in 37% yield by simple heating $Pd(OAc)_2$ and 2.5 equivalents of SIPr·HCl (**13**) in THF (Scheme 36).[86] Despite the presence of a large excess of the NHC precursor, only a singly ligated Pd–NHC species was obtained. A mechanism for the formation of the complex, involving the attack of $Pd(OAc)_2$ on the 4,5-dihydroimidazolium cation, followed by ligand exchange with chloride and 1,2-elimination of acetic acid was proposed. Complex **111** was not further used in catalysis. In a similar fashion, heating **112** with $Pd(OAc)_2$ resulted in the unusual



Scheme 36.

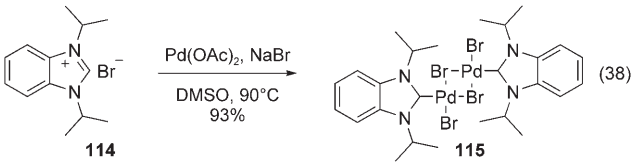
complex **113** (Scheme 37).[115] Decomposition of the second equivalent of the *N*-carbamoylimidazolium salt by acetic acid



Scheme 37.

(produced during the formation of the singly ligated Pd–NHC complex) to *N*-methylimidazole and *N*-acetylpyrrolidine, followed by complexation of the singly ligated Pd–NHC species with *N*-methylimidazole most likely accounts for this unusual transformation.

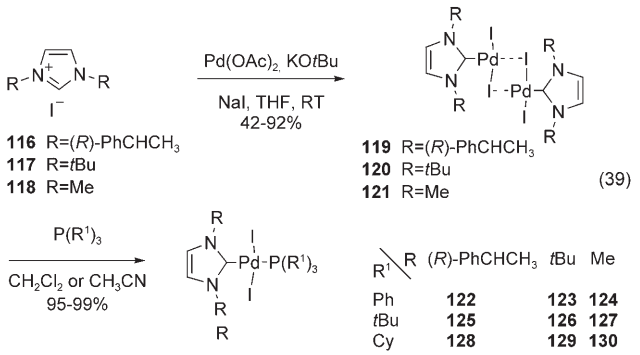
This approach is not restricted to imidazolium salts. Huynh et al. synthesized a benzimidazolyl-2-ylidene–$PdBr_2$ dimer **115** in 93% yield by heating **114**, $Pd(OAc)_2$, and NaBr in DMSO (Scheme 38).[116] The addition of N and P ligands



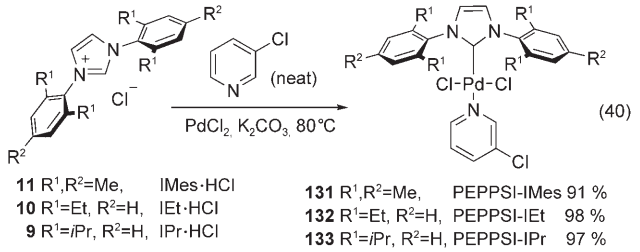
Scheme 38.

(L = CH_3CN, PPh_3) resulted in monomeric $[(NHC)PdBr_2(L)]$ complexes. Whereas the acetonitrile adduct had a *trans* configuration between the NHC and CH_3CN ligands, the *cis* adduct was more stable for the corresponding phosphane complex. A similar approach was previously revealed by Glorius and co-workers:[83] Heating IBiox6·HOTf (**48**) with $Pd(OAc)_2$ and LiCl in THF resulted in the corresponding NHC–$PdCl_2$ dimer in 91% yield. The more challenging IBiox12 precursor **51** required the addition of Cs_2CO_3 for complexation. However, the analogous complex was obtained in only 45% yield, most likely because of base-promoted decomposition. In an earlier study Herrmann et al. had shown that treatment of imidazolium salts **116**–**118** with KO*t*Bu, $Pd(OAc)_2$, and NaI resulted in the formation of bridged NHC–PdI_2 dimers **119**–**121**. Further treatment with triaryl- or trialkylphosphanes led to an array of mixed $[(NHC)PdI_2(PR_3)]$ complexes with the *trans* configuration (**122**–**130**,

Scheme 39).[117] The ease of synthesis and the modularity of this approach could in principle allow the preparation of catalyst libraries with tailored activity. Very recently, our research group described the preparation of [(NHC)$PdCl_2$(3-ClPy)] complexes **131**–**133** in excellent yields (91–98%) by heating a mixture of $PdCl_2$ and 1.1 equivalents of the imidazolium salts **9**–**11** with K_2CO_3 in 3-chloropyridine, without the need to use anhydrous conditions (Scheme 40).[118] The excess 3-chloropyridine could be recycled through distillation. The reaction was later scaled up to a kilogram scale.

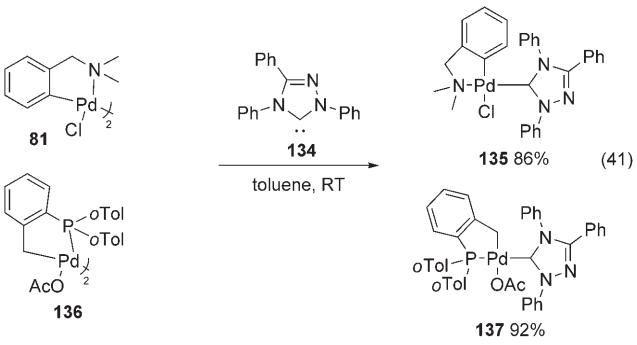


Scheme 39.

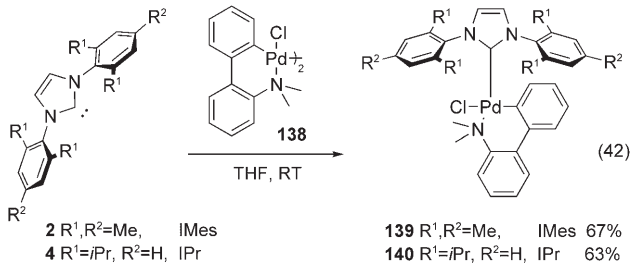


Scheme 40.

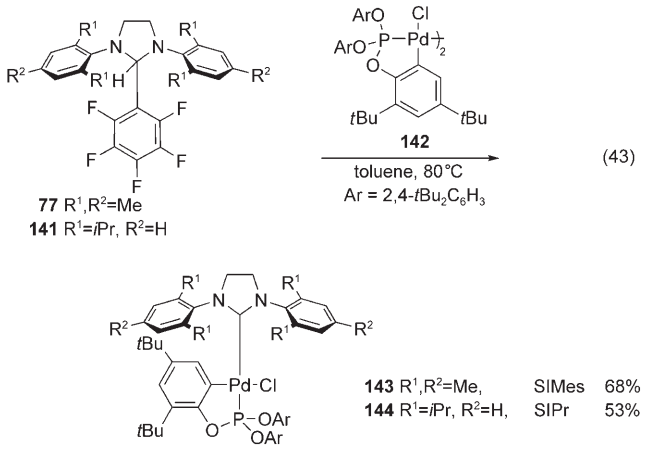
Complexes with bidentate replaceable ligands have also received much attention. NHC palladacycles are often prepared by displacement of the bridging chloride ligand of the corresponding dimeric palladacycle by the free NHC, as demonstrated in a recent study by Herrmann and co-workers (Scheme 41).[97] Afterwards, the same research group disclosed an improved method for the preparation of similar palladacycles through the formation of an in situ carbene from the corresponding imidazolium salts by using a weak base (NaOAc) in DMSO. However, the use of KO*t*Bu was necessary for the more basic cyclic diaminocarbenes.[119] Palladacycle precatalysts ligated with IMes (**139**) and IPr (**140**) were prepared by Nolan and co-workers (Scheme 42),[120] from the isolated carbenes **2** and **4**. Bedford et al. synthesized (Scheme 43) saturated NHC-ligated phosphite palladacycles **143** and **144** in moderate yields by utilizing pentafluorobenzene carbene adducts **77** and **141** as the NHC source.[121] This approach is limited only to 4,5-dihydroimidazolium NHCs. Palladacycle adducts of *N*,*N*′-diphenyl-4,5-



Scheme 41.



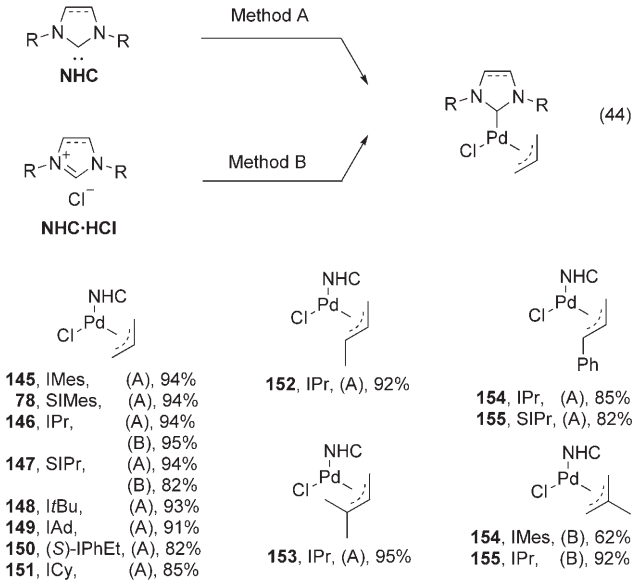
Scheme 42.



Scheme 43.

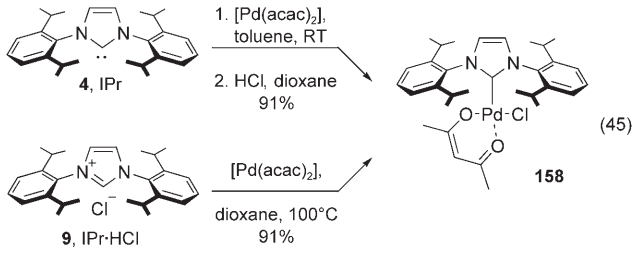
dihydroimidazolyl-2-ylidene (for example, **82**, Scheme 25, and **422**, Figure 10) have also been reported.[100]

Nolan and co-workers have described the development of [(NHC)Pd(π-allyl)Cl] complexes. Treatment of the corresponding π-allylpalladium chloride dimers with free carbenes at room temperature resulted in the formation of monomeric Pd–NHC species in high yields (Scheme 44).[122–126] As the handling of the sensitive free carbene limits the practicality and the scale of the precatalyst preparation, Nolan and co-workers have recently addressed this concern by developing a one-pot procedure: the carbene was generated on a large scale from the imidazolium salt and KO*t*Bu in technical grade 2-propanol followed by addition of $[\{Pd(\pi\text{-allyl})Cl\}_2]$.[122] However, in this case an excess of the ligand precursors (1.4 equiv NHC·HCl versus 1.1 equiv NHC, Scheme 44) had to be used. This precatalyst family is highly modular and a



Scheme 44. Method A: $^1/_2$[{Pd(π-allyl)Cl}$_2$], 1.1 equiv NHC, THF, RT. Method B: $^1/_2$[{Pd(π-allyl)Cl}$_2$], 1.4 equiv NHC·HCl, KO*t*BU, *i*PrOH, RT. NHC precursors are shown in Tables 1 and 3

number of *N*,*N*′-diaryl or dialkyl NHCs as well as substituents on the allyl ligand could be introduced. An alternative route to these complexes of saturated NHC ligands was unveiled by Waymouth and co-workers (Scheme 23).[37] [(NHC)Pd(π-allyl)Cl] complexes can also be used as a starting point for other precatalysts. For example, treatment of **146** with HCl resulted in the formation of [{(IPr)PdCl$_2$}$_2$] (**110**).[127] This approach was also used by Stahl and co-workers in their recent synthesis of seven-membered carbenes with a biphenyl backbone.[128,129] Nolan and co-workers disclosed very recently the [(NHC)Pd(acac)Cl] complex **158** (Scheme 45).[130] Treatment of [Pd(acac)$_2$] with isolated IPr



Scheme 45.

(**4**) led to an Pd–IPr intermediate with one acac ligand bound through C3 and the other in the usual chelating manner. Treatment of this complex with one equivalent of HCl in dioxane yielded **158** in excellent overall yield. Complex **158** can be prepared directly from [Pd(acac)$_2$] and IPr·HCl (**9**, Table 1) in refluxing dioxane, by relying on the inherent basicity of the acetylacetonate ligand.[131]

4. Applications of Pd–NHC Catalysts in Cross-Coupling Reactions

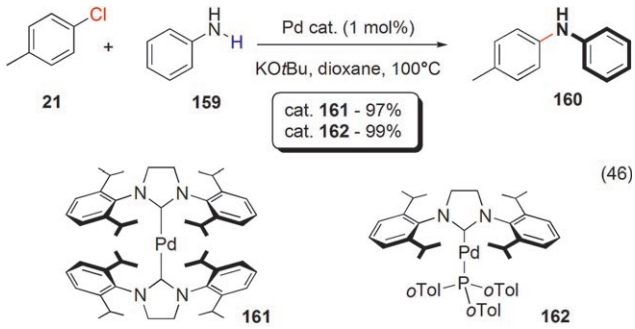
Metal-mediated cross-coupling reactions encompass an array of transformations that create a new single bond between a nucleophilic (usually an organometallic derivative, amine, or alcohol) and an electrophilic (an organic halide or pseudohalide) reaction partner.[8] The reaction is thermodynamically driven by the formation of an inorganic salt. Even though a number of metals have been used to mediate this process, the versatility of palladium compounds has remained unsurpassed.[7] The advantages of using NHCs as ligands in Pd mediated reactions are: 1) the strong σ-donating ability of NHCs results in a Pd center capable of oxidative addition into bonds traditionally considered resistant, for example, in chloroarenes[132] or alkyl halides;[133,134] 2) the steric bulk of NHCs facilitates reductive elimination in a manner analogous to bulky phosphanes;[135,136] and 3) the strong Pd–NHC bond and limited decomposition pathways available ensure that the metal is kept in a soluble, catalytically active state even when only a single NHC is attached. As a consequence of the special complexation properties of NHCs to Pd, well-defined complexes that are stable, easy to synthesize, yet readily activated under the reaction conditions offer definite advantages over catalysts formed in situ. Ideally, such precatalysts should be prepared from the corresponding imidazolium salts directly, thereby avoiding the handling of an isolated, highly moisture- and air-sensitive carbene. At the same time, the product yield should be high, irrespective of the reaction scale. Therefore, besides high catalytic activity, practical considerations such as ease of synthesis, commercial availability, price, and ease of use must be taken into account if Pd–NHC cross-coupling reactions are to be widely used in academia and industry. With the advent of commercial precatalysts that fulfill these criteria, the goal of a universal cross-coupling catalyst is now within reach.

4.1. The Catalytic Cycle of the Pd–NHC-Mediated Cross-Coupling Reaction

To date, there have been very limited mechanistic studies (experimental or computational) on the catalytic cycle of C–C cross-coupling reactions mediated by Pd–NHC complexes.[53,137] In addition to the results from these investigations, the following mechanistic discussions will mostly rely on what is known for reactions mediated by Pd–phosphane complexes (especially with bulky, strongly σ-electron-donating trialkylphosphanes). Comparisons of the catalytic activity of Pd–NHC catalysts produced either from well-defined complexes or in situ, and studies of well-defined Pd–NHC complexes related to proposed intermediates in the catalytic cycle are also given.

The uncertainties arising from in situ generation of the catalyst (Section 3.1) aside, the actual mechanism for the activation of the precatalyst is not well-established, especially at high temperature, even when well-defined precatalysts are employed. The isolated complex [(SIPr)$_2$Pd] (**161**) acted as an excellent catalyst for the Buchwald–Hartwig amination of

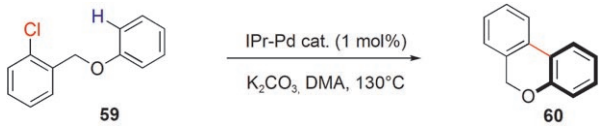
chloroarenes at 100 °C (Scheme 46).[138,139] These complexes are very labile in the presence of phosphanes at ambient temperature.[139] Caddick, Cloke, and co-workers thus reasoned that the activation step amounts to simple dissociation



Scheme 46.

of the NHC ligand. Consistent with this rationale, the mixed complex [(SIPr)Pd{P(*o*-Tol)$_3$}] (**162**) showed catalytic activity identical to that of the homoleptic carbene analogue **160**. Palladium(II) complexes with one NHC ligand are also suitable as catalyst precursors provided that reduction to the [(NHC)Pd^0] species is facile. The nature of the replaceable ligands determines the ease of reduction. Therefore, substantial variations in catalyst performance are to be expected with different precatalysts, as confirmed experimentally: Fagnou and co-workers observed that various singly ligated IPr–Pd precatalysts (Table 5) resulted in yields of 32–66 % in

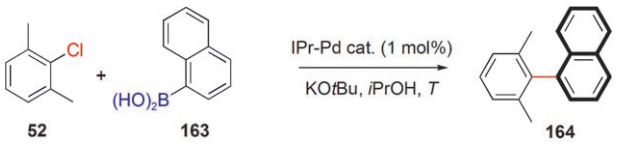
Table 5: Effect of the precatalyst on the efficiency of the intramolecular arylation reaction.[89]



Entry	IPr–Pd cat.	Yield [%]
1	IPr·HCl (**9**) + Pd(OAc)$_2$ (1:1)	55
2	[(IPr)PdCl(π-allyl)] (**146**)	54
3	[{(IPr)PdCl$_2$}$_2$] (**110**)	48
4	[(IPr)Pd(OAc)$_2$(OH$_2$)](**62**)	66
5	[{(IPr)Pd(NQ)}$_2$] (**109**)	32

the intramolecular arylation reaction.[89] Even though complex **146** was as efficient as the catalyst prepared in situ, the hydrated complex [(IPr)Pd(OAc)$_2$(OH$_2$)] (**62**) was superior. In contrast, the complexes [{(IPr)PdCl$_2$}$_2$] (**110**) and [{(IPr)Pd(NQ)}$_2$] (**109**) led to yields of less than 50 %. Nolan and co-workers investigated the activation of the π-allyl,[123,124] acetate,[112] and palladacycle[124] complexes of IPr under the conditions of a challenging room-temperature Suzuki–Miyaura coupling (1.1 equiv arylboronic acid, 1.2 equiv KO*t*Bu, *i*PrOH). In addition, the performance of the complex [(IPr)PdCl$_2$(3-ClPy)] (**133**), prepared by our research group, is shown.[118] A few points are noteworthy. First, whereas both IPr- and IMes-derived precatalysts showed equal performance in the coupling of *para*-chlorotoluene and phenylboronic acid (not shown), the coupling of the sterically hindered substrates 2-chloro-1,3-xylene (**52**) and 1-naphthylboronic acid (**163**; Table 6) was only facile with IPr.

Table 6: Effect of the precatalyst on the efficiency of room-temperature Suzuki–Miyaura reactions of challenging substrate combinations.[112,118,123,124]



Entry	IPr–Pd cat.	Yield [%][a]	
		50 °C	RT
1	[(IPr)PdCl(π-allyl)] (**146**)	92	39
2	[(IPr)PdCl(π-methallyl)] (**156**)	94	27
3	[(IPr)PdCl(π-crotyl)] (**152**)	-	91[b]
4	[(IPr)PdCl(π-cinnamyl)] (**154**)	-	94[c]
5	[(IPr)PdCl(π-prenyl)] (**153**)		95[c]
6	[(IPr)PdCl(palladacycle)] (**140**)	96	93
7	[(IPr)Pd(OAc)$_2$] (**79**)	100[d]	-
8	[(IPr)Pd(dvds)] (**106**)	0	0
9	[{(IPr)Pd(NQ)}$_2$] (**109**)	95	42
10	[(IPr)PdCl(3-ClPy)] (**133**)	-	85[e]

[a] 1 h. [b] 45 min. [c] 25 min. [d] 3 h at 40 °C. [e] 2 h.

These findings are in accord with data obtained from in situ prepared catalysts (Table 4), thus implying that the intrinsic reactivity of the ligand rather than the formation of active species are responsible for the levels of activity measured. Second, the performance of all the IPr-derived precatalysts (with the exception of **106**) was excellent at 50 °C; a major difference in the performance of the precatalyst was observed only at room temperature. Activation of the catalysts was facile at elevated temperature regardless of the nature of the replaceable ligands. However, for room-temperature coupling reactions, careful tuning of the precatalyst structure is the key to success. Third, there was a pronounced time dependence of the cross-coupling efficiency of π-allyl-derived complexes **146**, **152**–**154**, and **156**. Couplings promoted by precatalysts possessing substituents at C1 of the allyl moiety were considerably faster,[123] whereas substitution at C2 had no effect.[124] Such rate enhancement is only possible if the production of the actual catalysts—a singly ligated IPr–Pd^0 species in all cases—is the rate-determining step of the whole catalytic process! We have conducted ab initio computation of the singly ligated [(IPr)Pd] species (Figure 5) at the HF/3-21G level, and found weak interactions between the methyl hydrogen atoms of the *ortho*-isopropyl substituents and the Pd center.[53] Similar weak Pd···H–C interactions have been observed in complexes of highly catalytically active trialkylphosphanes.[140] Moreover, PEHS was found to be flat, thus implying a considerable degree of conformational freedom. Such conformational flexibility of the isopropyl groups might be important for the adjustment of the topography around the metal center during the subsequent stages of the catalytic

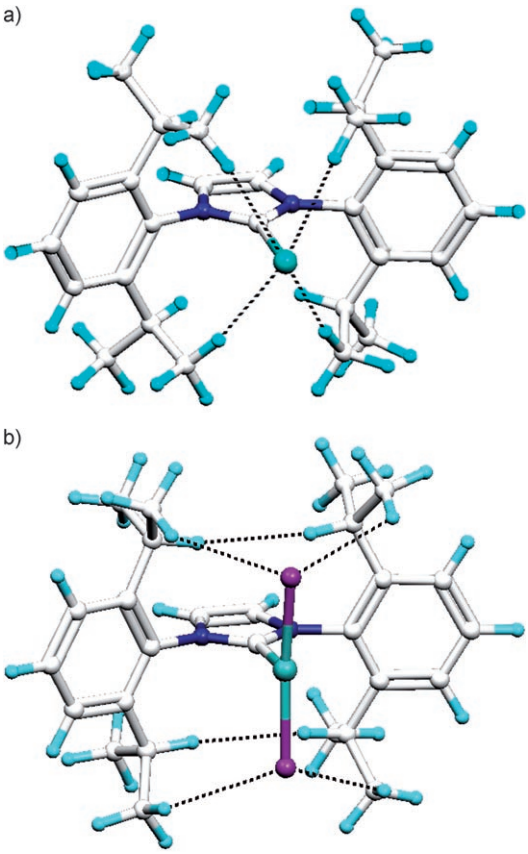


Figure 5. The computed structure (HF/3-21G) of a) Pd^0–IPr and b) IPr–$PdCl_2$ species.[53] Weak interactions found by AIM analysis are shown as dotted lines. There is a pronounced conformational change in the *ortho*-isopropyl groups upon conversion from Pd^0 into $PdCl_2$. Such conformational changes can be important during catalysis. Copyright Elsevier, 2005. Reproduced with permission.

cycle, similarly to the "flexible bulk" ligands developed by Glorius and co-workers (Scheme 15).[83]

Nolan and co-workers conducted detailed investigation of the activation mechanism of the π-allyl–Pd complexes. Simple substitution of the chloride ligand with *tert*-butoxide at the Pd center followed by reductive elimination or, alternatively, direct S_N2' attack on C1/C3 of the allyl moiety both lead to formation of allyl-*tert*-butyl ether (isolated from the reaction) and the singly ligated [(IPr)Pd] species (trapped as an tricyclohexylphosphane adduct).[126] Substitution of the π-allyl group at C3 leads to a lowering of the symmetry and an elongation of the C3–Pd bond. Overall, the allyl group becomes much more susceptible towards either nucleophilic attack or reductive elimination. The observed enhanced activation of the π-cinnamyl and π-prenyl complexes (**154** and **153**, respectively) is consistent with this rationale.[123] In the case of $[(IPr)Pd(OAc)_2]$ (**79**) and IPr palladacycle **140**, substitution of the chloride with isopropoxide (formed from *i*PrOH and KO*t*Bu) followed by β-hydride elimination leads to the formation of a palladium hydride, which undergoes reductive elimination. Eventually, $[(IPr)Pd^0]$ is formed.[112,141] An alternative activation mechanism for **140** in Suzuki–Miyaura reactions is also possible, as reported for palladacycle–phosphane adducts.[142] In this case, transmetalation by the arylboronic acid is followed by reductive elimination within the newly formed IPr–palladacycle–aryl complex to produce $[(IPr)Pd^0]$.

