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PEPPSI-Effect on Suzuki–Miyaura Reactions Using 4,5-Dicyano-1,3-dimesitylimidazol-2-ylidene-Palladium Complexes: A Comparison between *trans*-Ligands

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The PEPPSI (Pyridine Enhanced Precatalyst Preparation, Stabilization and Initiation) complexes **12**–**15** with the structure $[PdCl_2\{(CN)_2IMes\}(3\text{-R-py})]$ (**12**: R = H; **13**: R = Cl; **14**: R = Br; **15**: R = CN) bearing the maleonitrile-based N-heterocyclic carbene (NHC) $(CN)_2IMes$ ($\{(CN)_2IMes\}$: 4,5-dicyano-1,3-dimesitylimidazol-2-ylidene) were prepared. Solid state structures of **14** and **15** were obtained. Complexes **14** and **15** adopt a slightly distorted square-planar coordination geometry in the solid state with the substituted pyridine ligand *trans* to the NHC. Catalytic activities of precatalysts **12**–**15** were studied and subsequently compared to complexes $[PdCl_2\{(CN)_2IMes\}(PPh_3)]$ (**4**) and $[PdCl(dmba)\{(CN)_2IMes\}]$ (**5**) recently reported by our group in the Suzuki–Miyaura reaction of various aryl halides and phenylboronic acid. Reactions using previously reported $[PdCl_2(IMes)(py)]$ (IMes: 1,3-dimesitylimidazol-2-ylidene) (**1**) were also carried out and their results contrasted to those involving **12**–**15**, **4** and **5**. Differences in initiation rates and the catalytically active species related to the seven complexes in regards to the "throw away ligand" were investigated. Poisoning experiments with mercury show that palladium nanoparticles are responsible for the catalytic activity.

Introduction

Since the early 1970s, palladium catalyzed carbon–carbon coupling reactions (e.g. the Suzuki–Miyaura or the Mizoroki–Heck coupling reaction) have been a major research interest for inorganic and organic chemists. These reactions are often critical to the total synthesis of natural products as well as the formation of pharmaceuticals.[1] The importance of this field was driven home by the awarding of the Nobel Prize in 2010 to R. F. Heck, A. Suzuki and E. I. Negishi for the development of the Mizoroki–Heck, the Suzuki–Miyaura and the Negishi reactions, respectively.

Originally, palladium phosphine complexes were used as precatalysts for cross-coupling reactions.[2] Huge drawbacks of these precatalyst systems include, but are not limited to, the intolerance of such precatalysts for moisture and especially air and the fact that phosphines often have to be used in super-stoichiometric ratios. Surplus ligands or their oxidation products often have to be removed laboriously from the product following the reaction. The discovery of N-heterocyclic carbenes (NHCs) by Arduengo et al. in 1991[3] opened the door to new precatalysts. In the mid-90s, the first palladium precatalysts bearing NHCs were presented.[4] It proved to be a huge advantage that NHC ligands could be used in a stoichiometric ratios and that the NHC-palladium precatalysts could be formed, isolated and easily stored prior to use under aerobic conditions; crucial to these qualities is the high tolerance of palladium-NHC complexes to air and moisture. In the last 20 years, custom made NHCs for specific applications have become available due to the high degree of steric and electronic variability of NHCs. The steric and electronic abilities of NHCs are readily fine-tuned by alteration of the *N*-substituents or those at the 4,5-positions of the NHC ring.[5,6]

In recent years, not only the NHC ligand in palladium precatalysts, but also the *trans*-coordinated ligands, have become the focus of increasing attention.[6b,7] In 2006, Organ et al. presented a coordination pattern with a pyridine ligand *trans*-coordinated relative to the NHC.[8b] Due to the facile synthesis of such complexes, the fast initiation in catalytic transformations, and the high stability of the catalytically active species, these complexes became known as PEPPSI (Pyridine Enhanced Precatalyst Preparation, Stabilization and Initiation) complexes. Further developments lead to PEPPSI complexes in which very bulky NHCs such as IPent {1,3-(2,6-diisopentylphenyl)imidazol-2-ylidene} can be coordinated to the palladium center and pyridine (py), 3-chloropyridine (3-Cl-py) or 3-bromopyridine (3-Br-py) can be coordinated *trans* to the NHC moiety (Scheme 1). Less bulky NHCs such as IMes (IMes: 1,3-dimesitylimidazol-2-ylidene), are less suitable ligands for PEPPSI precatalysts due to the prospect of palladium leaching.[8b,9] The pyridine ligands are so called "throw