Our research group investigated the activation of $[(IPr)PdCl_2(3\text{-}ClPy)]$ (**133**, Scheme 40) in the alkyl–alkyl Negishi reaction. Computations[118] showed that the pyridine ligand has a lower binding energy to Pd^0 than to Pd^{II}. Therefore, the dissociation of the replaceable 3-chloropyridine ligand most likely takes place after the initial formation of the Pd^0 species by means of rapid reduction with two equivalents of an organometallic reagent or a hydride produced by β-hydride elimination. The formation of *n*-tetradecane was observed when **133** was treated with an excess of *n*-heptylzinc bromide, which is consistent with the above mechanism of activation. The replaceable pyridine ligand plays a pivotal role in the development of the catalyst—it stabilizes complex **133** and dissociates upon activation. Therefore, for this family of complexes the generic name PEPPSI (pyridine-enhanced precatalyst preparation, stabilization, and initiation) was coined. A quantitative investigation of the catalyst formation by the in situ method was conducted for the first time with the aid of PEPPSI-IPr complex **133** (Figure 6).[118] At identical yield and reaction

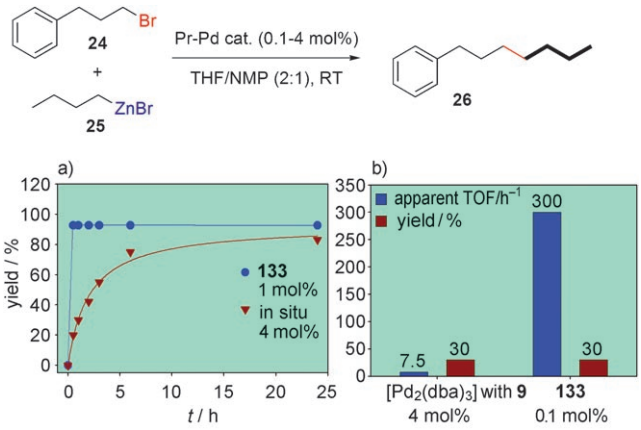
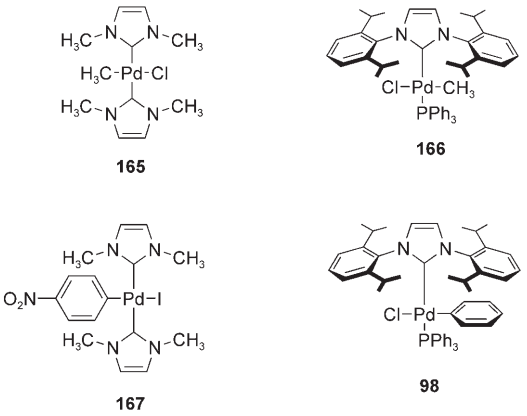


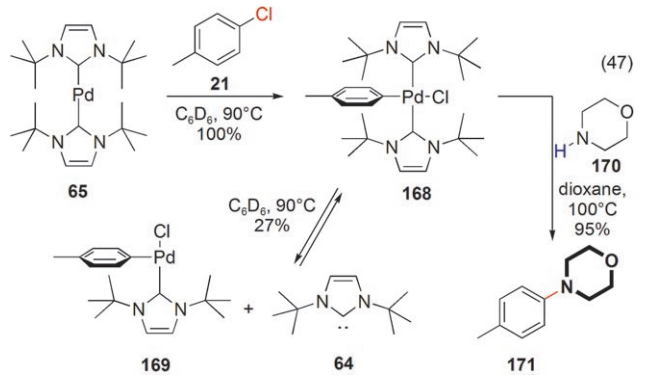
Figure 6. Comparison between an Pd^0–IPr catalyst produced in situ and well-defined PEPPSI–IPr complex **133**. a) Rate study; b) comparison of TOF and yield at $t = 1$ h. The chemical yield of the active species in situ is estimated to be only 2.5%.[118]

time, the TOF with the in situ catalyst system was found to be only 7.5 h^{-1} whereas the value with **133** was 300 h^{-1}. Assuming that the same catalyst is generated and that the TOF is an inherent property of a molecule, only approximately 0.1 mol% of active catalyst is actually formed when the in situ protocol is employed, even though 4 mol% of each of the precursors is used.

Once the singly ligated Pd–NHC complex is produced, it enters the catalytic cycle, which is assumed to consist of three discrete stages: oxidative addition, transmetalation, and reductive elimination. Among these, oxidative addition is the best studied. A number of tetracoordinate Pd–NHC complexes related to the putative intermediate after the oxidative addition step are known. These complexes with an σ-alkyl (**165** and **166**)[106,143] or an σ-aryl ligand (**167** and **98**)[106,144,145] and a halide ligand exhibit substantial stability



and hence are not likely to participate directly in the catalytic cycle. A quantitative yield of **171** was observed when a similar complex (**168**) was heated with morpholine (**170**, Scheme 47), thus signifying that **168** can be used as a source of the active catalyst, and if formed during the actual cross-coupling process, would act as a resting state. Heating **168** in [D_6]benzene resulted in the dissociation of free carbene I*t*Bu (**64**) and formation of the tricoordinate species **169**.[146] It is reasonable to propose that similar transformations could take place in the actual catalytic cycle, and that tricoordinate Pd–NHC species analogous to **169** would continue to the next step in the cycle. Green et al. conducted a detailed computational study on the Buchwald–Hartwig amination reaction of the Pd–I*t*Bu catalyst (Figure 7).[137] The singly ligated [(I*t*Bu)Pd^0] complex was found to be less stable by 119.4 kJ mol^{-1} than the doubly ligated species **65**. However, such a barrier is not insurmountable under the temperatures relevant for catalysis and does not preclude the formation of small amounts of [(I*t*Bu)Pd^0]. Such findings are in line with the moderate activity (19%) of [(I*t*Bu)$_2$Pd] (**65**; Table 3) under the conditions of the Buchwald–Hartwig amination (Scheme 47).[139] Coordination of a solvent molecule (benzene) was found to have a stabilizing effect on the singly ligated Pd–NHC species. Similar coordination of chlorobenzene to form a η^2 complex was found to be favorable by 28 kJ mol^{-1}. The oxidative addition proceeds from this complex with a barrier of 19 kJ mol^{-1} to a T-shaped intermediate having I*t*Bu and Cl in a *cis* orientation. Isomerization of this intermediate to **169**, with the carbene and Cl mutually *trans*, was found to be exothermic (39 kJ mol^{-1}). Coordination of aniline to this complex results in tetracoordinate complexes of various configurations, from which the complex having aniline and I*t*Bu in a *trans* arrangement was found to be the most stable. Deprotonation of the Pd-bound aniline by KO*t*Bu then takes place. As this process is driven by the formation of KCl and *t*BuOH, it was omitted from the calculations. At this stage, a new tricoordinate, T-shaped [(NHC)Pd(Ph)(NHPh)] complex is formed. The activation energy for the reductive elimination was calculated to be 64 kJ mol^{-1}, much higher than the activation energy for oxidative addition. Finally, the newly formed diphenylamine forms a η^2-coordinated complex and it is replaced by another molecule of chlorobenzene, thereby completing the cycle. For comparison, oxidative addition to CH_3Cl was found to be much less favorable than that to chlorobenzene: the activation energy was found to be 47.3 kJ mol^{-1}. On the other hand, the oxidative addition product, a T-shaped, three-coordinate complex, was found to be much more stable. As the oxidative addition intermediate is some 25 kJ mol^{-1} higher in energy than [(I*t*Bu)Pd^0], the



Scheme 47.

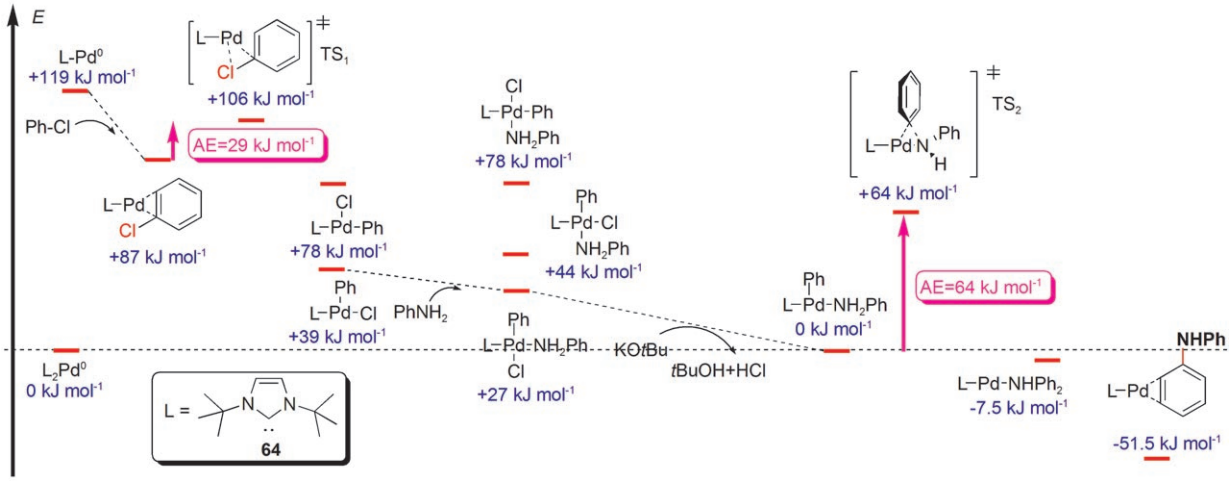
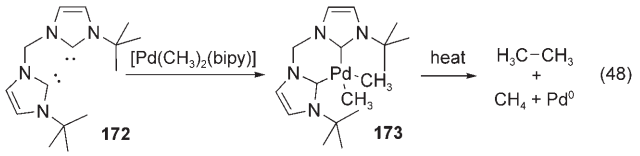


Figure 7. Computational study of the intermediates and transition states in the Buchwald–Hartwig amination (L = I*t*Bu). The reductive elimination was found to have higher activation energy (64 kJ mol^{-1}) than the oxidative addition (29 kJ mol^{-1}).[136]

authors concluded that chloromethane would not undergo oxidative addition in the gas phase. However, cross-coupling reactions of alkyl halides, including chlorides,[147] are facile with Pd–NHC catalysts in polar solvents (Scheme 54).

The steric bulk of the NHC ligand plays an important role in facilitating the reductive elimination between the two reaction partners. Only very rarely can dialkyl– or diaryl–Pd complexes related to the intermediate before the reductive elimination step be isolated.[148,149] By using complex **173**, Douthwaite et al. have shown that reductive elimination between two alkyl groups is more favorable than reductive elimination between an NHC and an alkyl group (Scheme 48); the latter is an important side reaction leading



Scheme 48.

to catalyst death.[143–145] Such side products have been observed by MALDI-TOF MS analysis of crude reaction mixtures.[89] This finding has important implications for chiral or immobilized[150] Pd–NHC precatalysts, for example, in which case catalyst decomposition must be suppressed.

In summary, the production of the active catalyst, a singly ligated Pd–NHC species initiates the catalytic cycle (Figure 8). The next step, the oxidative addition, is aided by the strongly electron-donating nature of the NHC. After transmetalation, the least studied stage of the catalytic cycle, reductive elimination takes place, which is facilitated by the steric bulk of the NHC.

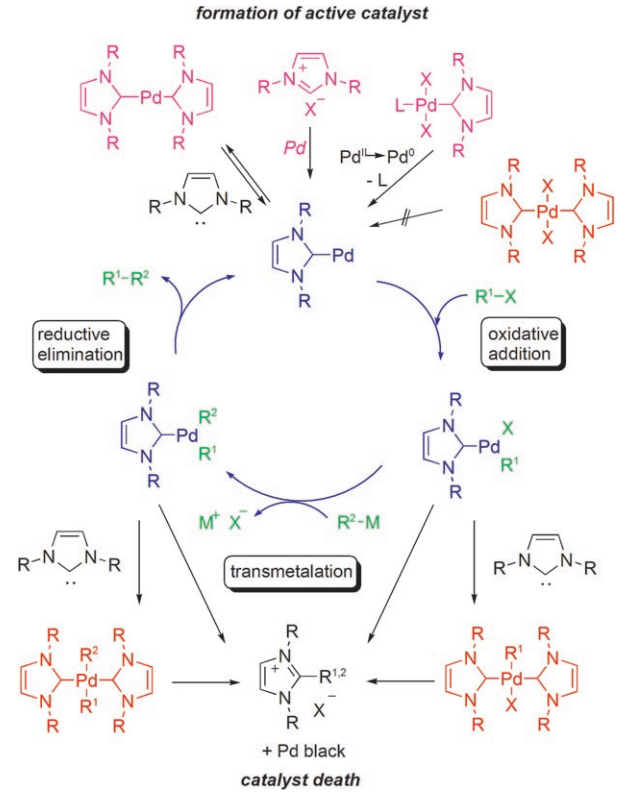
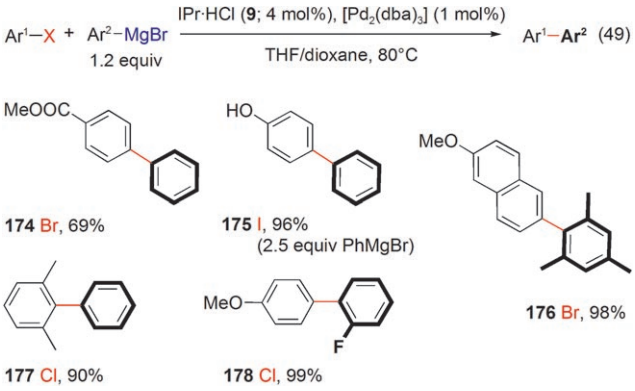


Figure 8. The putative catalytic cycle of Pd–NHC-mediated cross-coupling reactions occurs in three stages: formation of the active catalyst, turnover, and catalyst death (see text). Color code: pink: catalyst precursors; red: inactive, resting states; blue: active catalyst; green: substrates.

4.2. The Kumada–Tamao–Corriu Reaction

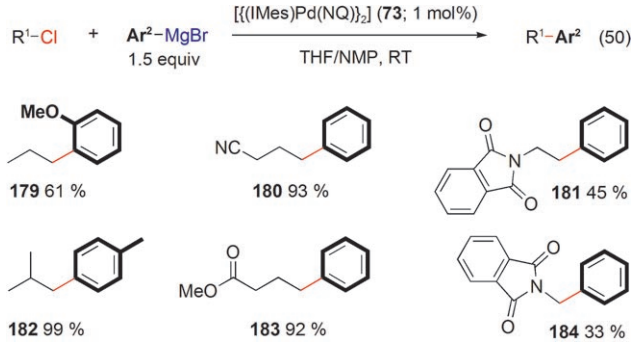
The main advantage of coupling organomagnesium reagents (Kumada–Tamao–Corriu or KTC reaction)[151] is the direct, facile preparation of the Grignard reagent from Mg and organohalides; these reagents often serve as starting materials for organozinc, organoboron, or organosilicon derivatives used in other cross-coupling reactions. This methodology is to a certain degree handicapped by limited substrate-group tolerance. However, when the Grignard reagents are stable, the low cost, high reactivity, and non-toxicity of magnesium renders the KTC reaction one of the best options available.

As early as 1999, Huang and Nolan published the first KTC coupling (Scheme 49) in which they used a catalyst generated in situ from IPr·HCl (**9**, Table 1) and $[Pd_2(dba)_3]$ in THF/dioxane at 80 °C.[152] Aryl chlorides, bromides, and iodides were all coupled in near quantitative yield. However, di-*ortho*-substituted aryl chlorides reacted only with aryl Grignard reagents without *ortho* substituents (**177**, Scheme 49). In 2003 and 2004, Beller and co-workers extended the KTC methodology to aryl[110] and alkyl[153] halides (Scheme 50) by using the singly ligated NHC-Pd-



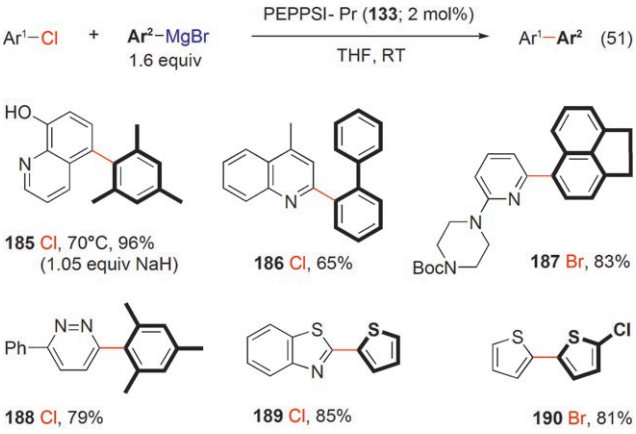
Scheme 49.

naphthoquinone complexes. While both IPr (**109**) and IMes (**73**) complexes were equally active for the $C(sp^2)$–$C(sp^2)$ KTC couplings, surprisingly, the highest yields for the $C(sp^3)$–$C(sp^2)$ couplings were obtained with the IMes complex. The corresponding dvds complexes **105** and **106**, as well as catalysts formed in situ, led to much lower yields. A notable feature of this protocol is the variety of functionalities on the alkyl chloride that can be tolerated in the reaction with the Grignard reagent. Alkyl chlorides with branches or functional groups in the α-position also coupled, albeit at lower yields.

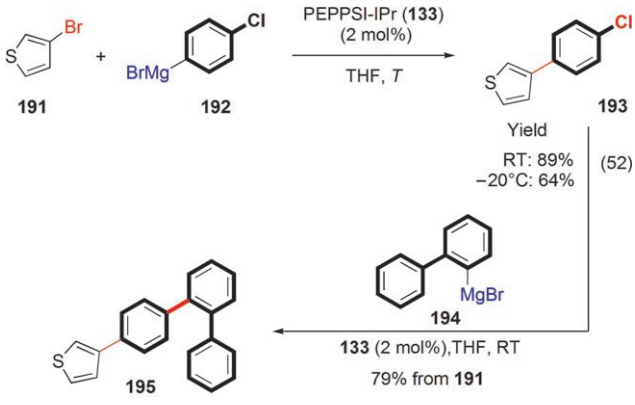


Scheme 50.

The PEPPSI–IPr complex **133** (Scheme 40) is an excellent precatalyst for the KTC coupling of challenging aryl coupling partners including *ortho*-substituted and heterocyclic aryl halides or aryl Grignard reagents (Scheme 51) as well as sequential one-pot couplings (Scheme 52), in THF at room temperature.[154] For challenging substrate combinations, the addition of LiCl or increasing the temperature to 50 or 70 °C was found to be effective. The tolerance of a Boc-protected amine (**187**) and a phenol (**185**; after deprotonation with NaH) is noteworthy. Moreover, PEPPSI–IPr **133** gave good coupling efficiency even at −20 °C (Scheme 52). The corresponding IEt (**132**) and IMes complexes (**131**) were much less



Scheme 51.



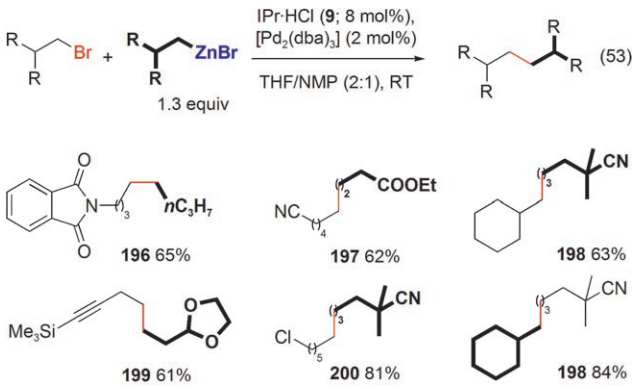
Scheme 52.

efficient, probably because of catalyst degradation as a consequence of the slower reductive elimination with these less sterically hindered ligands.

4.3. The Negishi Reaction

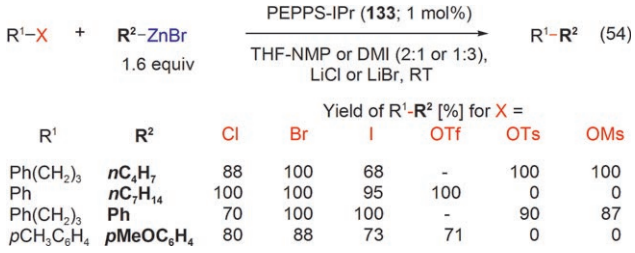
The coupling of organozinc, organoaluminum, or organozirconium derivatives (the Negishi reaction)[155,156] is the most versatile cross-coupling reaction. Their activity is as high as their organomagnesium counterparts, while they have enhanced functional group tolerance and there is a wider variety of routes for access to these organometallic reagents. Therefore, the Negishi reaction is one of the top choices for the preparation of complex, sensitive substrates.

Surprisingly, until 2005, there were only two reports of Pd–NHC-mediated Negishi coupling in the literature, and they were unsuccessful.[100,157] Zhou and Fu attempted the cross-coupling of a simple, primary alkyl electrophile with a simple alkylzinc reagent in the presence of IMes·HCl (**13**)/[$Pd_2(dba)_3$] at 70 °C in the presence of a stoichiometric amount of *N*-methylimidazole (NMI) as the organozinc activator, but only obtained a low yield.[157] Our research group found that IPr·HCl (**9**) performed much better in this reaction (Table 1, Schemes 6 and 18).[158] Under optimized conditions, the coupling of functionalized alkyl bromides and alkylzinc reagents was achieved in high yield at room temperature without the need for NMI (Scheme 52). Notably, branching at the β-position to the reactive functionality (**198**, Scheme 53) was also well tolerated. The use of the well-



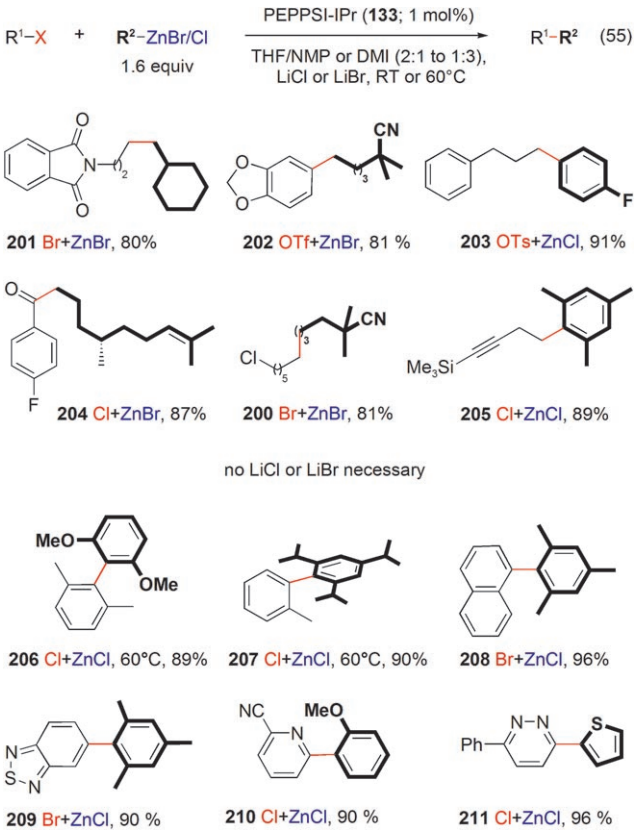
Scheme 53.

defined PEPPSI–IPr precatalyst **133** led to significant improvement with respect to the rate and the substrate scope of the Negishi reaction. This precatalyst could be used to promote the cross-coupling of alkyl or aryl halides and sulfonates with alkylzinc bromide or arylzinc chloride reagents (Scheme 54) at room temperature by judicious choice of the solvent and additive (LiCl or LiBr).[147] Whereas alkyl tosylates and mesylates underwent cross-coupling in high yields, the aryl analogues were unreactive. In this case, the conversion of alkyl sulfonates into halides takes place through an S_N2[159] mechanism before oxidative insertion. A similar exchange reaction is not possible with the aryl



Scheme 54.

sulfonates. Moreover, lithium halide additives were necessary for the cross-coupling of alkylzinc halides regardless of the choice of the electrophile partner. This finding is indicative that the activation of the alkylzinc reagent by the LiCl or LiBr takes place, presumably by formation of a zincate.[160,161] Complex substrates were also well tolerated (Scheme 55).



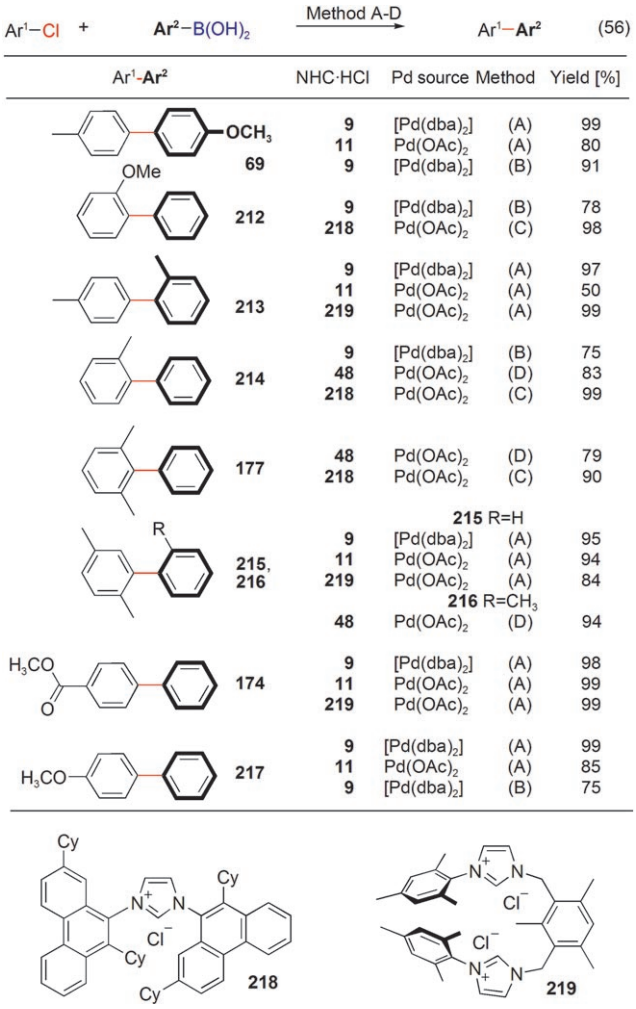
Scheme 55.

An array of functionalized alkanes (**200**–**204**), including the chiral terpene-derived ketone **204**, as well as sterically hindered biaryls (**206**–**208**) or heteroaromatic molecules (**209**–**211**) were obtained in high yields. Increasing the proportion of the polar solvent (THF/NMP or DMI to 1:2 or 1:3) and/or the temperature to 60 °C was necessary for high yields when challenging substrate combinations were used.

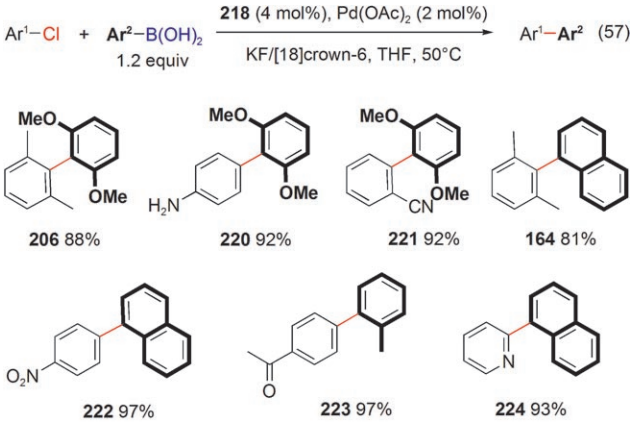
4.4. The Suzuki–Miyaura Reaction

The cross-coupling of organoboron derivatives (Suzuki–Miyaura reaction)[162–164] is currently the most widely used cross-coupling protocol because of the commercial availability of a wide selection of solid as well as air- and moisture-tolerant boronic acids. In addition, the by-products formed are nontoxic and the reaction proceeds well in a wide range of solvents, including alcohols and water. The reaction is tolerant of a wide range of functional groups and complex reaction partners can be used. The addition of a stoichiometric amount of a base is necessary, presumably for activation of the boron derivative. The nature of the initial precatalyst, solvent, and base is crucial for the success of the coupling, especially in challenging cases.

Arylboronic acids are the most frequently used nucleophilic partners in the Suzuki coupling. High levels of activity in the coupling of aryl iodides and bromides as well as activated aryl chlorides with simple arylboronic acids have been recorded for a number of Pd–NHC catalysts.[44,48,49,92,100,107,165–172] Furthermore, the stability of the Pd–NHC species has been exploited in terms of catalyst immobilization on polymer supports[173–177] or in ionic liquids.[178,179] Aryl chlorides are attractive as feedstocks for industrial cross-coupling reactions as a consequence of their low cost and wide availability, but are much less reactive than aryl bromides and iodides. Not surprisingly, the development of catalysts for the cross-coupling of non-activated chloroarenes has attracted considerable attention.[132] Pd–NHC catalysts produced in situ from imidazolium salts and common Pd sources have shown high activity in cross-coupling reactions of simple aryl chlorides and arylboronic acids. Nolan and co-workers have carried out extensive studies on the Suzuki–Miyaura coupling of chloroarenes with a number of *N*,*N*′-diaryl imidazolium salts (Scheme 5, Table 1). Under optimized conditions—IPr·HCl (**9**)/[Pd(dba)$_2$] or IMes·HCl (**13**)/Pd(OAc)$_2$ in dioxane with Cs_2CO_3 as the base—substituted biphenyls were synthesized in high yields (Scheme 56) at 80 °C.[75] Independently, Caddick, Cloke, and co-workers employed the same catalyst precursor—IPr·HCl (**9**)/[Pd(dba)$_2$]—in a biphasic mixture of toluene and methanol with NaOMe used as the base (Scheme 56).[180] Even though the temperature employed in this protocol was only 40 °C, the use of two solvents and 10 mol % TBAB as an additive limits its practical usefulness. In a very elegant study, Fairlamb et al. were able to enhance the performance of this catalytic protocol by using [Pd$_2$(dba)$_3$] analogues prepared from *para*,*para*′-disubstituted dibenzylideneacetone (dba) derivatives carrying electron-donating substituents.[181] This ability was attributed to in situ formation of a [(IPr)Pd(η^2-dba)] species as the active catalyst; the dba ligand coordinated through one of the two alkene bonds serves as a replaceable ligand in this case. The electron-donating methoxy groups in this ligand led to weaker coordination as a result of suppressed π-back donation under the effect of the strongly σ-electron-donating NHC ligand. Zhang and Trudell developed chelating IMes analogues with different topologies.[182] The bis(imidazolium) salt **219** (Scheme 56) was found to be the most active in the

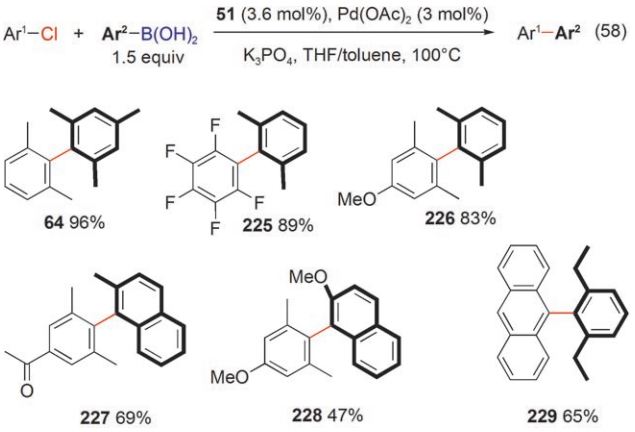


Scheme 56. Method A: IPr·HCl (**9**) or IMes·Cl (**11**; 2 mol%), $Pd(OAc)_2$ or $[Pd(dba)_2]$ (1 mol%); **219** (2.5 mol%), $Pd(OAc)_2$ (2.5 mol%), Cs_2CO_3, dioxane, 80°C. Method B: IPr·HCl (**9**; 2 mol%), NaOMe, MeOH/toluene, 10 mol% TBAB, 40°C. Method C: **218** (2 mol%), $Pd(OAc)_2$ (2 mol%), KF/[18]crown-6, THF, 50°C. Method D: **48** (3 mol%), $Pd(OAc)_2$ (3 mol%), CsF, THF, RT.



Scheme 57.

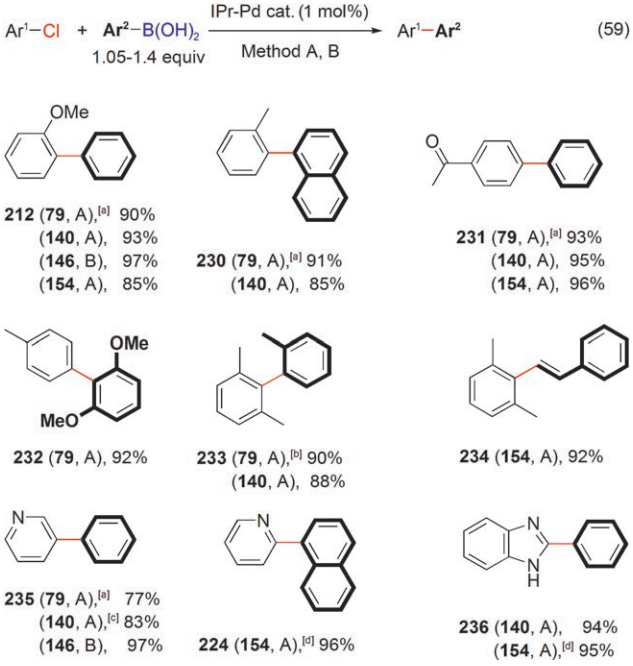
Suzuki–Miyaura coupling reactions of non-activated aryl chlorides under the conditions developed by Nolan and co-workers (Scheme 56). Very recently, Andrus and co-workers disclosed a novel *N*-phenanthryl family of NHC precursors. The most active ligand, **218** (Scheme 56) led to the facile formation of biphenyl at room temperature with $Pd(OAc)_2$ in THF using KF/[18]crown-6 as the base.[183] Even though the yields were generally moderate at room temperature, increasing the temperature to 50°C led to a significant increase in the yields and a shortening of the reaction time. Ligand **218** proved to be highly active in the synthesis of multiply *ortho*-substituted, functionalized or heterocyclic biaryls (Schemes 56 and 57). The pentacyclic carbene ligands developed by Glorius and co-workers are some of the most active to date. When the spirocyclohexyl-substituted ligand precursor **48** (Scheme 31) was used,[84] nonsterically hindered biaryls were obtained in excellent yields at room temperature (Scheme 56). The couplings of functionalized and sterically hindered aryl chlorides with sterically hindered boronic acids (Scheme 58) required the spirocyclododecyl analogue **51** (Scheme 31) as the ligand at high temperatures (100–110°C).[83] Benzimidazolium salts with bulky *N*-adamantyl substituents were also used by our research group for the synthesis of *para*,*para*′-substituted biphenyls with different combinations of electron-deficient and electron-rich reacting partners (Figure 4).[74] Benzimidazolium salts with less sterically hindered substituents have also been used successfully.[184] Glorius and co-workers recently disclosed novel, pyridine-fused bulky NHC ligands capable of forming sterically hindered biaryls (products **216** and **231**, Scheme 56; up to 86% yield). Unfortunately, detailed substrate evaluation was not undertaken.[185] Well-defined Pd–NHC precatalysts have been instrumental in the further development of the Suzuki–Miyaura methodology. $[(IAd)_2Pd]$ (**67**, Scheme 21) was the first well-defined Pd–NHC complex to be an excellent catalyst for the coupling of non-activated aryl chlorides at room temperature in dioxane with CsF as the base.[91] However, the topology that the bulky carbene IAd created around the palladium center precluded the use of *ortho*-substituted reacting partners. Similarly, $[(IPr)_2Pd]$ and $[(SIPr)_2Pd]$ (**161**, Scheme 46) prepared by Caddick, Cloke, and co-workers were also effective at 40°C in toluene/



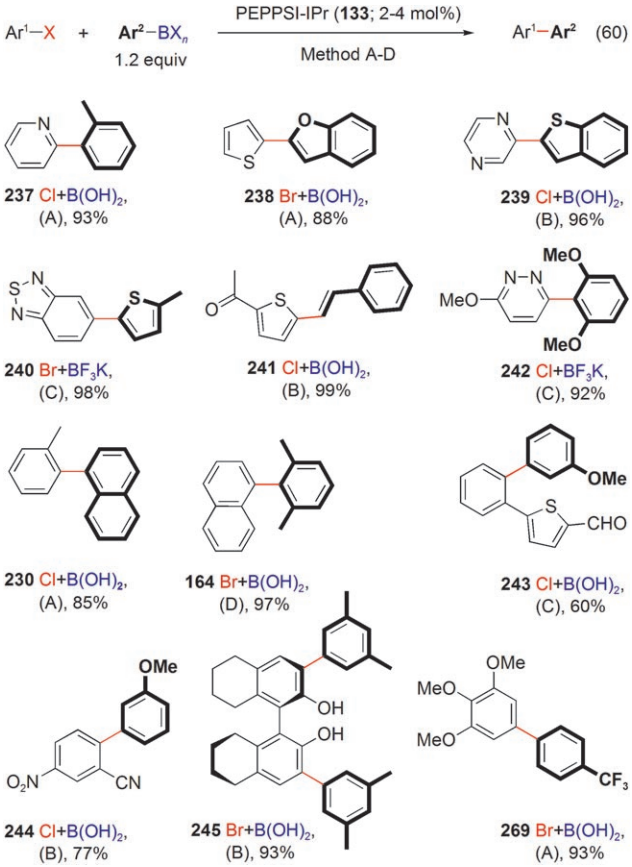
Scheme 58.

methanol with NaOMe as the base. However, the use of the imidazolium salts and [Pd(dba)$_2$] resulted in higher yields and much faster coupling reactions, again highlighting the importance of the activation of the precatalyst.[138] Shi and Qian obtained moderate yields in the coupling of chlorobenzene and phenylboronic acid with a PdI_2 complex of a chiral benzimidazolyl-2-ylidene ligand (**431**, Scheme 81) at high temperature; bromo- and iodoarenes, as expected, coupled much more easily.[186] An NHC-ligated palladacycle (**82**, Scheme 25) showed a TON of 185 (catalyst loading 0.0014 mol%) for the coupling of chlorobenzene and phenylboronic acid (25% yield).[100] Singly ligated, Pd^{II} complexes with replaceable ligands have attained the highest activity and substrate tolerance to date. The mixed complex [(IPhEt)PdI_2-(PCy_3)] (**128**) prepared by Herrmann et al. (Scheme 39) led to high yields in the cross-coupling of chlorobenzene and simple boronic acids in xylene at 130 °C with K_2CO_3 as the base.[117] Nolan and co-workers have utilized precatalysts **79** (Scheme 24), **140** (Scheme 42), **146**, and **154** (Scheme 44) in the synthesis of a number of sterically hindered and heteroaromatic biaryl (Scheme 59);[101,112,123,141,187,188] vinylboronic acids also showed high conversions. It is noteworthy that conversions with [(IMes)Pd(OAc)$_2$] (the analogue of **79**) were also excellent unless the product was a multiply *ortho*-substituted biphenyl.[112] The most active catalyst **154** (0.05 mol%) gave greater than 90% yields within 15 h.[187] This protocol is highly advantageous because of the use of an inexpensive solvent, namely technical grade isopropanol, and the use of as little as 1.05 equivalents of the boronic acid at room temperature. As expected, aryl bromides and triflates also cross-coupled with ease. The PEPPSI–IPr complex **133** (Scheme 40) also shows excellent activity under these conditions (Scheme 60).[118] However, the use of the moisture-sensitive, strongly basic potassium *tert*-butoxide, which limits the range of compatible functional groups, is a potential liability. To address this issue, we have developed an alternative method based on **133**. In this method a mild base is used that is compatible with base-sensitive substrates (Scheme 60). Poly-heteroaromatic compounds as well as highly functionalized and sterically hindered biaryl derivatives were all accessible in excellent yields. In addition, trifluoroborates were also suitable as nucleophilic partners when K_2CO_3 in methanol was used as the base (Scheme 60).

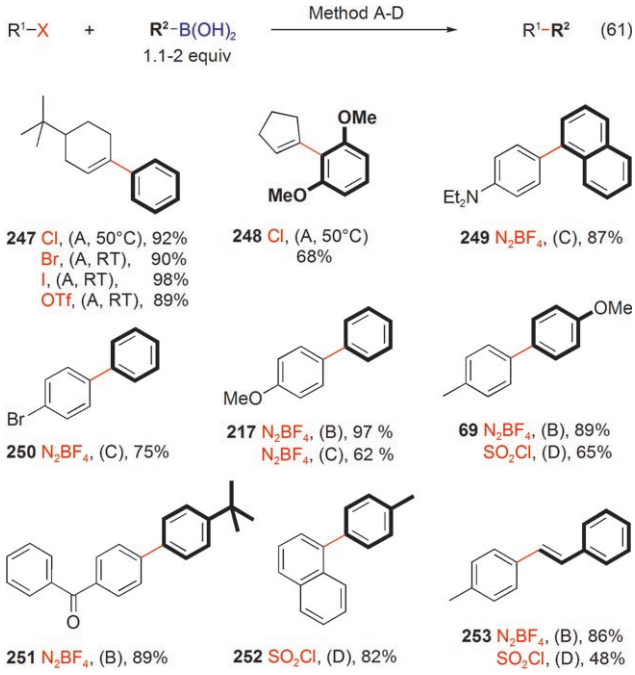
Andrus and co-workers have been pioneers in the extension of the Pd–NHC methodology to coupling reactions of less-represented classes of reaction partners (Scheme 61). Vinyl halides and triflates[183] and arenediazonium salts[189] underwent coupling reactions with arylboronic acids in the presence of $Pd(OAc)_2$ and bulky ligand precursors, the phenanthrene-substituted imidazolium salt **218** (Scheme 56) and SIPr·HCl (**13**, Table 1). Coupling reactions of electron-rich diazonium salts with aryl boronic acids were also mediated by [{(IMes)Pd(NQ)}$_2$] (**73**, Scheme 20) in methanol at 50 °C;[99] the reaction showed excellent chemoselectivity with respect to bromoarenes. Aryl sulfonyl chlorides also reacted successfully in cross-coupling reactions when a



Scheme 59. IPr–Pd catalysts: **79**, **140**, **146**, or **154**. Method A: KO*t*Bu or Na, *i*PrOH, RT. Method B: NaO*t*Bu, dioxane, 60 °C. [a] [(IMes)Pd-($OAc)_2$]. [b] Reversed substrate pairing. [c] 45 °C. [d] 0.05 mol% **154**.



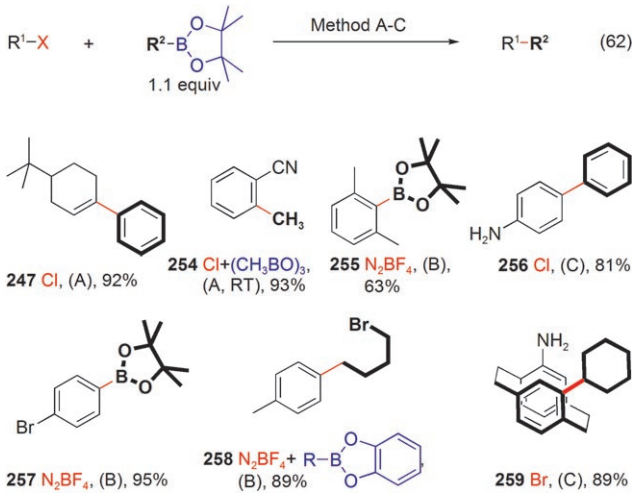
Scheme 60. Method A: KO*t*Bu, *i*PrOH, RT. Method B: K_2CO_3, dioxane, 60 °C. Method C: K_2CO_3, methanol, 60 °C. Method D: KOH, dioxane, RT.



Scheme 61. Method A: **218** (4 mol%), $Pd(OAc)_2$ (2 mol%), KF/[18]crown-6, THF. Method B: **13** (2 mol%), $Pd(OAc)_2$ (2 mol%), THF, 0°C or RT. Method C: **73** (1 mol%), MeOH, 50°C. Method D: **11** (6 mol%), $[Pd_2(dba)_3]$ (1.5 mol%), Na_2CO_3, THF, reflux.

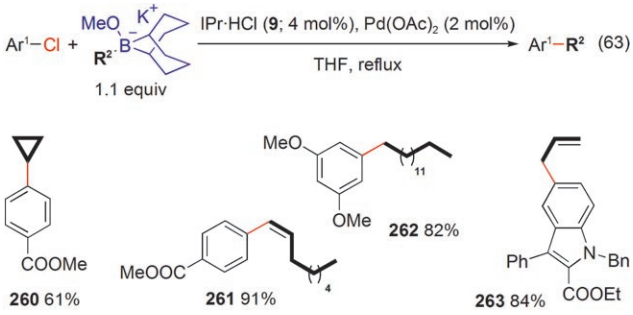
catalyst prepared from IMes·HCl (**11**, Table 1) and $[Pd_2(dba)_3]$ was utilized.[190] Similarly, the sulfonyl chloride group could be activated selectively over a chloro or bromo, but not an iodo substituent.

The coupling of boronic esters has so far only been published by the Andrus research group (Scheme 62). The ligand precursor **218** (Scheme 56) in the presence of $Pd(OAc)_2$ promoted the coupling reactions of a range of deactivated, sterically challenging aryl chlorides with the



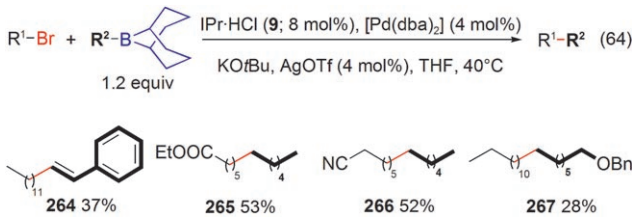
Scheme 62. Method A: **218** (4 mol%), $Pd(OAc)_2$ (2 mol%), KF/[18]crown-6, THF/H_2O, 50°C. Method B: **13** (2 mol%), $Pd(OAc)_2$ (2 mol%), THF, RT. Method C: **13** (2 mol%), $Pd(OAc)_2$ (2 mol%), CsF, THF, 50°C.

pinacol ester of phenylboronic acid.[183] Also, borylation of aryl diazonium salts with bis(pinacolato)borane using a catalyst produced from SIPr·HCl (**13**) and $Pd(OAc)_2$ (1:1) proceeded in high yield in THF at room temperature without the presence of base. The actual catalyst was proposed to be $[\{(SIPr)PdCl_2\}_2]$ (**111**, Scheme 36).[86] Alkyl catechol[189] and pinacolboranes[191] were also used successfully by Andrus and co-workers for chemoselective cross-coupling with aryl diazonium salts by using the SIPr/$Pd(OAc)_2$ protocol in the presence of an alkyl bromide (Scheme 62). Especially noteworthy is the coupling of cyclohexylpinacolborane, the only example of the cross-coupling of a secondary alkyl nucleophile (product **259**, Scheme 62) with a Pd–NHC catalyst to date.[191] The combination of ligand **218** (Scheme 56) and $Pd(OAc)_2$ also successfully promoted the coupling reactions of methylboroxine with aryl and vinyl chlorides (Scheme 62).[183] Fürstner and Leitner reported that Pd–NHC catalysts were also effective for coupling reactions of *B*-alkyl (including allyl and cyclopropyl) and *B*-vinyl-*B*-methoxy-9-BBN adducts with a variety of aryl chlorides (Scheme 63);[192] IPr·HCl (**9**, Table 1) was the ligand precursor of choice.



Scheme 63.

The activation of alkyl halides has been less successful than their aryl counterparts. $[(IMes)Pd(OAc)_2]$ was used by Nolan and co-workers for the coupling of activated benzyl halides with phenylboronic acid in the presence of KO*t*Bu in technical grade 2-propanol at room temperature.[112] The reaction times were generally short and yields excellent. Ligand precursor **218** (Scheme 56) also showed excellent activity for the coupling of benzyl chloride.[183] Benzylsulfonyl chloride was also coupled with 3-nitroboronic acid in 52% yield by using IMes·HCl (**11**, Table 1) and $[Pd_2(dba)_3]$ as the catalyst.[190] The attempts by Bedford et al. to couple 2-phenylethylbromide with phenylboronic acid in the presence of the IMes or IPr palladacycles **143** or **144**, respectively (Scheme 43), failed.[193] These palladacycles also showed unsatisfactory performance in biaryl Suzuki–Miyaura couplings: even though aryl bromides coupled well, the yields with aryl chlorides were around 10% or less.[121] Recently, Caddick, Cloke and co-workers described the application of an in situ generated Pd–IPr catalyst (4 mol%) for the alkyl–alkyl and alkyl–vinyl cross-coupling reactions at 40°C of *B*-alkyl- or *B*-vinyl-9-BBN derivatives activated with KO*t*Bu and AgOTf (4 mol%) used as an additive (Scheme 64).[180]



Scheme 64.

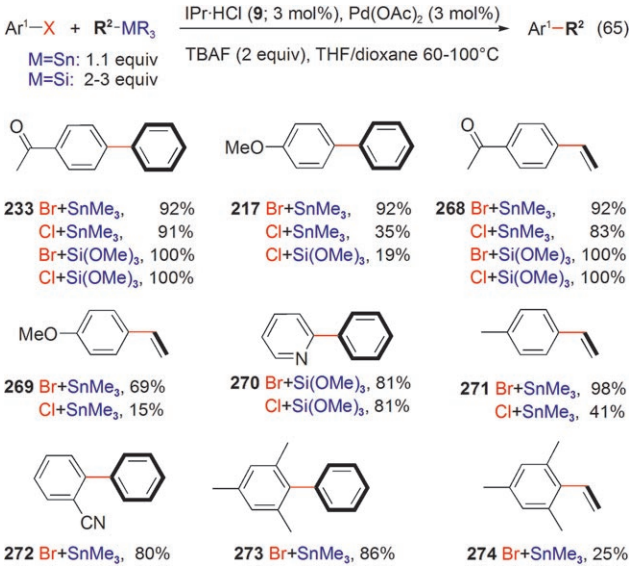
Despite low to moderate yields, this landmark work has paved the way for successful alkyl–alkyl Suzuki–Miyaura cross-coupling reactions. Although we have published a single example of a fast, quantitative sp^3–sp^3 cross-coupling of tri-*n*-butylborane promoted by PEPPSI–IPr (**133**, Scheme 40),[118] synthetically useful alkyl–alkyl Suzuki–Miyaura methodology with Pd–NHC catalysts is still awaiting development.

4.5. Coupling Reactions of Si– and Sn–Organic Derivatives

Historically, the cross-coupling of organotin compounds (Stille reaction)[194,195] was the most widely used cross-coupling reaction alongside the Suzuki–Miyaura reaction. However, the toxicity of the organotin compounds and the difficulty of their removal from the products of interest has resulted in this reaction now being superseded by more environmentally friendly protocols. Even though silicon, like tin, is a Group 14 element, the reaction protocols[196] are markedly different—largely because of the fact that while transmetalation from tetraalkyl-substituted Sn to Pd is possible, the transmetalation of Si to Pd occurs only from hypervalent, pentacoordinate silicon intermediates. The use of silicon reagents is especially attractive from an industrial point of view because of their low cost, nontoxicity, and high stability.

The Stille coupling of aryl bromides and aryl stannanes was initially investigated by Herrmann et al. Unlike the corresponding Suzuki–Miyaura coupling, [(IPhEt)PdI_2(PPh_3)] (**122**, Scheme 39) showed the highest activity in the cross-coupling of *para*-bromoacetophenone and phenyltri-*n*-butylstannane without any base or activator (100% yield). This system was not suitable for the coupling of aryl chlorides.[117,197]

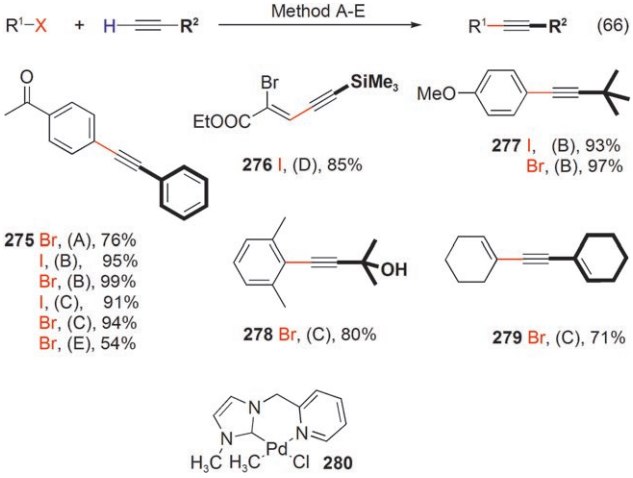
The addition of fluoride salts activates the organotin reagent towards transmetalation through the formation of an anionic hypervalent tin center. Under these conditions, phenyl- or vinyltrialkylstannanes readily undergo couplings to non-activated aryl chlorides and bromides with two equivalents of TBAF at 100 or 80°C, respectively (Scheme 65). Surprisingly, both IPr·HCl (**9**, Table 1) and IAd·HCl (**18**) showed equal activity.[198] Under similar conditions, phenyl- and vinyltrimethoxysilanes underwent cross-coupling reactions at slightly lower temperature (60°C), but a large excess of the silicon reagent (2–3 equiv) was required.[199] Furthermore, the single example of an Pd–IPr-mediated Stille coupling in the presence of CsF is shown on Scheme 19.[89]



Scheme 65.

4.6. Alkyne Cross-Coupling Reactions and the Sonogashira Reaction

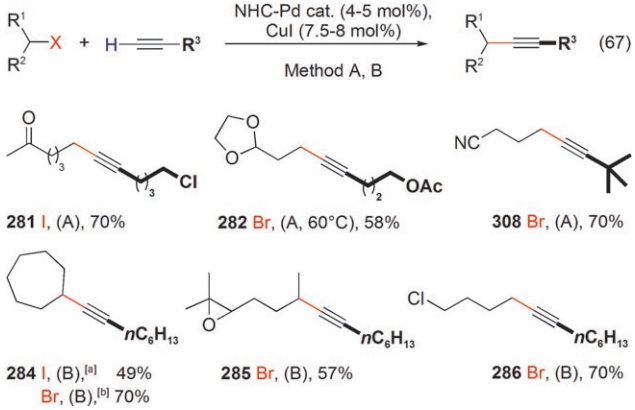
The coupling of terminal acetylenes encompasses a family of related transformations in which an sp-hybridized carbon nucleophile is generated.[200,201] The most widely used protocol relies on Cu salts as co-catalysts, most often in the presence of amine bases (the Sonogashira reaction).[201] The first Sonogashira reaction with a Pd–NHC catalyst was published by Caddick, Cloke et al. (Scheme 66): the coupling of a trisubstituted alkene carrying a bromo and an iodo substituent as well as an ester group using [($ItBu)_2$Pd] (**65**, Scheme 26) as the catalyst. As expected, the coupling occurred at the vinyl iodide site (product **276**, Scheme 66).[102] Batey et al. used a



Scheme 66. Method A: **92** (1 mol%), Et_3N, 90°C. Method B: **113** (1 mol%), PPh_3 (2 mol%), CuI (2 mol%), DMF; for ArI: Et_3N, RT; for ArBr: Cs_2CO_3, 80°C. Method C: **218** (3 mol%), [$PdCl_2(PPh_3)_2$] (3 mol%), KO*t*Bu/[18]crown-6, THF; for ArI: RT; for ArBr: 65°C. Method D: 65 (1 mol%), CuI (0.2 equiv), iPr_2NEt, DMF, RT. Method E: **280** (0.1 mol%), Et_3N, 90°C.

catalyst comprisng the PdI_2 complex **113** (1 mol%, Scheme 37) with an *N*-acyl-*N'*alkyl NHC and an *N*-methylimidazole ligand for the Sonogashira reaction of simple bromo- and iodoarenes with terminal acetylenes in the presence of PPh_3 as a coligand and 2 mol% CuI (Scheme 66).[115] A similar approach was taken by Andrus and co-workers: The catalyst prepared from a bulky imidazolium salt (**218**, Scheme 56) and $[PdCl_2(PPh_3)_2]$ promoted the coupling of various iodo- and bromosubstituted arenes and alkenes with terminal acetylenes (Scheme 66).[202] Surprisingly, SIPr·HCl (**13**, Table 1) showed only moderate activity. Copper-free alkyne coupling reactions (Scheme 66) were also published by Herrmann et al.[105] (with 1 mol% **92**) as well as McGuinness and Cavell (with 0.1 mol% **280**, Scheme 66).[94]

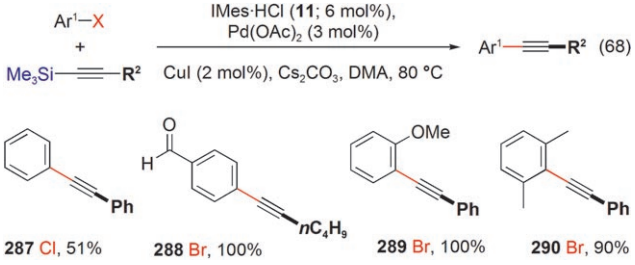
The Sonogashira coupling of terminal acetylenes with alkyl bromides and iodides, a milder alternative for the uncatalyzed, direct substitution process, was first published by Eckhardt and Fu (Scheme 67).[78] A variety of functional



Scheme 67. Method A: **18** (10 mol%), $[\{Pd(\pi\text{-allyl})Cl\}_2]$ (2.5 mol%), CuI (7.5 mol%), Cs_2CO_3, DMF/Et_2O, 45°C. Method B: $[\{(IBiox7)PdCl_2\}_2]$[c] (4 mol%), CuI (8 mol%), Cs_2CO_3, DMF/DME, 60°C. [a] 1,2-diaminocyclohexane (20 mol%) was used as additive. [b] 1,2-diaminocyclohexane (8 mol%) was used as additive. [c] For the structure of IBiox7 see Table 2.

groups were compatible, including alkyl chlorides. Even though IAd·HCl (**18**, Table 1) was the ligand of choice (Schemes 29 and 67; Table 1), IPr·HCl (**9**) also showed high levels of activity. This reaction represents the first example of the coupling of simple alkyl halides by a Pd–NHC catalyst. However, later attempts to use this methodology in the course of a total synthesis of the polyacetylene natural product callyberyne B were unsuccessful.[203] Very recently, Glorius and co-workers showed that the IBiox-NHC ligands **46–51** also catalyzed the Sonogashira cross-coupling reaction of alkyl halides (55–62%).[204] In contrast to the work of Eckhardt and Fu, IAd·HCl (**18**, Table 1) was only moderately effective (41%). The best catalyst was the preformed $[\{(IBiox7)PdCl_2\}_2]$ complex (Scheme 67). This work is particularly noteworthy for the successful coupling of secondary alkyl halides (the first such case published with Pd–NHC catalysts) and the excellent chemoselectivity and functional-group tolerance: primary and secondary bromides with chloride, ester, and even epoxide groups could be coupled in greater than 57% yields. The coupling of a chiral secondary bromide resulted in complete racemization.

The use of organometallic alkyne derivatives of main-group elements is also possible with Pd–NHC catalysts. Fürstner and Leitner have used *B*-(phenylethynyl)-*B*-methoxy-9-BBN as a nucleophile in the Suzuki–Miyaura reaction of non-activated chloroarenes (which are inactive under the classical Sonogashira conditions) in the presence of IPr·HCl (**9**, Table 1) and $Pd(OAc)_2$ in refluxing THF. 4-Methoxycarbonyl- and 3,5-dimethoxydiphenylacetylene were obtained in 82 and 85% yields, respectively.[192] Complex **102** with a phosphane and a cyclic diaminocarbene ligand (Scheme 33) also catalyzed the reaction of *para*-bromoacetophenone and *B*-(2-propyn-1-yl)-*B*-methoxy-9-BBN in 82% yield.[107] Colobert and co-workers later published studies on the more atom-economical alkynyltrimethylborates (prepared in situ from lithium acetylides and trimethylborane) in refluxing dioxane/DME (1:1) by relying on catalysts prepared in situ from $[Pd_2(dba)_3]$ (3 mol%) and SIPr·HCl(**13**, 6 mol%) in the presence of CsF. Under these conditions, *n*-octyne was coupled with deactivated (2-chloroanisole, 65%) and heteroaromatic aryl chlorides (2-chloropyridine, 70%).[205] Yang and Nolan explored the coupling of trimethylsilylalkynes with deactivated bromoarenes and chlorobenzene (Schemes 23 and 68) by using a catalyst prepared in situ from IMes·HCl (**11**, Table 1) and $Pd(OAc)_2$.[77] Even though the reaction proceeded well under copper-free conditions, the addition of CuI facilitated the process.



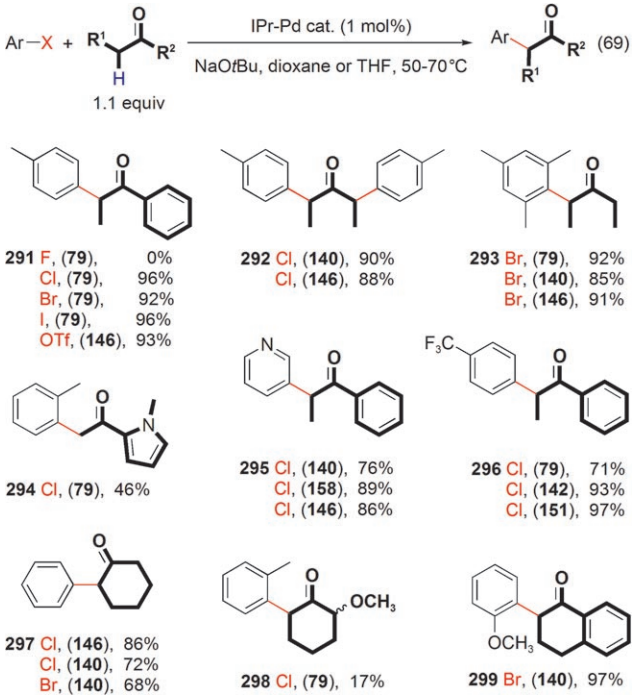
Scheme 68.

4.7. Arylation of Enolates

Among the cross-coupling reactions, the arylation of enolates[206] is unique in a number of aspects. It is well-established that even though the alkylation of enolates is facile, arylation with simple, non-activated aryl halides is impossible without the help of a transition metal. Palladium-catalyzed arylation of enolates is the only method that allows the formation of useful α-arylated ketones, esters, nitriles, and amides from simple aryl halides. Moreover, if suitable reaction partners are used, a new tertiary or quaternary stereogenic center is established, thus opening up possibilities for asymmetric catalysis. Hence, this synthetically important transformation has attracted considerable attention.

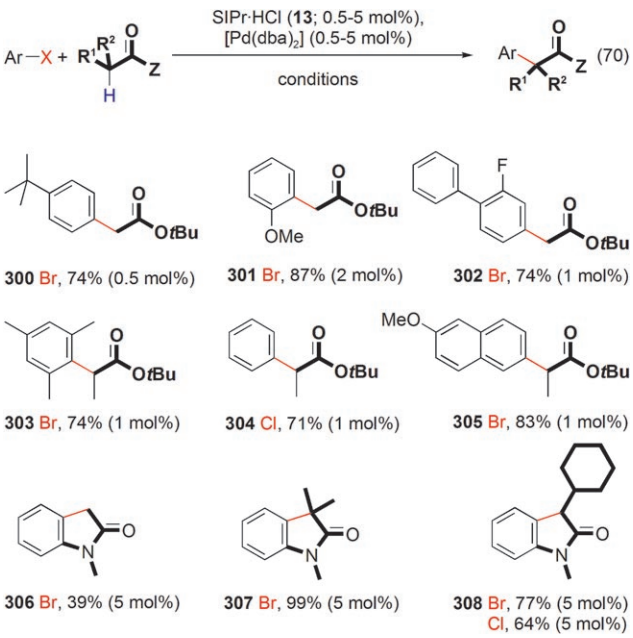
Nolan and co-workers have shown that well-defined singly ligated Pd–IPr complexes are efficient catalysts for the

arylation of simple ketones with non-activated aryl chlorides, bromides, iodides, and triflates in the presence of NaO*t*Bu (Scheme 69).[120,130,141,207,208] Even though the π-allylpalladium chloride complexes of IPr (**166**), SIPr (**147**), IMes (**145**), IAd



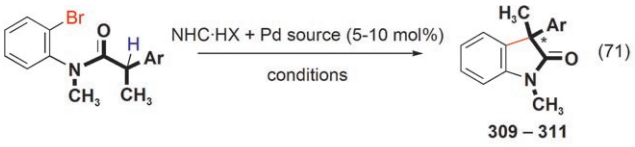
Scheme 69. Pd–IPp catalysts: **79**, **140**, **146**, or **158**.

(**149**), and I*t*Bu (**148**, Scheme 44) all showed conversions greater than 90% in the arylation of propiophenone with chlorobenzene at 70°C, the IPr or SIPr complexes were the precatalysts of choice.[208] A variety of functional groups (with the exception of nitrile and aldehyde)[207] were tolerated on the arene moiety, and sterically hindered or heterocyclic substrates also gave moderate to high yields. Aryl–alkyl, dialkyl, and cyclic ketones all proved suitable. Strict control of the amount of ketone and base is needed to suppress multiple arylation—in the presence of 1.1 equivalents of ketone and base, monoarylated products were typically obtained in high yields. The reaction was also performed under microwave conditions.[141] Substituents in the α-position to the carbonyl group usually had a detrimental effect on the coupling. Consequently, arylation occurred preferentially at the least sterically hindered carbon atom of the unsymmetrical ketones. For example, the arylation of 2-butanone with chlorobenzene led to a 4:1 ratio of methyl to methylene arylation (10:1 under microwave conditions).[141] However, quaternary carbon atoms in the α-position are not currently accessible by this methodology. Hartwig and co-workers explored the arylation of ester or amide enolates (Scheme 70) with a variety of aryl bromides and chlorobenzene in the presence of catalysts formed in situ from SIPr·HCl (**13**, Table 1) and $[Pd_2(dba)_3]$.[209] While *tert*-butyl acetate and propionate reacted smoothly with a range of aryl bromides, methyl isobutyrate gave poor yields. However, the intramolecular arylation of the 2-bromo-*N*-methylanilide of isobutyric acid resulted in a quantitative yield of **303** with both IPr·HCl (**9**, Table 1) and SIPr·HCl (**13**).[210] Whereas amides required 5 mol% catalyst loading, esters reacted well with only 0.5–2 mol%. To date, the arylation of nitriles has been explored only in the case of malononitrile. A range of aromatic chlorides and bromides were converted in excellent yields into the corresponding 2-aryl malononitlriles in pyridine by using NaH as the base (Scheme 26).[79]

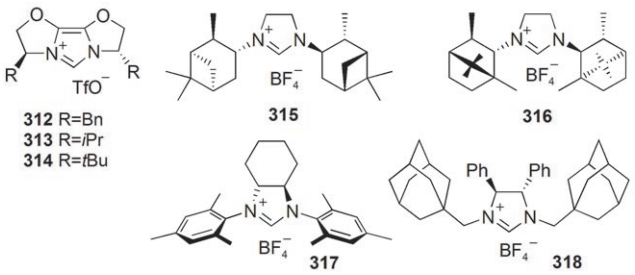


Scheme 70. Conditions: Z = NR_2: NaO*t*Bu, dioxane, 50°C. Z = OR: LiHDMS (R¹ = H), toluene, RT.

The cyclization of an oxindole is the only case of catalytic enantioselective arylation of enolates that has been explored to date. Glorius et al. prepared chiral, C_2-symmetrical tricyclic imidazolium salts **312**–**314** (Scheme 71) from commercially available (*S*)-valinol, (*S*)-phenylalaninol, and (*S*)-*tert*-leucinol, respectively.[70] Catalysts prepared in situ from these salts and $Pd(OAc)_2$ or $[Pd_2(dba)_3]$ (10 mol%) promoted an oxindole cyclization leading to product **309** in excellent yields at 20–50°C, albeit in low enantioselectivity (< 43% *ee*). Interestingly, the $[(NHC)_2PdI_2]$ complex prepared from **313** also showed excellent activity (10 mol%), even though much higher temperatures and longer reaction times were required. Lee and Hartwig synthesized two novel 4,5-dihydroimidazolium salts **315** and **316** with bulky, chiral terpene groups attached to the nitrogen atoms (Scheme 71)[210] which gave products with 71% *ee* (**315**) and 76% *ee* (**316**). Notably, the catalysts derived from **315** and **316** exhibited activities sufficient for the reactions to be conducted below room temperature, at which the highest *ee* values were obtained. In contrast, the chiral SIMes analogue **317** (Scheme 71) showed modest *ee* values. Very recently, 1,3-di-(1-adamanthylmethyl)-substituted saturated ligand precursor **318** was also tested in a similar reaction in the presence of 10 mol% $Pd(OAc)_2$, but although an *ee* value as high as 67% was obtained, the yield was very low (14%). The use of a milder base, *t*BuOLi instead of *t*BuONa, resulted



NHC·HX	Pd source	Conditions	Ar	Yield	*ee*
312	$Pd(OAc)_2$	*t*BuONa, DME, 50°C	**309** Ph	92%	32%
313	$[Pd_2(dba)_3]$	RT		95%	43%
314	$[Pd_2(dba)_3]$	50°C		90%	11%
315	$[Pd(dba)_2]$	*t*BuONa, dioxane, RT	**310** 1-naphthyl	-	71%
316	$[Pd(dba)_2]$	*t*BuONa, DME, RT		93%	67%
		0°C		-	76%
317					<40%
318	$Pd(OAc)_2$	*t*BuONa, DME, 100°C	**309** Ph	14%	67%
		*t*BuOLi, DME, 100°C	**311** *p*MeOC$_6$H$_4$	59%	65%



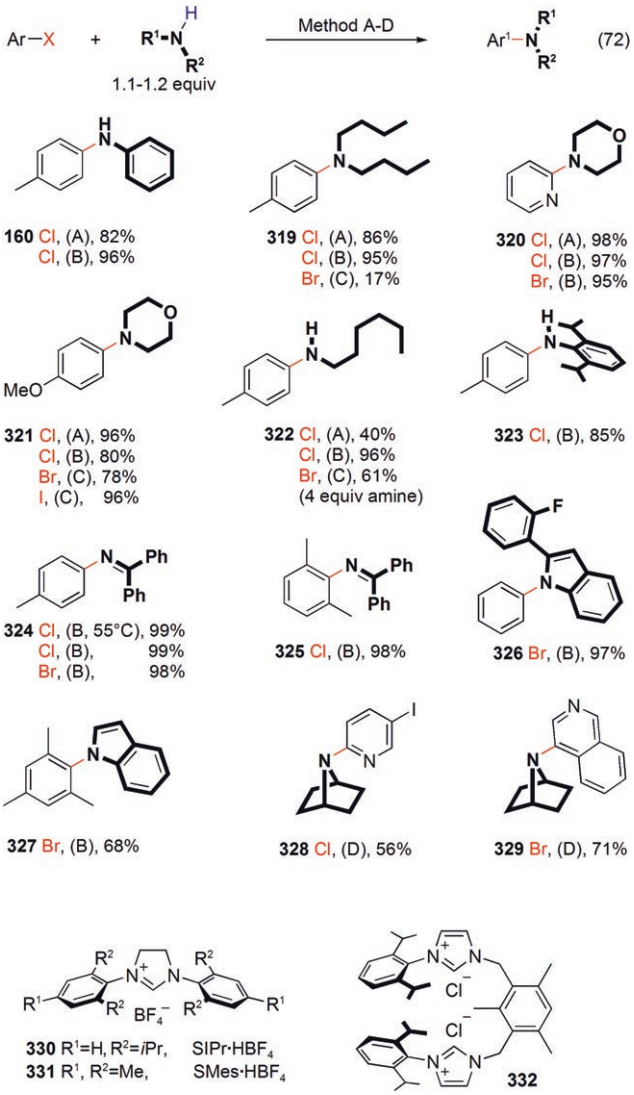
Scheme 71.

in a significant improvement in the yields without a significant erosion of the *ee* value.[211] Independently of our research group, Togni and co-workers prepared (NHC)PdI_2–pyridine complexes with chiral, *N*-ferrocenyl-substituted NHCs.[212] Even though good yields of **309** were obtained (70%), the *ee* value was only 9%. Similarly, Douthwaite and co-workers observed 90% yield, but only 11% *ee* of **309** when they used complex **76** (Scheme 22).[45]

4.8. The Buchwald–Hartwig Amination and Related C–N Coupling Reactions

The palladium-catalyzed cross-coupling reactions can also be extended to the formation of carbon–heteroatom bonds. The most significant among these is the Buchwald–Hartwig amination,[213] a method for the synthesis of aryl amines by the direct coupling of aryl chlorides and primary or secondary amines, amides, sulfonamides, imines (with N–H bonds), heterocycles, and, as of very recently, ammonia.[214] This reaction has attracted a strong industrial interest[215] because of its versatility, atom economy, and the practical utility of the products. The importance of the Buchwald–Hartwig amination reaction is emphasized by the fact that this is the only Pd–NHC-catalyzed cross-coupling reaction for which a thorough computational study of the catalytic cycle,[137] supported by experimental data,[144,146] has been published (Section 4.1, Figure 7).

Pd–NHC catalysts prepared in situ from imidazolium salts and common Pd sources are efficient catalysts for the Buchwald–Hartwig amination reaction. By using a high-throughput fluorescence assay based on the quenching of *N*-dansylpiperazine upon formation of the cross-coupling product by an azo dye attached to the aryl chloride coupling partner, Stauffer and Hartwig identified a number of highly active phosphane and NHC ligands by a rapid quantitative analysis.[216] Imidazolium salts **9**, **11**, **13** (Table 1), **330** and **331** (Scheme 72) were all confirmed to be excellent ligands for

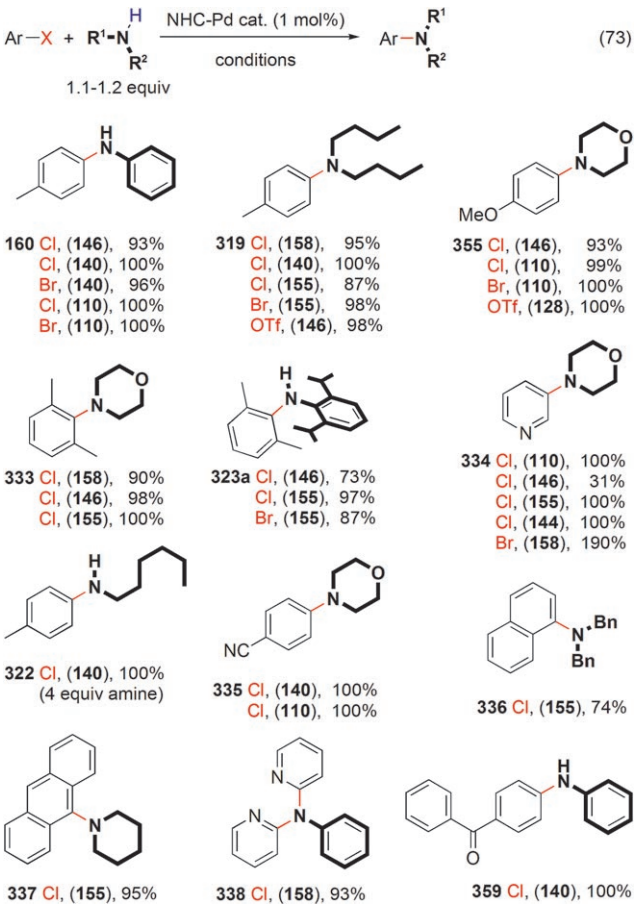


Scheme 72. Method A: **330** (0.08–2 mol%), $[Pd(dba)_2]$ (0.08–2 mol%), NaO*t*Bu, DME, RT→55°C. Method B: **9** or **331** (2–4 mol%), $[Pd_2(dba)_3]$ (1 mol%), dioxane, 100°C. Method C: **13** (4 mol%), $[Pd_2(dba)_3]$ (1 mol%), LiHMDS, THF, RT. Method D: **332** (4 mol%), $[Pd_2(dba)_3]$ (4 mol%), NaO*t*Bu, dioxane, 100–110°C.

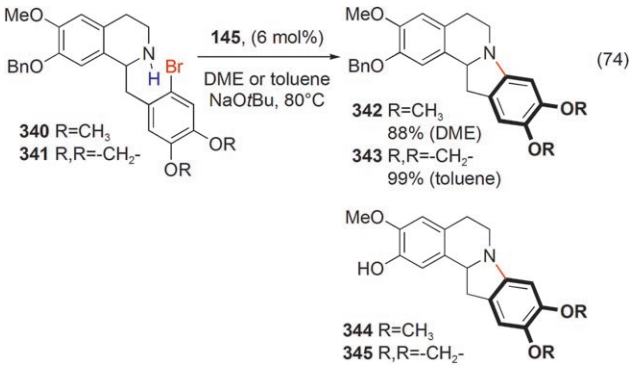
this reaction. A number of synthetic studies by the research groups of Hartwig,[206,217] Nolan,[57,218] Caddick and Cloke,[219] Trudell,[220] and Beller[110] have addressed the use of the in situ Pd–NHC protocol for aryl amination (Scheme 72). Usually, KO*t*Bu or NaO*t*Bu was used in DME or dioxane between room temperature and 100°C. The reaction proceeded well with aryl halides and aromatic or aliphatic amines as well as heterocycles with NH groups. However, the use of primary alkyl amines was problematic, and required higher temperatures and catalyst loading, as well as a large excess of the

amine (4 equiv) to suppress unwanted double arylation. With respect to more challenging substrates, Cheng and Trudell[220] carried out aminations of 7-azabicyclo[2.2.1]heptane with aryl and heteroaryl chlorides, bromides, and iodides (Scheme 72) using the bis(imidazolium) ligand **332**. Weigand and Pelka have disclosed the only amination reaction on a solid support with a Pd–imidazolium salt catalyst prepared from IPr·HCl (**9**, Table 1) or SIPr·HBF_4 (**330**, Scheme 72, 30 mol%) and [$Pd_2(dba)_3$] (10 mol%). The yields of the reaction were moderate (58–63%) as was the purity (87–89%).[221]

Considerable improvement in Pd–NHC-promoted Buchwald–Hartwig aminations has resulted from the use of well-defined palladium catalysts under conditions very similar to the in situ protocol described above. Caddick, Cloke, and co-workers showed that homoleptic [$(NHC)_2$Pd] complexes (**161** and **162**, Scheme 46) are excellent candidates for the Buchwald–Hartwig amination of aryl chlorides. At 100°C, a number of *N*-mono and *N*,*N*-disubstituted anilines were obtained in excellent yields within 1 h.[102,138,139] The singly ligated [{(NHC)Pd(NQ)}$_2$] or [(NHC)Pd(dvds)] complexes were generally found to give unsatisfactory yields. However, excellent yields were obtained by the in situ formed catalysts under the same conditions. Palladium(II)–phosphane complexes of cyclic and acyclic mono- and diaminocarbenes (for example, **102**, Scheme 33), prepared by Fürstner and co-workers, efficiently catalyzed the amination of bromobenzene and 2-chloropyridine with morpholine (47–100% yields).[107] Nolan and co-workers have invested considerable effort in the development of Buchwald–Hartwig amination protocols involving a number of singly ligated Pd–NHC complexes (Scheme 73).[113,120,123,126,130,188] The coupling reactions of deactivated and sterically hindered substrates proceeded well even at room temperature. At 80°C, decreasing of the amount of catalyst to 0.001–1 mol% still led to amination yields in the range of 90%. [(SIPr)Pd(π-cinnamyl)Cl] (**155**, Scheme 44) was the most active and versatile precatalyst to emerge from these studies, and attained greater than 95% yield within 2 h.[123,187] By using these methods, Nolan and co-workers also accomplished the formal total synthesis of cryptauswoline (**344**) and cryptowoline (**345**), two alkaloids with a dibenzopyricoline skeleton that exhibit curare-like paralytic action as well as antileukemic and antitumor activity (Scheme 74).[222] Surprisingly, [(IMes)Pd(π-allyl)Cl] (**145**, Scheme 44) was the best catalyst for the intramolecular Buchwald–Hartwig amination.



Scheme 73. Pd–NHC catalysts: **110**, **140**, **146**, **155**, or **158**. Base: KO*t*Bu, NaO*t*Bu, or NaO*t*Am. Solvent: DME, dioxane, or toluene at RT to 100°C. *t*Am = *tert*-amyl.

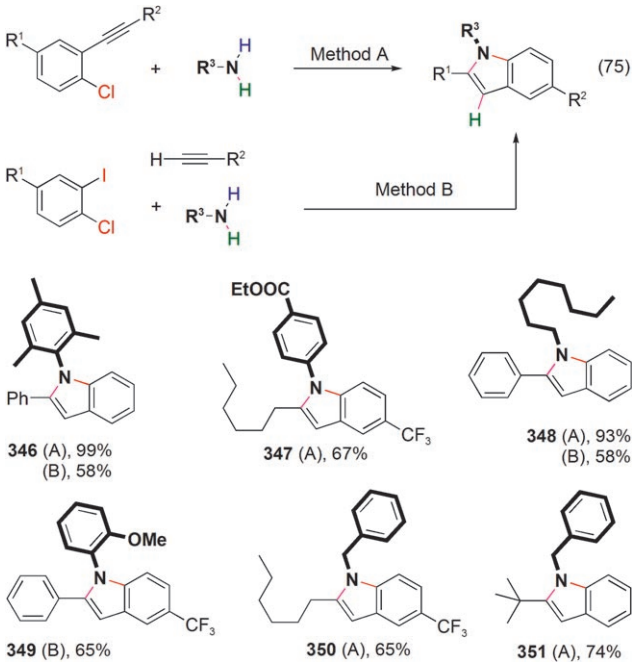


Scheme 74.

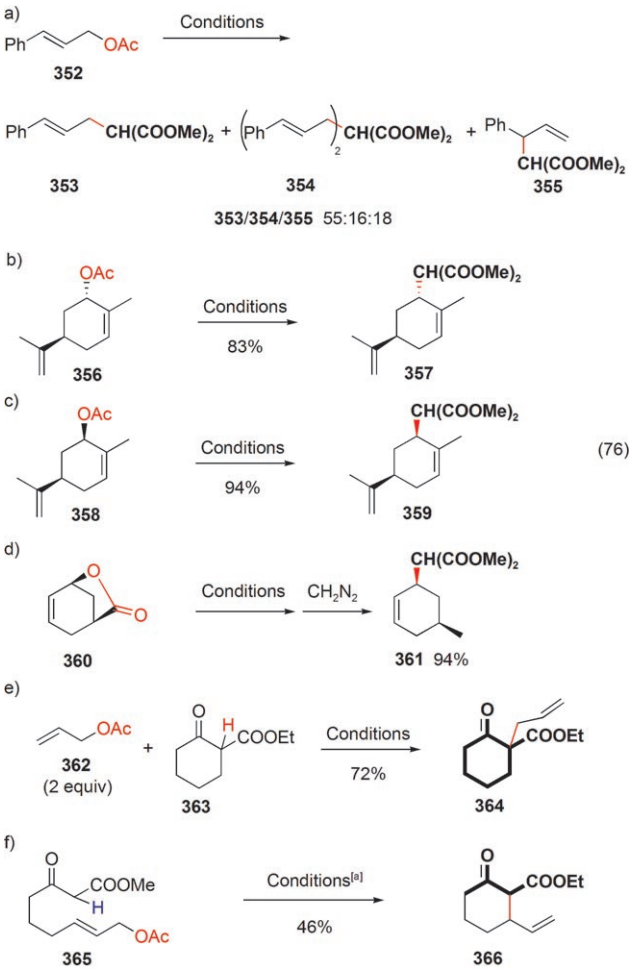
Amination of arenes can occur within more complicated reaction sequences. Ackermann described an approach to N-substituted indoles (an aryl amination–alkyne hydroamination sequence, Scheme 75) in which they used a catalyst prepared in situ from IPr·HCl (**9**, Table 1) and 5 mol% $Pd(OAc)_2$;[223] weak bases (Cs_2CO_3, K_3PO_4) were also suitable. The reaction was also executed as a tandem, one-pot Sonogashira coupling/indole cyclization sequence, albeit in generally lower yields. Also in this case, the use of a stronger base (KO*t*Bu, up to 2.5 equiv) was necessary.[224]

5. π-Allylpalladium Chemistry with NHC Ligands: The Tsuji–Trost Reaction

π-Allylpalladium complexes are the basis of some of the most versatile and useful synthetic transition-metal-mediated methodologies. These transformations are mechanistically distinct from the proper cross-coupling reactions and will be discussed separately here. A common way to produce π-allyl intermediates is the oxidative insertion of Pd^0 into allyl electrophiles. This intermediate can further react with organ-



Scheme 75. Method A: **9** (5 mol%), $Pd(OAc)_2$ (5 mol%). KOtBu or K_3PO_4, toluene, 105 °C. Method B: 1. aryl halide, alkyne, **9** (10 mol%), $Pd(OAc)_2$ (10 mol%), CuI (10 mol%), Cs_2CO_3, toluene, 105 °C; 2. amine, KO*t*Bu.



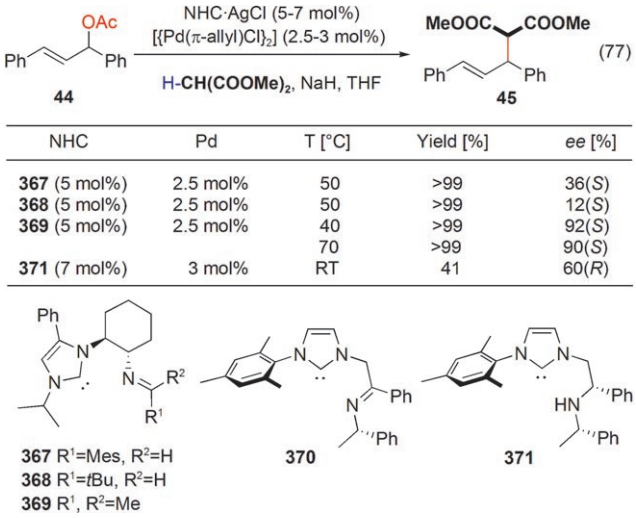
Scheme 76. Conditions: **9** (5 mol%), $[Pd_2(dba)_3]\cdot CHCl_3$ (2.5 mol%), $CH_2(COOMe)_2$ (2 equiv), Cs_2CO_3, THF, reflux. [a] NaH was added.

ometallic reagents and heteroatom nucleophiles (Tsuji–Trost reaction).[225] The double bond adjacent to the carbon atom bearing the leaving group has a profound effect not only on the reactivity, but also on the mechanism of the activation with Pd. Even though Pd-mediated allyl alkylations (including catalytic enantioselective variants)[226] have been extensively studied with phosphane ligands, the use of NHCs so far has been limited, and mechanistic studies are non-existent. An alternative route to π-allylpalladium compounds is the migratory insertion of a 1,3-diene coordinated to a palladium(II) center.[227] Examples of such diene transformations published with NHC ligands to date all involve a Pd^{II} species containing a Pd–C bond. Hence, these carbopalladation reactions will be discussed in Section 6.

The classic Tsuji–Trost methodology with Pd–NHC ligands was initially explored by Mori, Sato, and Yoshino using catalysts prepared from various imidazolium salts and $PdCl_2$ by treatment with *n*BuLi at low temperatures (Scheme 14), Table 1).[82] IPr·HCl (**9**) was found to be the best ligand precursor, yielding 77% of **45** alongside 16% of recovered starting material **44**. Further studies showed that the weaker base Cs_2CO_3 was equally effective.[228] The reaction of dimethyl malonate with the unsymmetrical allylic acetate **352** led to a 55% yield of the product arising from substitution at the primary carbon atom (**353**) as well as 16% of the disubstitution product **354** and 18% of the product arising from substitution at the secondary allyl carbon atom (**355**, Scheme 76a). Cyclic acetates (**356** and **358**) or lactones (**360**) also reacted in moderate to excellent yields with overall retention of the configuration (Scheme 76b–d). These results imply that the mechanism operating with phosphane ligands is most likely retained with NHCs (both ionization of the leaving group and the nucleophilic attack are *anti* events). Similarly, β-ketoesters (**363** and **365**) underwent intra- or intermolecular alkylation (Scheme 76e,f). An important limitation of this methodology was that allylic carbonates failed to activate, and C–N substitution with nitrogen nucleophiles (amines and tosylamides) did not occur.

Whereas soft nucleophiles, such as malonates, react by a direct S_N2 mechanism with overall retention of configuration, allylpalladium complexes undergo an alternative reaction pathway with hard organometallic reagents: transmetalation at Pd and subsequent *syn*-reductive elimination to give the corresponding allylated hydrocarbons with formal inversion of configuration. Nolan and co-workers observed that $[(IMes)Pd(OAc)_2]$ efficiently catalyzed the cross-coupling of phenylboronic acid with allyl, methallyl, and cinnamyl (but not prenyl) chloride and bromide substrates with KO*t*Bu in technical grade *i*PrOH.[112] Similarly, the catalyst produced from IMes·HCl (**11**, Table 1) and $[Pd_2(dba)_3]$ catalyzed the Suzuki–Miyaura cross-coupling of methallylsulfonyl chloride and 3-nitrophenylboronic acid in 50% yield.[190]

Asymmetric allylic alkylation with chiral NHC ligands has also been explored (Scheme 77). Douthwaite and co-workers disclosed a series of chiral, chelating NHC-imine ligands from



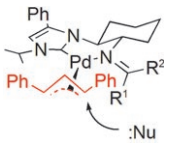
NHC	Pd	T [°C]	Yield [%]	*ee* [%]
367 (5 mol%)	2.5 mol%	50	>99	36(*S*)
368 (5 mol%)	2.5 mol%	50	>99	12(*S*)
369 (5 mol%)	2.5 mol%	40	>99	92(*S*)
		70	>99	90(*S*)
371 (7 mol%)	3 mol%	RT	41	60(*R*)

367 R^1=Mes, R^2=H
368 R^1=*t*Bu, R^2=H
369 R^1, R^2=Me

370 **371**

Scheme 77.

trans-1,2-diaminocyclohexane.[229] Bulkier N-substituents at the imidazolium ring resulted in higher *ee* values. Ketimines derived from acetone were also more enantioselective than aldimines. Among all the ligands examined, **369** was the most enantioselective, and resulted in 92% *ee*, the highest value recorded to date for a chiral NHC-derived Pd catalyst. The ligand **369** showed no erosion of enantioselectivity when the corresponding imidazolium salt was used or its AgCl adduct. The enantioselectivity was also not temperature dependent, and 90% *ee* was recorded even at 70°C. A Pd/ligand ratio of 1:1 was found to be optimal. A mechanistic proposal to explain the enantioselectivity observed was also proposed: a palladium–π-allyl species with minimal steric repulsion lies between the 1,3-diphenylallyl group and the NHC-imine ligand. This species then undergoes attack by the nucleophile at the allylic carbon atom *trans* to the more electron-rich NHC ligand (see left). Very recently, Roland and co-workers published novel, chelating NHC-imino ligands (for example, **370**)[230] that were further reduced stereoselectively by $NaBH_4$ to give NHC-amino ligands (for example, **371**) bearing two chiral centers.[230] A single example of moderately effective asymmetric induction by **371** in the Pd–NHC-mediated allylic alkylation was published (41% yield, 60% *ee*). The corresponding NHC-imino ligand **370** could not be used because of its lability under conditions leading to the formation of the Pd complex.



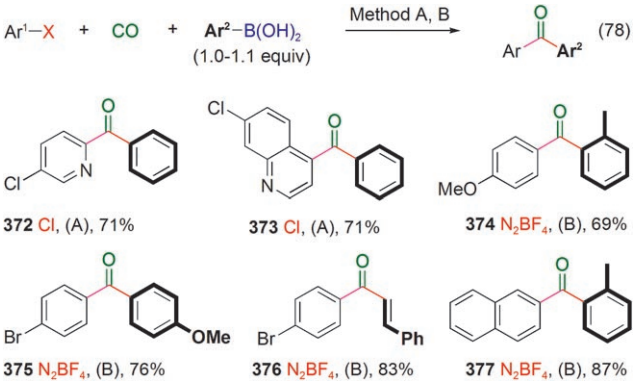
6. Pd–NHC Catalysts in Carbopalladation Reactions

The carbopalladation reactions encompass a number of related transformations in which a palladium-coordinated ligand possessing a π orbital undergoes a migratory insertion into a Pd–C bond. Formally, this reaction is an inter- or intramolecular addition of a Pd–C species across a π bond, hence the name "carbopalladation".[231] Applications of Pd–NHC catalysts in such transformations will be the subject of the final section of this Review.

6.1. Carbonylations

Migratory insertion of CO into a transition-metal–carbon bond is a common reaction in organometallic chemistry. With respect to palladium complexes, the arylpalladium species produced after oxidative addition generally react rapidly with CO to produce an acylpalladium intermediate.[232] After further transformations, a carbonyl group is incorporated into the final product.

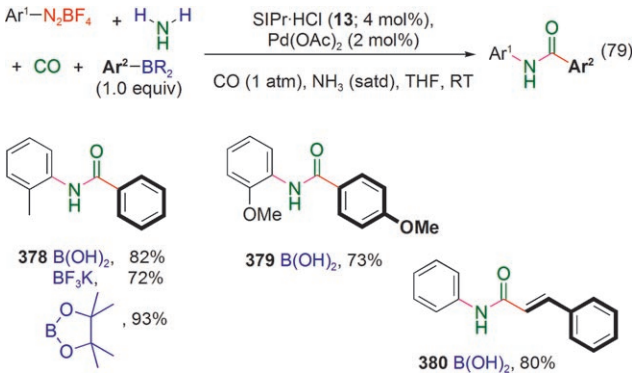
There are only a few examples published to date of carbonylation sequences involving Pd–NHC catalysts. Castanet and co-workers focused on the synthesis of benzoylpyridines by carbonylative Suzuki–Miyaura cross-coupling reactions of variously substituted chloropyridines and phenylboronic acid in dioxane with Cs_2CO_3 as the base (Scheme 78).[233] Even though 5 bar of CO were sufficient



Scheme 78. Method A: **11** (5.7 mol%), $Pd(OAc)_2$ (2.8 mol%), CO (50 atm), Cs_2CO_3, dioxane, 140°C. Method B: **13** (2 mol%), $Pd(OAc)_2$ (2 mol%), CO (1 atm), dioxane, 100°C.

for good conversions, the reaction was typically conducted under 50 bar at 140°C. IMes·HCl (**11**) was much more active than IPr·HCl (**9**) and SIPr·HCl (**13**), and a ligand/Pd ratio of 2:1 was optimal. As expected, 2-chloropyridine reacted in much higher yields than the 3- and 4-chloro derivatives. The reaction could also be extended to dichloroazines, which reacted preferably at the most activated position: C2 for pyridine (**372**) and C4 for quinoline (**373**). The targeted monoketones were the major products, along with smaller amounts of biaryls and diketones. Andrus et al. carried out carbonylative Suzuki–Miyaura reaction of arenediazonium salts with an array of arene and vinylboronic acids in dioxane at 100°C under 1 atm CO (Scheme 78)[234] using a catalyst derived from SIPr·HCl (**13**, Table 1) and $Pd(OAc)_2$ (1:1); IPr·HCl (**9**) was also effective. Biaryls were the major side products (2–23% yields), and their formation could be suppressed by increasing the CO pressure to 10 atm. On the basis of this study, Andrus and co-workers later developed an unusual four-component amidation reaction of arenediazo-

nium salts, CO (10 atm), NH_3 (saturated solution in THF), and aryl boronic acids (Scheme 79) at room temperature.[235] Catalyst loadings as low as 0.1 mol% was sufficient for good conversions. Potassium phenyltrifluoroboronate also resulted



Scheme 79.

in a high-yielding coupling reaction. A mechanism was proposed involving initial oxidative addition of the arenediazonium salt to give the cationic Pd–NHC complex, which further yielded a Pd–amido complex after complexation to ammonia. Reductive elimination of a C–N bond then afforded a palladated aniline. After complexation with the CO and its migratory insertion into the Pd–N bond, the mechanism was completed by transmetalation with the arylboronic acid and, finally, reductive elimination.

The cationic palladium(II) complex **93**[104] (Scheme 30) promoted alternate copolymerization of CO (20 bar) and ethylene (50 bar) in methanol at 50 °C. The molecular weight and polydispersity of the polyketone polymer produced were not determined. Styrene and propene did not copolymerize under these conditions. Similar results were obtained with Pd complexes of chelating NHC-phosphane ligands.[148]

6.2. Carbopalladations of Alkenes and the Heck–Mizoroki Reaction

Alkenes are the most common carbopalladation acceptors. In particular, the sequence of oxidative addition, alkene carbopalladation, and β-hydride elimination is known as the Heck–Mizoroki reaction (Figure 9),[236] a process of significant impact on modern organic synthesis both academically and industrially. Usually, the reaction requires high temperatures to proceed, even with activated substrates. The thermal stability NHC ligands impart on the Pd center implies that Pd–NHC catalysts would be particularly suitable for the Heck–Mizoroki reaction. Indeed, the first ever application of an NHC in transition-metal-mediated catalysis was published by Herrmann et al. in 1995 in the context of the Heck–Mizoroki reaction of bromo- and activated chloroarenes with *n*-butyl acrylate.[4] Subsequent DFT computations[237] (LANL2DZ basis set + ECP for Pd, 6-311G** basis set for all other atoms) conducted on the model system [{$(H_2N)_2C$}$_2$Pd]] showed that oxidative addition of a bromoarene is exergonic (-31.4 kcal mol^{-1}). The activation barrier for oxidative addition was not calculated. The calculated palladium–carbene bonding energy was 105.3 kcal mol^{-1}. For comparison, the bonding energy for 1,3-dimethylimidazolyl-2-ylidene used by Herrmann et al.[4] was 106.9 kcal mol^{-1}, thus demonstrating that the use of the unsubstituted carbene in the model system did not deviate significantly from the experimental system. For the small, unsubstituted diamino carbene, the *cis*-oxidative addition complex (Figure 9, **14.1**) was found to be more stable than the *trans* complex, the configuration being primarily determined by the electrostatic interaction between the Br atom and the two carbene ligands (L). This result is in agreement with later calculations by Green et al.[137] on the oxidative addition of chlorobenzene: the tricoordinated, T-shaped [(I*t*Bu)Pd(Cl)Ph] (**169**, Figure 7) complex was found to be more stable by 39 kJ mol^{-1} with NHC and Cl in a *trans* position. With the exception of X = triflate,[238] Pd–X bonds are stronger than Pd–phosphine bonds. Therefore, in the course of the reaction one phosphane ligand (L) is expected to dissociate to free a site for coordination of the alkene. However, dissociation of the halide ligand was proposed instead, because of the higher binding energy of the carbene. Even though dissociation of a bromide in the gas phase was found to be highly disfavored (114.9 kcal mol^{-1}), the estimated compensation by solvation (100 kcal mol^{-1}) confirmed the feasibility of such a pathway (leading to complex **14.2**) in polar solvents, which are the most suitable for Heck–Mizoroki reactions promoted by Pd–carbene catalysts. To address different mechanistic possibilities, the authors considered both a cationic Pd complex and a tight ion pair between this complex and a bromide ion. Energies and geometries calculated for the subsequent steps for both complexes were very similar when the energy of Br dissociation was factored in. Coordination of ethylene to the tricoordinated, cationic complex was found to be highly favorable (-19.5 kcal mol^{-1}). The rotational barrier of the ethylene molecule was very low (0.1 kcal mol^{-1}). The migratory insertion of ethylene was facile (activation barrier of 8.3 and 11.5 kcal mol^{-1}, respectively) and exergonic (-15.4 and -10.3 kcal mol^{-1}, respectively) for the cationic and ion-paired intermediate. The β-hydride elimination step was preceded by a strong Pd–H interaction and was calculated to proceed with an overall activation barrier of about 9 kcal mol^{-1}. The precise transition state could not be calculated because of the extremely flat PEHS. The overall carbopalladation/β-hydride elimination sequence for the cationic pathway was found to be exergonic (8.9 kcal mol^{-1}). This study also included a model bidentate ligand (a simple imidazolyl-2-ylidene with a CH_2PH_2 substituent) as well as chlorobenzene as the oxidative addition partner. The presence of a labile phosphane and chloride ion did not cause significant deviation from the dicarbene model discussed above, thus confirming the viability of similar bidentate ligands in the context of the Heck–Mizoroki reaction. Based on the observation that cationic NHC–palladiumalkyl complexes undergo rapid decomposition even at low temperatures,[19,239] Cavell and co-workers proposed an alternative associative mechanism for alkene coordination and insertion through a pentacoordinate intermediate.[240] The trigonal bipyramidal complex **14.3** with the *cis* arrangement between the alkene and the aryl

ligand required for migratory insertion was proposed to be in equilibrium with the square pyramidal complex **14.4** formed by initial alkene coordination to the intermediate **14.1** (Figure 9). Cavell and co-workers also observed the reductive elimination products (1-substituted imidazolium salts) of the NHC ligand with all proposed aryl or alkyl palladium intermediates in the Heck–Mizoroki catalytic cycle by ^{1}H NMR spectroscopy and ESI-MS.[145]

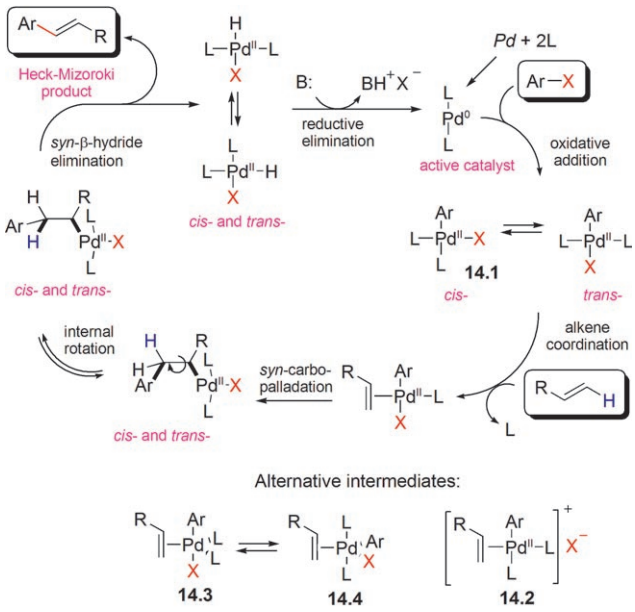
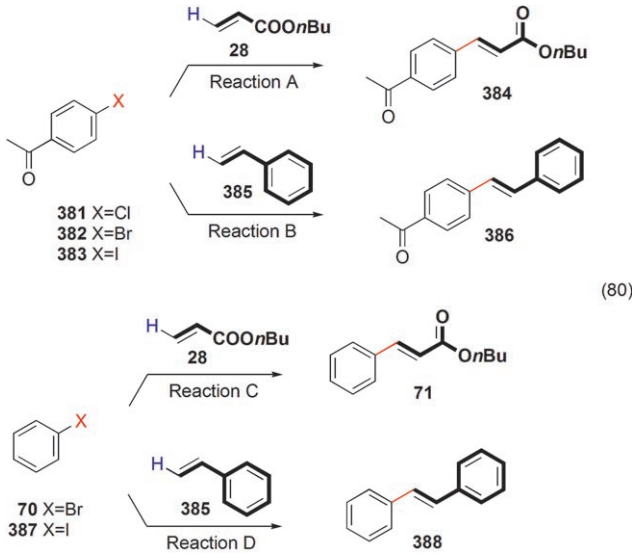


Figure 9. General, simplified mechanism of the Heck–Mizoroki reaction. L = NHC, phosphane, and/or weakly-coordinated ligands.

It is noteworthy that the catalysts used in the initial work by Herrmann et al.[4,105] (**92**, Scheme 30) and the corresponding nonchelating analogue **389**, Figure 10) showed a long induction period, which is indicative of a slow conversion of the *cis*-[(NHC)$_2$PdI$_2$] complex into an active species. The addition of TBAB or a reducing agent (sodium formate or hydrazine) caused immediate activation of precatalyst **389**. Also, the corresponding [(NHC)$_2$Pd] complex **390** (prepared in situ from the free carbene and [Pd(dba)$_2$]) was approximately 800 times more active (Figure 10). These results are in agreement with studies of cross-coupling reactions of organometallic derivatives (Section 4) that show the activation of the Pd precatalysts is the rate-determining step of the overall process and [(NHC)$_2$Pd^{II}] complexes are relatively inert. After the seminal work by Herrmann et al.,[4] olefination of simple iodo- and bromoarenes with activated acceptors such as styrene (**385**) or *n*-butyl acrylate (**28**) became a favorite benchmark for evaluation of the catalytic activity of Pd–NHC precatalysts (Scheme 80). Most often, the reaction was performed in polar aprotic amide solvents (DMA, DMF, or NMP) at 120–170 °C with sodium acetate as the base. Quarternary ammonium bromides, such as TBAB, were found to be highly beneficial. The relatively low activity of **92** was later confirmed independently by Lee et al.[169] as well as Biffis and co-workers.[241] Lee and co-workers explored a range of *N*-benzyl-substituted chelating, doubly ligated Pd–



Scheme 80.

NHC complexes. The performance of the bulkier α-naphthylmethyl-substituted derivatives (**391** and **392**) was comparable to Herrmann's complex **92**.[169] Biffis and co-workers conducted a detailed evaluation of this catalyst system.[241] Under optimized conditions, complex **92** led to a TON of 13000. Increasing the bulk of the substituent (from Me to Ph) led to a sevenfold increase in the TON value, a change to benzimidazolyl-2-ylidene (**394**) also had a similar effect. The length and rigidity of the tether (related to the bite angle)—methylene, ethylene, or 1,2-phenylene—also had a significant impact on the catalyst performance. In a related study, Baker et al. achieved very high TONs (up to 7100000) for the Heck–Mizoroki reaction of iodobenzene with a PdX$_2$ complex (X = Br, I) with a cyclophane-embedded chelating NHC ligand (for example, **397**). In contrast, the chelating analogue **396** was less reactive. The rigidity, length, and topology of the tether could in principle affect the ease of precatalyst activation, catalyst longevity, or coordination geometry. Additional studies are needed to probe the detailed structure–activity relationships of such tethered systems. In addition, the research groups of Shi[186] (**431**, Scheme 81) and RajanBabu[242] prepared palladium complexes with chelating dicarbenes derived from chiral amines that showed reasonable activity in the Heck–Mizoroki arylation of acrylate esters. Doubly ligated complexes of carbenes derived from heterocycles other than imidazole have also shown excellent applicability in the Heck–Mizoroki reaction. Biffis, Cavell, and co-workers synthesized a *trans*-[(NHC)$_2$PdI$_2$] complex from simple *N*-methyloxazolium iodide (**398**).[243] Interestingly, complexes derived from related, bis(oxazolium) salts were less reactive. Buchmeiser and co-workers investigated the analogous complex of a six-membered cyclic diaminocarbene **400**.[244] Very high TONs were observed with bromoarenes, and good yields with *para*-chloroacetophenone (**381**), an activated aryl chloride. Huynh et al. investigated the complexes of simple, *N*-methyl-substituted benzimidazole-2-ylidene ligands with palladium iodide[245] and carboxylates.[246] Both the *cis*- (**401**) and *trans*- (**402**) forms of the PdI$_2$-derived complex were equally

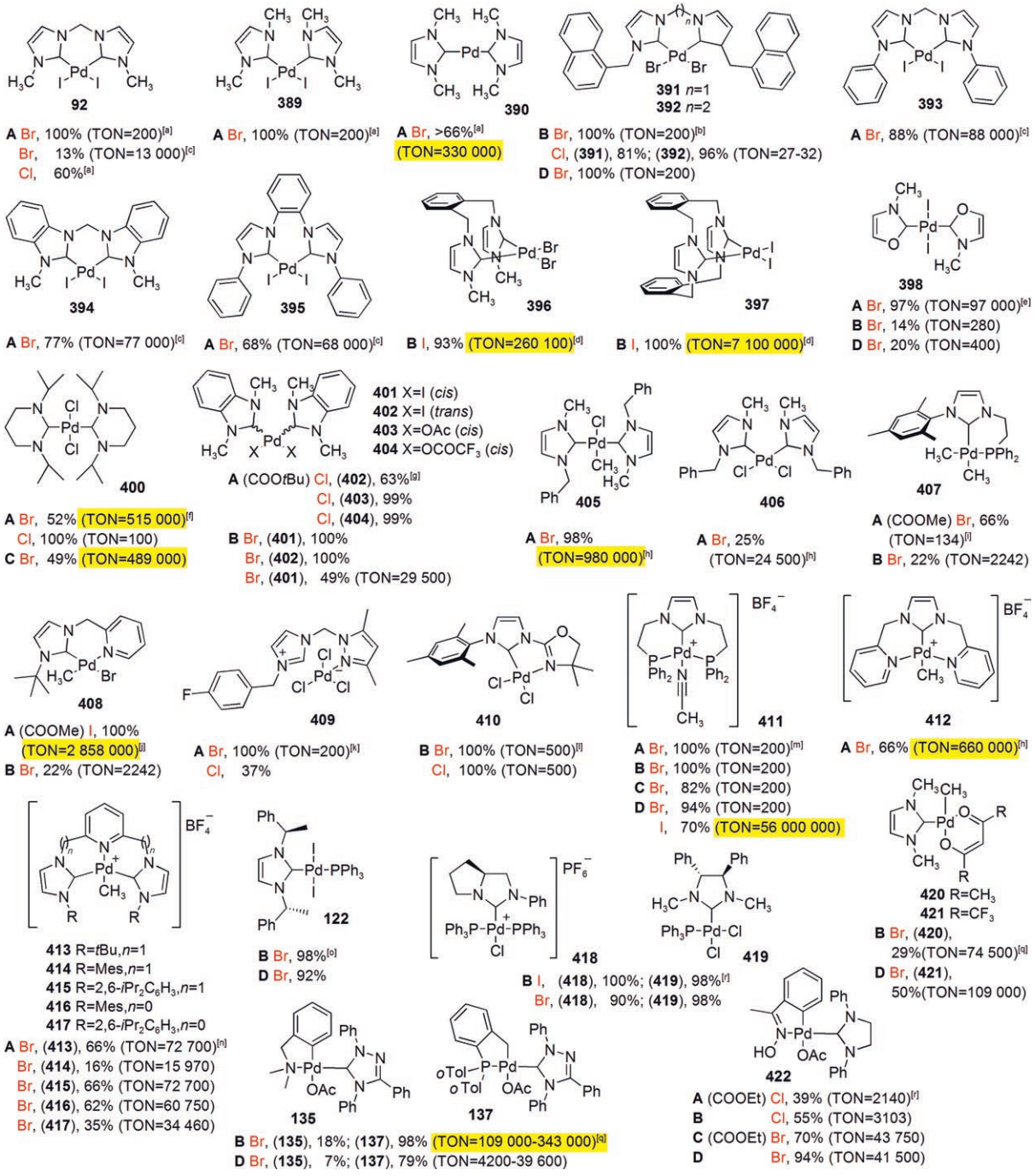
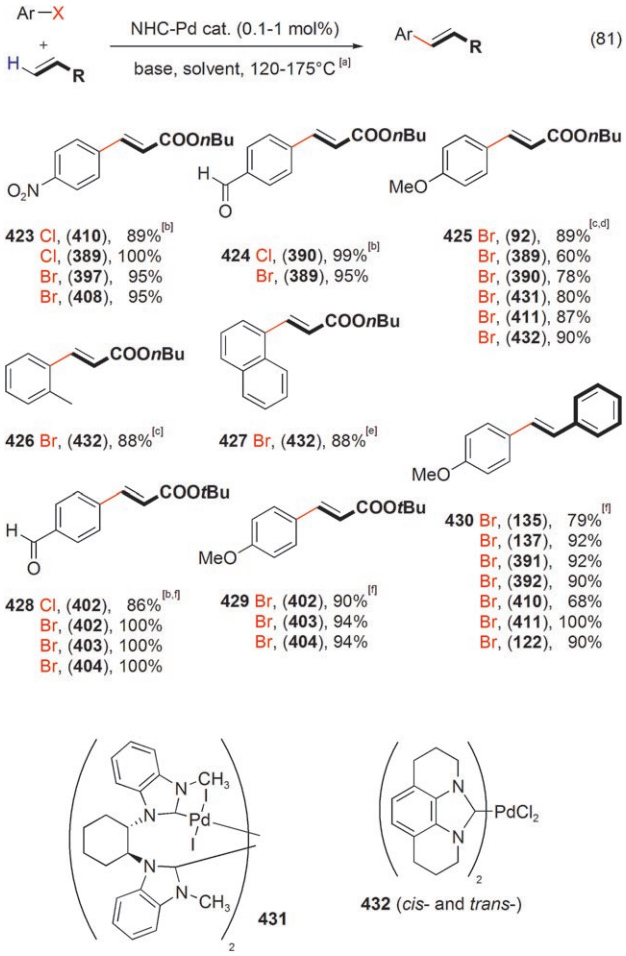


Figure 10. Evaluation of well-defined Pd–NHC precatalysts of different topologies in model Heck–Mizoroki reactions (Scheme 80). TON values greater than 10^5 are highlighted. [a] 0.5 mol% **92**, **389**; 2×10^{-4} mol% **390**, NaOAc, DMA, 125–140 °C. [b] 0.5 mol% (X = Br); 3 mol% (X = Cl), NaOAc, DMA, 165–175 °C. [c] 0.001 mol%, NaOAc, DMA, 120 °C. [d] 6.3×10^{-5} mol% **396**; 1.5×10^{-5} mol% **397**, Et_3N, DMF, 120 °C. [e] 0.001 mol% (**A**), 0.005 mol% (**B**, **D**), NaOAc, NMP, 135 °C. [f] 1×10^{-4} mol% (X = Br); 0.001 mol%, 20 mol% TBAB (X = Cl), NaOAc, DMA, 140–150 °C. [g] 1 mol%, NaOAc, DMF, 140 °C (**A**); 120 °C (**B**). The low catalyst loading experiment (0.002 mol%) was conducted in molten TBAB. [h] 1×10^{-4} mol% **405**, **412**; 1×10^{-3} mol% **406**, 20 mol% TBAB, NaOAc, DMA, 120 °C. [i] 0.5 mol% (**A**), 120 °C; 0.01 mol% (**B**), 140 °C, Et_3N, NMP. [j] 3.5×10^{-5} mol% (X = I), 130 °C; 7×10^{-3} mol% (X = Br), 140 °C, Et_3N, NMP. [k] 0.5 mol%, NaOAc, DMA, 173 °C. [l] 0.2 mol%, 20 mol% TBAB (X = Cl), K_3PO_4, DMA, 130 °C. [m] 0.5 mol%, NaOAc, DMA, 165 °C. Reaction D, X = I: 1.25×10^{-6} mol%. [n] 0.001 mol%, NaOAc, DMA, 120 °C. [o] 1 mol%, NaOAc, DMA, 130 °C. [p] 1 mol%, Cs_2CO_3, DMA, 130 °C. [q] 4×10^{-4} mol% **420**; 4.6×10^{-4} mol% **421**; 1.6×10^{-4} mol% (**B**) and 1.6×10^{-3} mol% (**D**) **135**; 2.5×10^{-4} mol% (**B**) and 2.5×10^{-4} mol% (**D**) **137**; NaOAc, DMA, 120–130 °C. [r] 4–18×10^{-4} mol%, NaOAc, NMP, 130–150 °C.



Scheme 81. Pd–NHC precatalysts: **92**, **122**, **135**, **137**, **389**–**392**, **397**, **402**–**404**, **408**, **410**, **411**, **431**, and **432** (see Figure 10). [a] Bases: NaOAc (most common), K_2CO_3, $NaHCO_3$, K_3PO_4. Solvents: DMA, DME, or NMP. [b] TBAB used as an additive with X = Cl. [c] n-$C_{16}H_{33}$-$(CH_3)3N^+Br^-$ used as an additive. [d] 0.003 mol% **390**. [e] 4×10^{-4} mol% **122**. [f] TBAB used as an additive with **137**, **403**, and **404**.

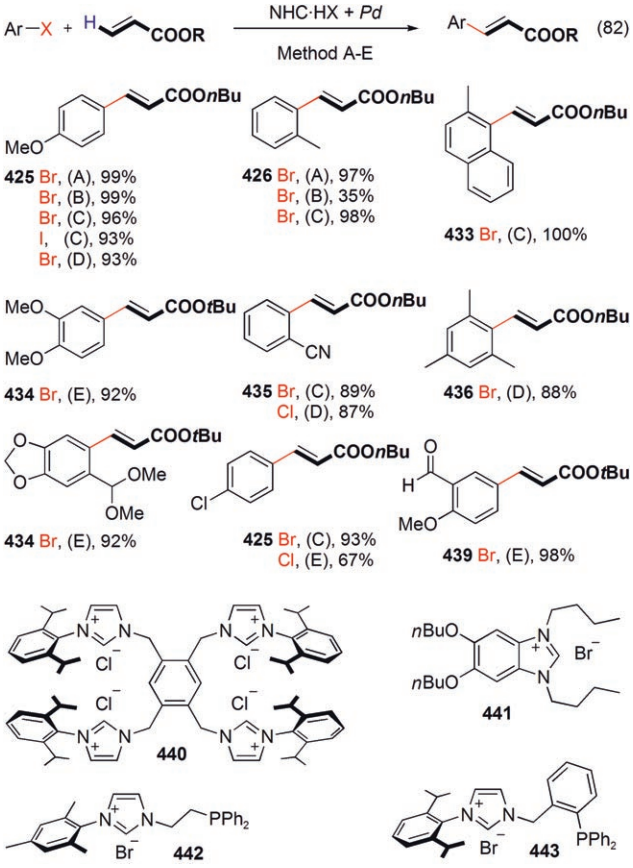
active in the Heck–Mizoroki arylations of *tert*-butyl acrylate. However, whereas the *cis* isomer activated almost instantaneously, the *trans* isomer showed an induction period of about 1 h. The complexes *cis*-$[(NHC)_2Pd(OAc)_2]$ (**403**) and *cis*-$[(NHC)_2Pd(OCOCF_3)_2]$ (**404**) were substantially more active with *para*-chlorobenzophenone (**381**, Scheme 80, Reaction A) than the *trans*-diodide complex **396**. Metallinos et al. prepared a mixture of *cis*- and *trans*-$[(NHC)_2PdCl_2]$ (**432**, Scheme 81) from a tricyclic benzimidazol-2-ylidene. This mixed precatalyst was moderately active in the Heck–Mizoroki arylation of *para*-bromoanisole and *n*-butyl acrylate (Scheme 81).[167] Consistent with the rationale of increased lability of alkyl palladium species, the doubly ligated $[(NHC)_2Pd(Me)Cl]$ complex **405** synthesized by Cavell et al. showed almost instantaneous activation, and a TON of 980000 was measured under optimized conditions (20 mol% TBAB). For comparison, the corresponding $PdCl_2$ complex **406** achieved a TON of only 24500. Bidentate ligands comprising an NHC and a P or an N donor have also been explored. The unusual dimethylpalladium complex **407** showed reasonably high activity.[148] Complex **408**, with an NHC and a pyridine donor linked by a methylene bridge, is one of the most active to date, reaching a TON of almost 3000000 in the arylation of methyl acrylate with iodobenzene (**387**).[93] Its closely related complex **280** (Scheme 66) was also very active (TON of 610000) in model reaction A (Scheme 80).[94] Lee et al. prepared an unusual $PdCl_2$ complex of a potentially bidentate imidazolium–pyrazole ligand **409**[247] which showed satisfactory activity in the Heck–Mizoroki arylation of *para*-chloro- and bromoacetophenone (**381** and **382**, Scheme 80, Reaction A). Whether the imidazolium salt is actually converted into a Pd–NHC species under the forcing reaction conditions is, however, uncertain. A $PdCl_2$ complex of a directly coupled NHC-oxazoline bidentate ligand (**410**) by Gade and co-workers showed a better performance in model reaction B (Scheme 80).[49] Closely related to bidentate ligands are the tridentate (pincer) systems. A cationic Pd complex with a PCP-pincer ligand (**411**) showed excellent activity in all four model reactions (Scheme 80).[166] In particular, the measured TON of 56000000 in the coupling of iodobenzene (**387**, Scheme 80, Reaction D) is the highest achieved with any Pd–NHC catalyst. However, this catalyst resulted in the formation of large amounts (up to 11%) of 1,1-diphenylethylene. A similar NCN-pincer complex (**412**) also showed impressive levels of activity.[92] Cavell and co-workers recently presented a series of CNC-pincer ligands containing two NHCs connected to a pyridine core. Their Pd–CH_3 derivatives **413**–**417** showed excellent performance in the Heck–Mizoroki arylations. The corresponding Pd–Cl derivatives also gave similarly good results.[248] Singly ligated Pd–NHC complexes have been explored to a lesser degree in the context of the model Heck–Mizoroki reactions. Herrmann et al. studied an array of $[(NHC)PdI_2(PR_3)]$ complexes (**122**–**130**, Scheme 39) in the arylation of styrene (**385**). The catalysts derived from IPhEt (**122**, **125**, and **128**) showed the highest levels of activity at 1 mol%, regardless of the nature of the phosphane ligand, and even $[\{(IPhEt)PdI_2\}_2]$ (**119**) was equally active.[117] The diaminocarbene–phosphane complexes developed by Fürstner and co-workers (for example, **418** and **419**, Figure 10) proved to be competent catalysts at 1 mol% in the Heck–Mizoroki coupling reactions of bromo- (**70**) and iodobenzene (**387**) with *n*-butyl acrylate (**28**).[107] Complex **102** (Scheme 33) also promoted the coupling of *para*-bromoacetophenone (**382**) in 86% yield. The presence of one or two triphenylphosphane ligands in the coordination sphere of the palladium center did not make any difference to the yields. The unusual $PdCl_2$ complex with one IMes ligand coordinated through C1 and one coordinated through C4 (**56**, Scheme 16) catalyzed model Reaction B in 77% yield at 2 mol% catalyst.[87] The β-Diketonato complexes **420** and **421** synthesized by Cavell and co-workers were also highly active and did not need any induction period, similar to other Pd–CH_3 precatalysts. Finally, Herrmann and co-workers[97] as well as Iyer and Jayanthi[100] showed that NHC-ligated palladacycles are excellent precatalysts for the Heck–Mizoroki reaction. It was observed that the TONs with the phosphane-derived palladacycle **137** were an order of magnitude greater that from N-donor palladacycles **135** and **422**. It is

noteworthy that **422** also showed high TONs in the arylation of *para*-chloroacetophenone (**381**).

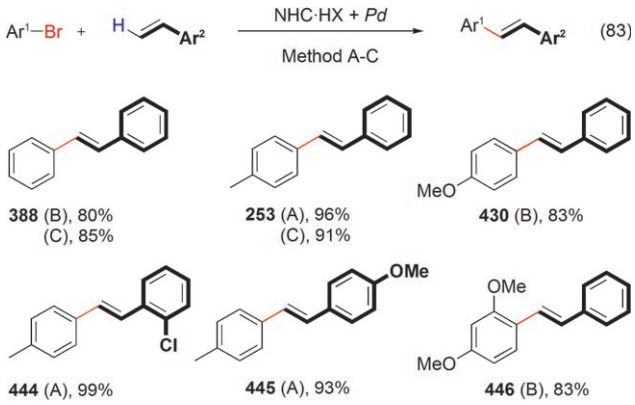
A great variety of well-defined Pd–NHC complexes have been shown to efficiently mediate model Heck–Mizoroki arylation reactions (Scheme 80). Almost all of these complexes are Pd^{II} species for reasons of stability and ease of preparation. No single class of ligand, topology, number of carbene ligands, and number/kind of additional ligands showed superior catalytic performance, in part because of the fact that these reactions were all conducted in temperatures much higher (120–175 °C) than cross-coupling reactions of organometallic derivatives. Under these forcing conditions, the formation of active catalysts from a wide range of precursors that would be inactive at lower temperatures should be facile. It is noteworthy that catalysts with carbenes other than (4,5-dihydro)imidazol-2-ylidene (for example, **398**, **400**, **135**, and **137**) show performance equal to the former. In the cases when TOF values were measured,[143,243,248] they were comparable with the most active phosphane or ligand-free palladium catalysts (up to 24000 h^{-1}). It is worth pointing out that when very low catalyst loadings (10^{-5}–10^{-3} mol% of the precatalysts shown on Figure 10) were used in model Reactions A–D in Scheme 80, the overall reaction times until no additional substrate formed were long (up to 120 h). Some of these complexes also showed significant activity for other substrates (Scheme 81). However, in most of these cases the catalyst loading was significantly higher (0.1–1 mol%), thereby resulting in excellent yields over shorter reaction times (< 48 h). Also, the utility of benzimidazol-2-ylidene catalysts (**402**–**404**, Figure 10; **431** and **432**, Scheme 81) in these more challenging Heck–Mizoroki reactions, especially with *para*-bromoanisole (**30**) is noteworthy.

However, caution is necessary when results from experiments with low catalyst loadings are evaluated. As pointed out by Farina, "for easy reactions, such as the Heck and Suzuki couplings coupling of aryl iodides and activated aryl bromides with acrylates and phenylboronic acid, respectively, virtually any Pd source is capable of reaching extremely high TONs".[249] A recent study by Biffis et al. measured TONs with $Pd(OAc)_2$ that were actually up to 10 times higher than with complexes **92** and **393**–**395** in the Heck–Mizoroki arylation of *para*-bromoanisole (**30**) and *n*-butyl acrylate (**28**). Detailed kinetic analysis showed that the $[(NHC)_2Pd]$ species was the active catalyst, and not ligand-free Pd leached out of the complex. Moreover, addition of excess imidazolium salt was found to have an inhibitory effect on the reaction, presumably through the formation of $[(NHC)_nPd]$ complexes ($n > 2$). This work highlights the necessity of proper controls and accurate, well-designed kinetic experiments if the nature of the Pd–NHC catalysts is to be well understood. No build up of Pd-black was reported with most of the complexes in Figure 10, even after prolonged reaction times at high temperatures, thus highlighting the excellent stability of the Pd–NHC bond. This stability is highly beneficial for the development of supported Pd catalysts for the Heck–Mizoroki reaction[150,173,176,250–255] (as well as other Pd-mediated processes), even though slow loss of activity as a result of the degradation of the Pd–NHC complex and deposition of colloidal Pd, as recently observed by TEM,[150,255] ensues. Interestingly, scavenger experiments[150] showed that catalytically active, ligand-free Pd released from the supported $[(NHC)_2Pd]$ complex was also present, whereas the analogous $[(NHC)_2PdCl_2]$ complex had much higher stability. The authors infer that the strain incurred during the immobilization led to increased lability of the supported catalyst.

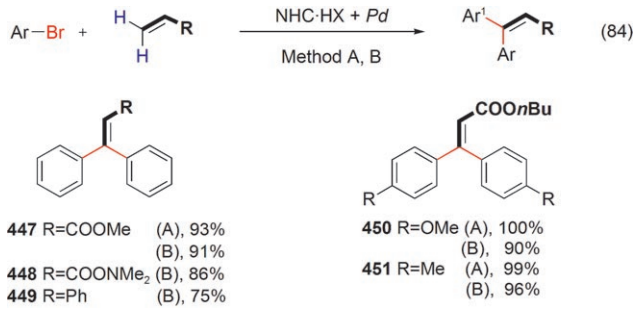
Pd–NHC catalysts prepared in situ from imidazolium salts and common Pd sources have received much less attention (Schemes 82–84). Nolan et al. conducted a detailed evaluation of a number of simple imidazolium salts (Scheme 7 and Table 1) with $[Pd(dba)_2]$ and $Pd(OAc)_2$ in the Heck–Mizoroki arylation of *n*-butyl acrylate (**28**) with a non-activated aryl bromide, *para*-bromotoluene (**30**).[76] IMes·HCl (**11**) was found to be the best ligand at Pd/IMes ratios of both 1:1 and 1:2.[87] IPr·HCl (**9**) was less active, but well within the synthetically useful range. Arylations of *n*-butyl acrylate (**28**) with a number of bromoarenes (Scheme 82) proceeded in high yields with **11**/$Pd(OAc)_2$ (1:2) and 2 mol% Pd. However, *ortho*-bromotoluene and *para*-bromoanisole (**30**) required TBAB (20 mol%) to achieve high conversion. Zhang and coworkers developed a tetradentate NHC ligand (**440**) that, when combined with $Pd(OAc)_2$, promoted the reactions of



Scheme 82. Method A: **11** (4 mol%), $Pd(OAc)_2$ (2 mol%), TBAB (20 mol%), Cs_2CO_3, DMA, 120 °C. Method B: **442** (0.5 mol%), $[Pd(dba)_2]$ (0.5 mol%), Cs_2CO_3, DMA, 120 °C. Method C: **443** (2 mol%), $[Pd(dba)_2]$ (1 mol%), K_2CO_3, DMA, 140 °C. Method D: **441** (0.2 mol%), $PdCl_2$ (0.1 mol%), TBAB, NaOAc, 120 °C. Method E: **440** (1 mol%), $Pd(OAc)_2$ (1 mol%), K_2CO_3, NMP, 120 °C.



Scheme 83. Method A: **443** (2 mol%), $[Pd(dba)_2]$ (1 mol%), K_2CO_3, DMA, 140°C. Method B: **441** (0.2 mol%), $PdCl_2$ (0.1 mol%), TBAB, NaOAc, 120°C. Method C: **440** (1 mol%), $Pd(OAc)_2$ (1 mol%), K_2CO_3, NMP, 120°C.

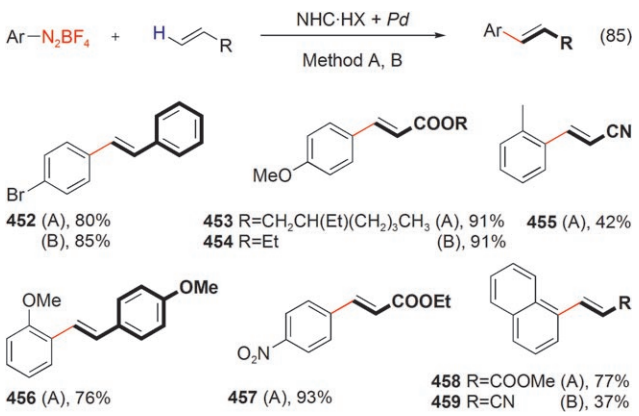


Scheme 84. Method A: **443** (2 mol%), $[Pd(dba)_2]$ (1 mol%), K_2CO_3, DMA, 140°C. Method B: **441** (0.2 mol%), $PdCl_2$ (0.1 mol%), TBAB, NaOAc, 120°C.

bromoarenes with *tert*-butyl acrylate in high yields even in air and in nonpurified, commercial dioxane containing measurable amounts of water and peroxides—a very important practical advantage.[256] Moreover, the reaction proceeded well in the presence of other oxidants (morpholine *N*-oxide or $NaBO_3$), thus suggesting that a possible Pd^{II}/Pd^{IV} catalytic cycle[257] might be operating in this case. This system catalyzed the Heck–Mizoroki reaction of *tert*-butyl acrylate (Scheme 82) and styrene (**385**; Scheme 83) with a number of deactivated or *ortho*-substituted aryl bromides in high yields. Very recently, Zou explored simple, alkyl-substituted benzimidazolium salts with electron-withdrawing (F) and electron-donating (OBu) substituents at positions C5 and C6 of the benzimidazole system. The results showed that the most electron-rich ligand precursor **441** was the most active, in line with previous results obtained by our research group for the Suzuki–Miyaura reaction (Figure 4). The catalyst prepared in situ from **441** and $PdCl_2$ promoted the arylations of *n*-butyl acrylate (**28**; Scheme 82), *N*,*N*-dimethylacrylamide (with bromobenzene, 89%), and styrene (**385**, Scheme 83) with an array of aryl bromides at 0.1 mol% Pd in molten TBAB at 120°C; even the di-*ortho*-substituted 2-bromo-1,3-mesitylene (albeit at higher Pd loading) as well as activated aryl chlorides. Also, geminal double Heck–Mizoroki arylation (Scheme 84) proceeded in high yields with 0.2–1 mol% **441**/$PdCl_2$. Bidentate NHC-phosphane ligand precursors have also been explored. Nolan and co-workers showed that an *N*-mesityl-substituted imidazolium salt carrying a pendant phosphane group (**442**) catalyzed the Heck–Mizoroki arylation of *meta*- and *para*-substituted bromoarenes with *n*-butyl acrylate (**28**) using $[Pd(dba)_2]$ (0.5%) as the Pd source (Scheme 82).[258] Attaching a phosphane group to the NHC ligand, therefore, did offer a tangible increase in catalyst efficiency in this case. A similar, *N*-2,6-diisopropylphenyl-substituted imidazolium salt linked to the *ortho* position of triphenylphosphane (**443**) showed a considerably enhanced performance (Scheme 82).[259] A very wide range of activated, non-activated, and deactivated (including di-*ortho*-substituted) aryl bromides coupled in high yields with *n*-butyl acrylate (**28**, Scheme 80). From the other side, *para*-bromotoluene (**27**) reacted with a number of styrene derivatives carrying electron-rich or electron-withdrawing substituents (Scheme 83). It is noteworthy that *meta*- and *para*-bromostyrene underwent Heck–Mizoroki polymerizations; however, the polymers formed were not characterized. The reaction showed good chemoselectivity for aryl bromides over aryl chlorides. Also, dibromoarenes underwent double Heck–Mizoroki reactions. Interestingly, with iodoarenes, geminal Heck–Mizoroki double arylations occurred (Scheme 84). Finally, imidazolium ionic liquids lacking C2 substituents have also been shown to form Pd–NHC complexes when used as reaction media for the Heck–Mizoroki reaction.[260,261]

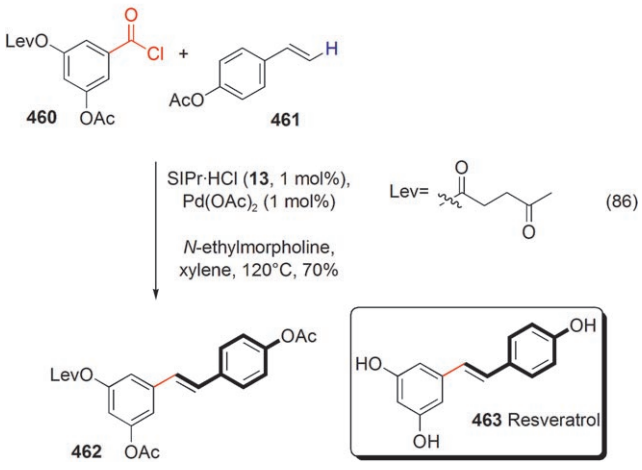
Unlike the cross-coupling reactions of organometallic derivatives, no synthetically useful, widely applicable Heck–Mizoroki intermolecular arylations of non-activated, functionalized chloroarenes have been developed to date. Böhm and Herrmann observed that using molten TBAB as solvent was necessary for the conversion of chlorobenzene and styrene into stilbene (**388**).[262] Precatalyst **122** (Scheme 39) was shown to be the most suitable among the carbene complexes tested (53% yield) whereas $[\{(IPhEt)PdI_2\}_2]$ (**119**, Scheme 39) and the *t*Bu analogue[263] of **92** furnished 48 and 45% yields, respectively (1 mol% Pd). Increasing the amount of **122** to 2 mol% furnished stilbene (**388**) in quantitative yield at 150°C, but so did precatalysts bearing phosphanes and also simple $PdCl_2$. It is reasonable to assume that under such forcing conditions, precatalyst degradation is likely, the nature of the actual active catalyst uncertain, and the benefit of having an NHC ligand doubtful. Complexes **391** and **392** synthesized by Lee et al. mediated the arylation of styrene with *para*-chlorotoluene (**21**) in 68 and 72%, respectively.[169] Other Pd–NHC precatalysts have shown only low yields (3–35%) when Heck–Mizoroki arylations of simple chloroarenes were attempted.[49,245,258,261,264]

Less-common leaving groups were explored by the research groups of Andrus and Beller. Andrus et al. showed that a catalyst formed in situ from SIPr·HCl (**13**, Table 1) and $Pd(OAc)_2$ (1:1, 2 mol% Pd) had high activity in the Heck–Matsuda arylation of *para*-substituted styrenes, methyl acrylate, and acrylonitrile with a slight excess of arenediazonium salts in THF at room temperature without any additional base required (Scheme 85). However, yields with acrylonitrile were modest. An NHC/Pd ratio of 2:1 and 3:1 led to almost



Scheme 85. Method A: **13** (2 mol%), $Pd(OAc)_2$ (2 mol%), THF, RT. Method B: **73** (0.5 mol%), MeOH, 50–75 °C.

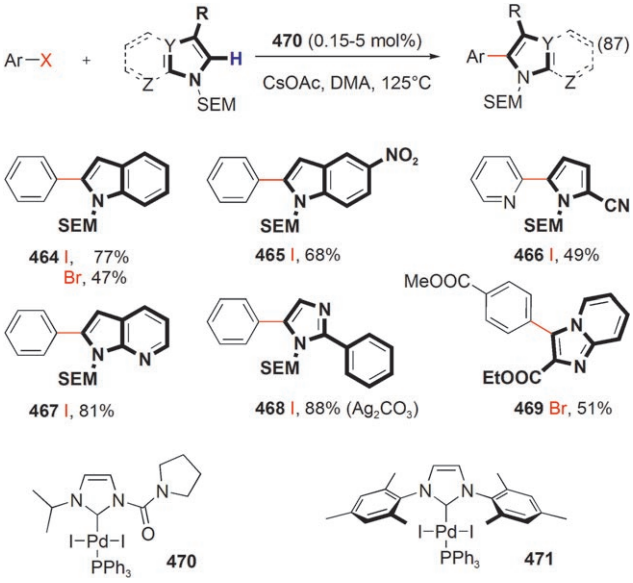
identical yields, as did a catalyst loading of 0.1 mol%. The reaction was also carried out as an in situ diazotation/Heck–Matsuda reaction sequence, which allowed direct arylation of anilines in moderate overall yields. Beller and co-workers obtained excellent yields using 0.5 mol% of precatalyst **73** (Scheme 20) in the Heck–Matsuda reaction of aryl diazonium salts bearing electron-donating and electron-withdrawing substituents with acrylate esters and styrene (**385**) in methanol at 50–75 °C (Scheme 85).[99] This process was used to prepare 2-ethylhexyl 4-methoxycinnamate (**453**, Scheme 85), a commercially important sun-screen agent. In both studies, arenediazonium salts coupled with excellent chemoselectivity over bromides. Andrus and Liu used an in situ formed Pd–SIPr precatalyst (1 mol%) to prepare analogues of the phytoalexin resveratrol (**463**), a natural product isolated from grapes and implicated in the lowering of the risk of heart disease and cancer associated with the moderate consumption of wine (Scheme 86).[265] A decarbonylative Heck arylation of electron-rich benzoyl chlorides with protected *para*-hydroxystyrene derivatives in xylene at 120 °C was the key step in this synthesis. *N*-Ethylmorpholine was used as the base and yields of 56–88% were obtained. This reaction proceeds by an



Scheme 86.

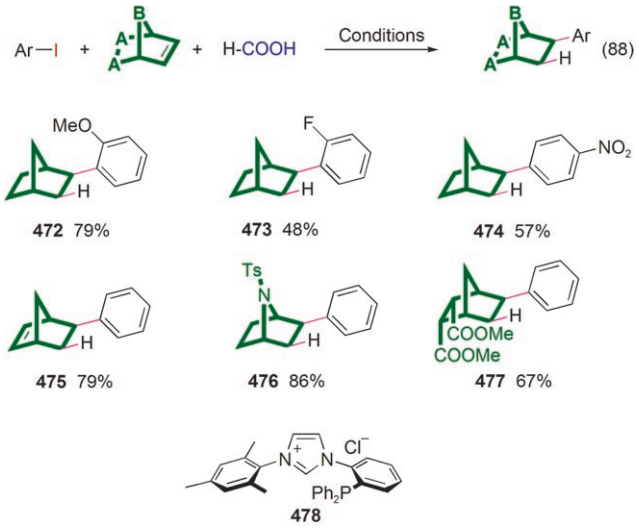
initial, facile oxidative insertion into the aroyl–chloride bond to form an acyl–Pd intermediate that loses CO at high temperature (compare with **204** in Scheme 55) to yield an aryl–Pd species that then proceeds through the typical catalytic cycle.

Until 2006, less reactive Heck-Mizoroki acceptors received no attention at all. Sames et al. developed a new method for the direct C–H arylation of SEM-protected azoles with aryl iodides by utilizing the (*N*-acyl-NHC)–palladium complex **470** (Scheme 87), similar to complex **113**



Scheme 87. SEM = trimethylsilylethoxymethyl.

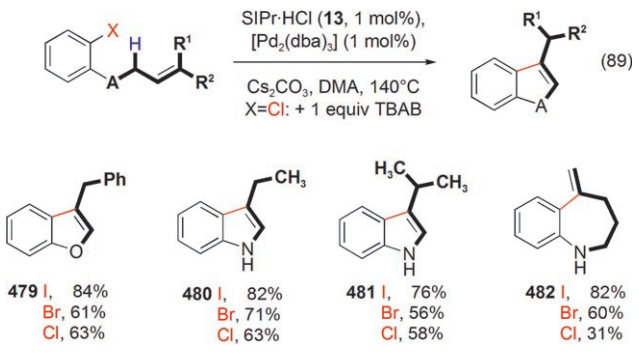
(Scheme 37) originally developed by Batey and co-workers. Even though complex **471** was found to be a superior catalyst, the arylations were performed using **470** because its synthesis is considerably more attractive (70% yield in air; the former was obtained in only 6% yield and required the use of the air- and moisture-sensitive KO*t*Bu). Bromoarenes reacted in moderate yields, and in some cases mixtures of products were obtained. Zhou et al. investigated the performance of directly coupled triphenylphosphane–imidazolium salt precatalysts (for example, **478**, Scheme 88) similar to **443** (Scheme 82) in a reductive Heck–Mizoroki arylation of norbornene derivatives with aryl iodides. In this version of the reaction, stoichiometric amounts of formate salts are added as a source of a palladium hydride after expulsion of CO_2. Subsequent reductive elimination with the Pd-bound β-arylalkyl moiety produced after the carbopalladation is faster than the elimination of β-hydride from the latter. The *N*-phenyl, *N*-mesityl (**478**), and *N*-diisopropylphenyl precatalysts all showed excellent performance in the test reaction of iodobenzene, norbornene, and formate (89–95%) yield. Precatalyst **478** (0.005 mol%) was used to catalyze the reductive Heck–Mizoroki reaction of a number of deactivated and *ortho*-substituted iodoarenes with norbornene, norbornadiene, and related bicyclic compounds (Scheme 88). TON values up to 19000 and TOF values up to 63000 h^{-1}



Scheme 88. Conditions: **478**, $Pd(OAc)_2$, KO*t*Bu (1:1:1, (2.5–5) × 10^{-3} mol%), Et_3N, DMSO, 120 °C.

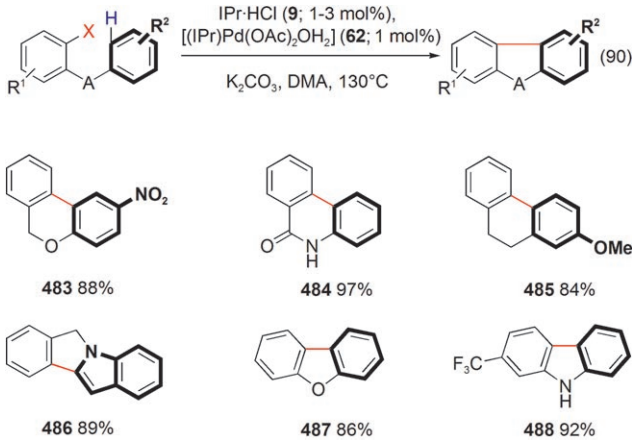
were recorded. The alkyl–palladium intermediates produced within the course of the catalytic cycle of the Heck–Mizoroki reaction could potentially undergo subsequent carbopalladation steps to form alkene oligomers and polymers. In 2006, Jin et al. investigated the polymerization of norbornene with the $PdCl_2$ analogue of complex **280** (Scheme 66) upon activation with MAO (Al/Pd 1000:1) at 40 °C. The insolubility of the poly(norbornene) meant that its molecular weight could not be determined; the polymer was characterized by solid-state ^{13}C CP/MAS NMR spectroscopy.

An aryl– or vinyl–palladium intermediate with a pendant alkene group could undergo a Heck–Mizoroki cyclization under suitable conditions. Despite the usefulness of this transformation for the synthesis of complex molecules, the application of Pd–NHC precatalysts in this context has received little attention. Caddick and Kofle have studied the intramolecular arylations of *ortho*-alkenyl-substituted aryl halides (I, Br, Cl) with 1 mol% catalyst prepared in situ from SIPr·HCl (**13**, Table 1) and $[Pd_2(dba)_3]$ (1:1) in DMA at 140 °C (Scheme 89).[266] Generally, iodo- and bromoarenes underwent cyclization in high yields, while aryl chlorides needed the addition of TBAB (1 equiv) to reach synthetically useful conversions. Fagnou and co-workers explored the



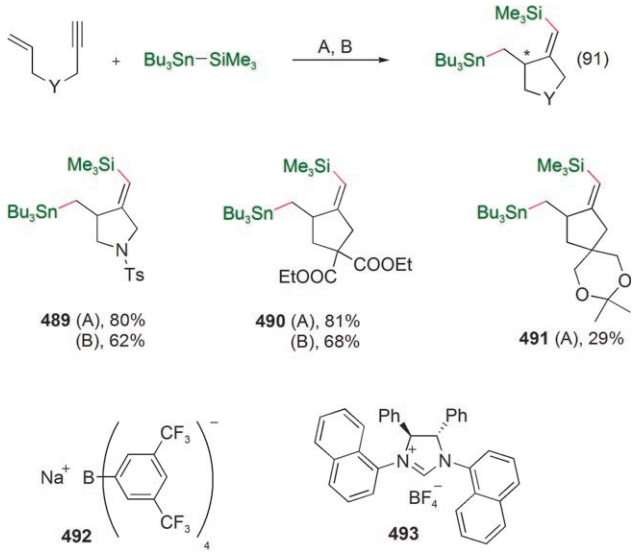
Scheme 89.

direct intramolecular arylation of aryl chlorides with a catalyst prepared from IPr·HCl (**9**; Table 1) and [(IPr)Pd-$(OAc)_2(OH_2)$] (**62**, Scheme 35) under similar conditions (Scheme 90; also see Scheme 19 and Table 5).[89] An interest-



Scheme 90.

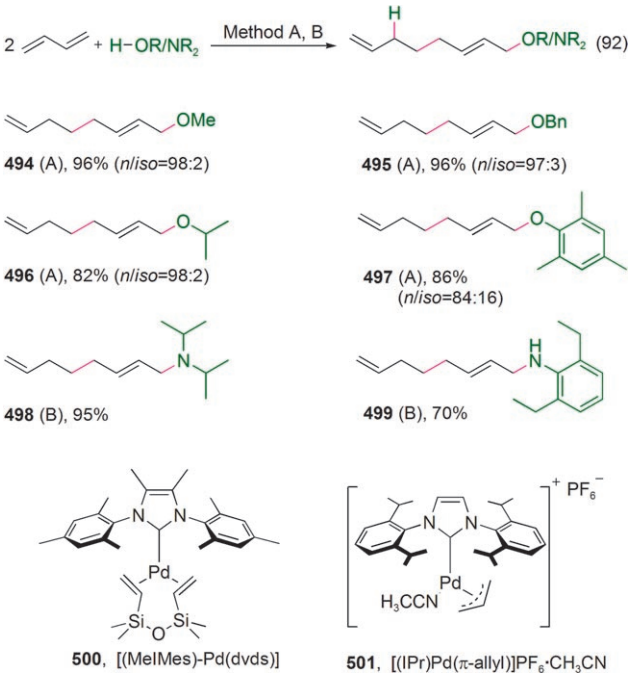
ing intramolecular alkene carbopalladation was developed independently by the research groups of Mori[267,268] and Lautens[269] in 2002 (Scheme 91). At the start, a Pd^0 species readily inserts into $Bu_3Sn{-}SiMe_3$ and similar dimetallic compounds. In the presence of a 1,6- or 1,7-enyne, insertion of the alkyne into the Pd–Si bond occurs. The vinyl–Pd species formed then undergoes intramolecular carbopalladation to give a new alkyl–Pd species concomitant with a formation of a five- or six-membered ring. Finally, a reductive elimination occurs at the C–Sn bond. Lautens et al. observed that complex **92** (Scheme 30) catalyzed a model silylstannation-cyclization in 81% yield with $Na(BAr^F)_4$ (**492**,



Scheme 91. Method A: **91** (1 mol%), $NaB(Ar^F)_4$ (**492**; 1 mol%), toluene or THF, 45 °C. Method B: **493** (6 mol%), $[Pd_2(dba)_3]{\cdot}CHCl_3$ (3 mol%), Cs_2CO_3 (12 mol%), $ClCH_2CH_2Cl$, 40 °C.

Scheme 91) as a co-catalyst. However, in further studies, Cy_2P(2-biphenyl) outperformed the NHC-based system. For a similar substrate, Mori et al. observed that the catalyst produced in situ from (*S*)-IPhEt·HCl (**20**, Table 1) and $[Pd_2(dba)_3]\cdot CHCl_3$ in the presence of Cs_2CO_3 led to a 47% yield of **490**. For comparison, IPr·HCl (**9**) and IMes·HCl (**11**, Table 1) were not active in this transformation. Since a new chiral center is created in the cyclization product, Mori et al. studied the asymmetric catalysis with chiral 4,5-dihydroimidazolium salts. The best yields were obtained with ligand precursor **493**. However, in all the cases enantiomeric excess (*ee*) did not exceed 8%.

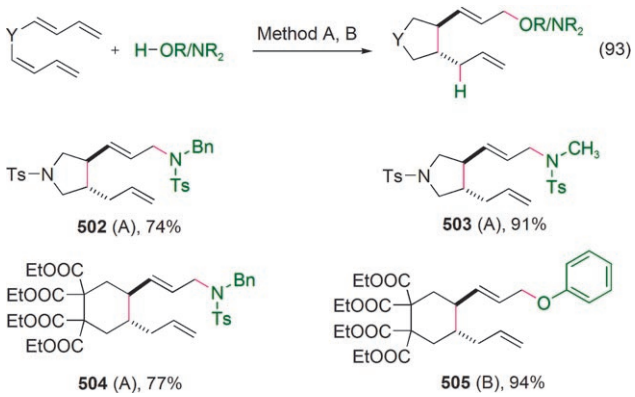
As the previous example demonstrates, the Heck–Mizoroki reaction can be enantioselective when suitable substrates are used and both the migratory insertion and β-hydride elimination are stereospecific (usually *syn*). However, all attempts at developing catalytic enantioselective alkene carbopalladations or Heck–Mizoroki reactions with chiral Pd–NHC catalysts have not yet met with any success to date.[50,267,268,270] In addition, even though chiral Pd–NHC complexes[107,186,242] have been shown to achieve good conversions in arylations of acrylate or styrene (for example, **418**, **419**, Figure 10; **431**, Scheme 81), neither of which generate any asymmetric centers, they have not been explored in asymmetric Heck–Mizoroki reactions.



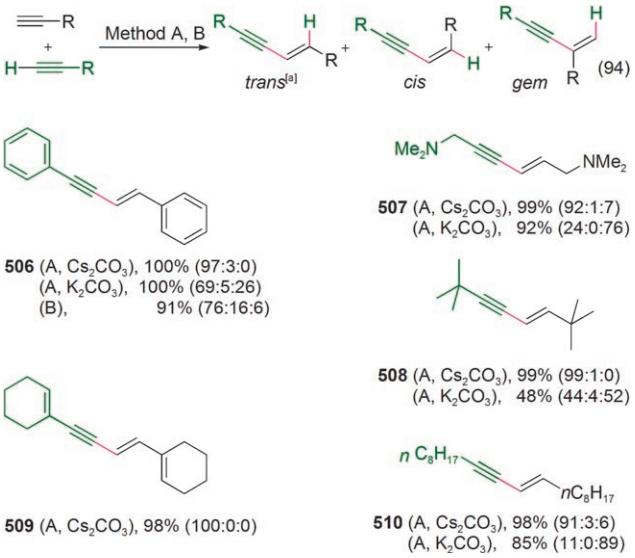
Scheme 92. Method A: **105** (0.005 mol%), NaOR (1 mol%), ROH, 70°C. Method B: **501** (0.2 mol%), THF, 60°C.

6.3. Carbopalladations Involving 1,3-Dienes

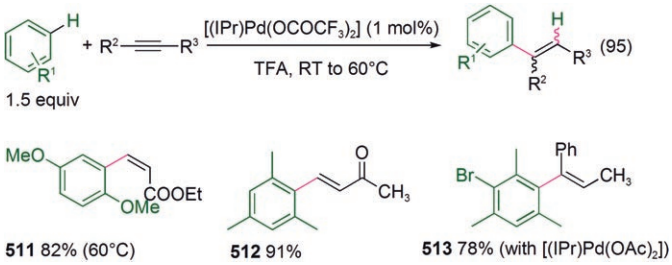
Similar to alkenes, 1,3-dienes undergo migratory insertion into Pd–C bonds. However, the conjugated double bond of the diene is also drawn into the reaction, which results in the formation of a π-allyl–palladium species. Therefore, carbopalladations of 1,3-dienes provide a nexus between carbopalladation/Heck type reactions (Section 6) and the Tsuji–Trost reaction (Section 5). Telomerization of a cheap feedstock material, 1,3-butadiene, in the presence of a nucleophilic heteroatom compound is a process of significant industrial importance in the fine-chemical industry for the preparation of functionalized, linear C_8 products. The research groups of Beller, Nolan, and Cavell have jointly reported, in collaboration with Degussa, the development of an industrially viable telomerization of 1,3-butadiene with methanol.[111,271,272] Among the number of different NHC ligand precursors screened, IMes·HCl (**11**, Table 1) achieved the highest TON (94000).[271,272] Singly ligated Pd–IMes complexes (**105**; **145**, Scheme 44) exhibited similar catalytic efficiencies. Under optimized conditions, complex **105** reached a TON of 1540000 (TOF 96250 h^{-1}) for the telomerization of 1,3-butadiene and methanol in the presence of 5×10^{-5} mol% **105**, 0.004 mol% IMes·HCl (**11**), and 1 mol% NaOMe at 90°C (77% yield of **494**, 98:2 *n*/*iso*-C_8, 99% chemoselectivity). Telomerizations of 1,3-butadiene with other alcohols and with phenols in the presence of 0.001–0.005 mol% **105** proceeded in good to excellent yields and selectivities (Scheme 92). The IPr-derived precatalyst **106** showed inferior performance. Interestingly, Beller et al. investigated the 4,5-dimethyl analogues of IMes (**2**) and IPr (**4**), MeIMes and MeIPr (for example, the ligand in **500**). DFT computations showed that these ligands bind Pd more strongly than the nonsubstituted ligands because of the presence of the electron-donating alkyl group. Even though in this particular reaction this was detrimental, the use of these ligands could be beneficial in other palladium-catalyzed reactions. Nolan and co-workers also reported the efficient telomerization of 1,3-butadiene with amines by utilizing NHC–Pd(π-allyl) complexes.[273] [(IPr)Pd(π-allyl)Cl] (**146**, Scheme 44) proved to be inefficient. Treatment of this complex with $AgBF_4$ or $AgPF_6$ in CH_3CN led to the formation of cationic Pd–IPr complexes with acetonitrile ligand (**501**, Scheme 92). The exchange of the strongly coordinating chloride ligand with a noncoordinating anion was thought to enhance the susceptibility to nucleophilic attack. Indeed, the PF_6 salt **501** was found to be an efficient catalyst of 1,3-butadiene telomerizations with primary and secondary aliphatic amines and anilines (Scheme 92). Based on these studies, a related intramolecular bis-1,3-diene cyclization terminated by trapping of the π-allyl–palladium species with phenols[274] or sulfonamides[275] was explored by Takacs et al. (Scheme 93). From a broad range of ligands and palladium precursors screened, IPr- and IMes-derived catalysts showed approximately equal activity. In contrast to the results obtained by Nolan et al., the addition of Ag or Na salts of noncoordinating anions had no beneficial effect. Preformed [(IPr)Pd(π-allyl)Cl] (**146**) and [(IMes)PdCl(π-allyl)] (**145**, Scheme 44) showed performance equal to catalysts prepared in situ. In the case of trapping with phenols, a TON of 7600 and a TOF of 280 h^{-1} were achieved by utilizing IPr·HCl (**9**)/$[Pd(\pi\text{-allyl})Cl]_2$ (2:1). In contrast, **145** was the best catalyst when sulfonamides were employed.



Scheme 93. Method A: **143** (0.1–0.05 mol%), Cs_2CO_3 (cat.), CH_3CN, 75 °C. Method B: **9** (0.1 mol%), [{Pd(π-allyl)Cl}$_2$] (0.05 mol%), Cs_2CO_3 (0.15 mol%), dioxane, 85 °C.



Scheme 94. Method A: **11** (2 mol%), $Pd(OAc)_2$ (1 mol%), DMA, 80 °C. Method B: **122** (1 mol%), Et_3N, 90 °C. [a] Only the major *trans* product shown; *trans*/*cis*/*gem* ratios are given in brackets.



Scheme 95.

6.4. Carbopalladations of Alkynes

Syn addition of a Pd–C species across a triple bond leads to a newly formed vinyl–Pd intermediate. Internal rotation to bring the Pd and a β-H atom mutually *syn*, as in the classical Heck–Mizoroki mechanism (Figure 9), is not possible because of the rigidity of the C–C double bond. Therefore, vinyl–Pd species do not easily undergo β-hydride elimination and reductive elimination is the preferred pathway for the catalytic cycle to continue. There are only a few alkyne carbopalladations mediated by Pd–NHC catalysts developed to date. Yang and Nolan showed that among the catalysts formed in situ from a number of common NHC precursors (Table 1), the one derived from IMes shows the highest activity (Scheme 13, Table 1) in the dimerization of terminal acetylenes.[81] A number of substrates underwent a head-to-tail dimerization with excellent regio- and stereoselectivity to afford substituted but-1-en-3-ynes with IMes·HCl (**11**)/Pd(OAc)$_2$ (2:1; 1 mol% Pd) in DMA using Cs_2CO_3 as the base (Scheme 94). When K_2CO_3 was employed, the selectivity of the reaction was greatly decreased; however, in a number of cases, preparatively useful selectivities for the alternative head-to-head dimerization products were achieved. Herrmann et al. also published a single example of phenylacetylene dimerization with 1 mol% of the mixed NHC–phosphane–palladium complex **122** (Scheme 39) in Et_3N. The geminal *cis*/*trans* selectivity in this case was lower than with the IMes-derived catalyst developed by Yang and Nolan (76:16:8 versus 97:3:0). Interestingly, the addition of CuI (>3 mol%) resulted in a complete switch in the course of the reaction, and 1,4-diphenylbutadiyne was formed in greater than 98% yield through head-to-head oxidative dimerization.

Nolan and co-workers showed that [(IPr)Pd(OCOCF$_3$)$_2$] and [(IPr)Pd(OAc)$_2$] (**79**, Scheme 24) are excellent catalysts at 1 mol% for the atom-economical hydroarylation of alkynes in the presence of TFA (Scheme 95).[101] In the case of Pd(OCOCF$_3$)$_2$,[276] the reaction is thought to proceed through an electrophilic arene substitution with a highly electrophilic, cationic Pd^{II} species to yield an aryl–palladium intermediate that undergoes a formal carbopalladation. Both *syn* and *anti* addition was observed, depending on the acetylene used. Protonolysis of the final vinyl–palladium intermediate by TFA regenerates the initial catalytically active Pd complex. However, Nolan and co-workers commented that this mechanism might not be operational in the case of a Pd–NHC precatalyst.

7. Conclusions and Outlook

Over the past 11 years, the field of palladium-catalyzed cross-coupling reactions has benefited enormously from the introduction of N-heterocyclic carbene ligands. When used to substitute even a highly active phosphane ligand, the resultant Pd–NHC catalysts generally show superior activity. The bulky carbenes **2**–**5**, introduced in the field's infancy, have been proven time after time to be the most active and widely applicable, not just for palladium complexes, but for a range of complexes with other transition metals. For palladium-catalyzed reactions in particular, IPr (**4**) and SIPr (**5**) have successfully conquered such challenging substrates as alkyl halides and deactivated aryl chlorides (Section 4). These catalytic systems show unprecedented versatility—both alkyl and aryl electrophiles with all common leaving groups[147] can be cross-coupled with a number of alkyl and aryl metal

compounds or, alternatively, participate in carbopalladation transformations with unsaturated acceptors—without sacrificing high levels of activity and functional-group tolerance. Attempts to synthesize NHC ligands with similar wide applicability and superior activity have not been successful.[53] The pentacyclic ligands with flexible steric bulk designed by Glorius and co-workers (Scheme 15)[83,84] show levels of activity and versatility approaching those of IPr and its analogues, but are, unfortunately, crippled by laborious synthesis. Many palladium-mediated transformations, such as enolate arylation (Section 4.7), π-allyl alkylation (Section 5), and various ring-closing reactions with carbopalladation (Section 6) open up the possibility for the development of enantioselective catalysis. However, a highly active and enantioselective Pd–NHC catalyst is a promise that so far has not been fulfilled.

The seminal paper by Herrmann et al.[4] was followed by the preparation and evaluation of a wide variety of NHC ligands and their Pd complexes (Figure 10) in the context of the Heck–Mizoroki reaction of simple, activated substrates. In many cases TONs of greater than 10^6 and TOFs of 10^4 h^{-1} were recorded, thus showing that Pd–NHC catalysts can successfully compete with the best phosphane and ligand-free systems. Nevertheless, the Heck–Mizoroki and related carbopalladation reactions (Section 6) of more complex, functionalized substrates still rely on the bulky, *N*,*N*′-diaryl-substituted carbenes.

An important research area that remains underdeveloped is the use of NHC ligands in palladium-mediated reactions outside of the cross-coupling/carbopalladation domain. What benefits NHC ligands will bring to those transformations is an exciting question that eagerly awaits an answer. Based on a superficial similarity with phosphanes as neutral two-electron donor ligands, NHCs are billed as "phosphane mimics" even today. However, in recent years it has become clear that NHCs also offer their own reactivity patterns. In this direction, the development of novel reactions catalyzed by Pd–NHC species that have no parallel with existing phosphane-based methodologies would be a significant breakthrough.

So far, Pd–NHC catalysts have rarely been utilized in the syntheses of molecules with useful function or activity. The examples of such studies to date have been limited to the syntheses of *Cryptocarya* alkaloid precursors **342** and **343** (Scheme 74),[222] Resveratrol analogues (for example, **462**, Scheme 86),[265] a cinnamate derivative used as a sun-screen ingredient (**453**, Scheme 85),[99] axially chiral amines as intermediates en route to highly enantioselective Rh–NHC catalysts (for example, **259**, Scheme 62),[191] and a highly enantioselective commercial Baylis–Hillman–Morita organocatalyst on a 10-g scale (**245**, Scheme 60).[118] The use of Pd–NHC catalysts for cross-coupling reactions involving highly functionalized, complex substrates, such as a key step in a complex total synthesis, is still awaited.

Low cost, commercially available catalysts are the key to a more widespread use of Pd–NHC catalysts in practical organic synthesis. The ligand precursors for IPr/IMes, and especially SIPr/SIMes, are expensive. The preparation of ligands that are cheaper yet retain or exceed the high levels of activity of IPr and SIPr will be an important contribution to the field. Among others, alkyl benzimidazolium salts[74,184,264] and palladium complexes of the corresponding carbenes,[116,245,246] which are easily prepared from inexpensive starting materials, can offer an adequate, economical alternative for the coupling of substrate pairs that do not pose significant challenges. Even though catalytically active mixtures can be prepared in situ from commercial azolium salts and common palladium sources, this method does not allow control of the amount and the chemical composition of the actual catalyst, as a result of the nontrivial complexation of NHCs to the palladium center. Poor reproducibility and waste of palladium and the catalyst precursor result. To remedy this shortcoming, well-defined Pd–NHC complexes that are activated easily when submitted to the reaction conditions have been developed. Today, a number of robust, user-friendly, versatile, and highly active Pd–NHC precatalysts—**109**,[99] **133**[118] (Scheme 40), and **146**[122] (Scheme 44)—are commercially available. Some of these are now cheaper than $[Pd(PPh_3)_4]$, the current choice for routine coupling reactions in industry and academia despite its inadequate stability and moderate activity.

It is the our intent that this Review will contribute to the initiation of further exploits in the remarkable potential of Pd–NHC catalysts in organic synthesis, both in academic and industrial laboratories.

Abbreviations

acac	acetylacetonate
Ad	1-adamantyl
AIM	atoms-in-molecules (calculation method)
9-BBN	9-borabicyclo[3.3.1]nonane
bipy	2,2′-bipyridyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	1,4-benzoquinone
3-ClPy	3-chloropyridine
cod	1,5-cyclooctadiene
CP/MAS	cross-polarization/magic-angle spinning
Cy	cyclohexyl
dba	*trans*,*trans*-dibenzylideneacetone
DFT	density functional theory
DMA	*N*,*N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dvds	divinyldisiloxane
ECP	effective core potential
ee	enantiomeric excess
ESI	electrospray ionization
HF	Hartree–Fock
KHMDS	potassium hexamethyldisilazide
KTC	Kumada–Tamao–Corriu
LANL2DZ	Los Alamos National Laboratory 2-double-zeta
LiHMDS	lithium hexamethyldisilazide
MALDI-TOF	matrix-assisted laser desorption/ionization

	time of flight
MAO	methylalumium oxide
Mes	mesityl; 2,4,6-trimethylphenyl
NHC	N-heterocyclic carbene
NMI	*N*-methylimidazole
NMP	*N*-methyl-2-pyrrolidone
NQ	1,4-naphthoquinone
PEHS	potential-energy hypersurface
PEPPSI	pyridine-enhanced precatalyst preparation, initiation, and stabilization
PhCN	benzonitrile
PhEt	1-phenylethyl
Piv	pivaloyl; trimethylacetyl
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TEM	transmission electron microscopy
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TOF	turnover frequency
*o*Tol	*o*-tolyl or 2-methylphenyl
TON	turnover number
Ts	*p*-tolylsulfonyl; 4-methylphenylsulfonyl

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