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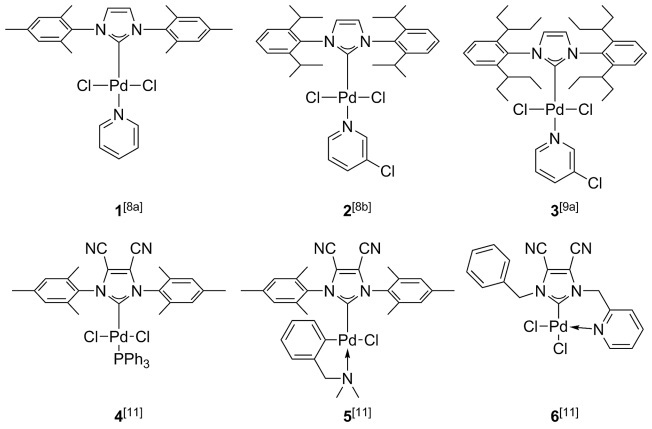
away ligands"; they dissociate easily and consequently enable catalytic reactions at low temperatures. Conversely, bulky NHC-ligands grant steric protection to the palladium center thus endowing high catalyst durability. Additionally, bulky ligands such as IPent, promote reductive elimination and transmetallation steps.[10] Thus, PEPPSI catalysis often proceeds with molecular [Pd^0(NHC)] particles and not via palladium nanoparticles.



Scheme 1. Literature known PEPPSI precatalysts **1**–**3** and precatalysts bearing (CN)$_2$IMes **4**–**6**.

Recently, we presented palladium precatalysts **4** and **5** bearing the π-acceptor NHC 4,5-dicyano-1,3-dimesitylimidazol-2-ylidene {(CN)$_2$IMes} and precatalyst **6**, bearing 4,5-dicyano-1-benzyl-3-picolylimidazol-2-ylidene {(CN)$_2$IBzPic} (Scheme 1).[11]

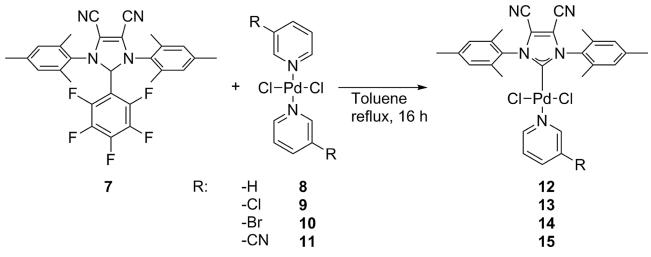
Complexes **4**–**6** showed good catalytic activities in Mizoroki–Heck reactions with *n*-butylacrylate and aryl bromides. Unexpectedly, the most efficient precatalyst **5**, outperformed its literature known analogue [PdCl(dmba)(IMes)]. Poisoning experiments have shown that reactions using these complexes are catalyzed by palladium nanoparticles and not by a molecular [Pd^0(NHC)] species.[11] Thus, we endeavored to overcome the effects of nanoparticle formation. For this reason, we prepared a series of the PEPPSI complexes **12**–**15** as precatalysts (Scheme 2). These complexes bear the NHC (CN)$_2$IMes and an assortment of different 3-substituted pyridines.

We performed the Suzuki–Miyaura reaction, which proceeds under milder conditions than those required of the Mizoroki–Heck reaction. Reaction yields using **12**–**15** were compared to those employing established precatalysts **1**,[8a] **4**[11] and **5**.[11] The reaction rates associated with the use of **1**, **4**, **5** and **12**–**15** were compared. Reaction rate experiments were conducted to view differences in the reactivity of precatalysts **1**, **4**, **5** and **12**–**15**. To investigate the nature of the catalytically active species, poisoning experiments with mercury and precatalysts **1**, **4**, **5** and **12**–**15**, were performed. Precatalyst **4** proved to be the top performer, especially when sterically hindered electron-rich substrates were used. PEPPSI precatalyst **12** exerted the fastest initiation of the precatalysts evaluated.

Results and Discussion

Syntheses

PEPPSI precatalysts **12**–**15** were prepared by refluxing the corresponding precursor complexes *trans*-[PdCl$_2$(3-R-py)$_2$] (R: H, Cl, Br, CN) **8**–**11** in the presence of NHC precursor 4,5-dicyano-1,3-dimesityl-2(pentafluorophenyl)imidazoline (**7**) in toluene for 16 h (Scheme 2). In these cases NHC is generated in situ by decomposition of the NHC precursor as shown by Waymouth and Hedrick for other NHC-pentafluorobenzene adducts in 2004.[12] Analytically pure precatalysts **12**–**15** were obtained in good yields (76–88%) following chromatographic purification over silica with $CHCl_3$/hexane (4:1) as eluent.



Scheme 2. Syntheses of PEPPSI complexes **12**–**15**.

Complexes **12**–**15** were characterized by means of ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, elemental analysis (C, H, N) as well as, in the cases of **12** and **14**, by HR-MS. Complexes **13** and **15** could not be characterized by means of mass spectrometry due to facile dissociation of the substituted pyridine ligand. Measurements in acetonitrile yielded only the [M – Cl + MeCN]$^+$ fragment at 536 amu and smaller fragments of the precatalysts **13** and **15**.

X-ray Analysis

Single crystals of complexes **14** (Figures 1 and 2), **15** (Figure 3) and established complex **1** (Figure 4), suitable for X-ray analysis, could be obtained by slow evaporation of

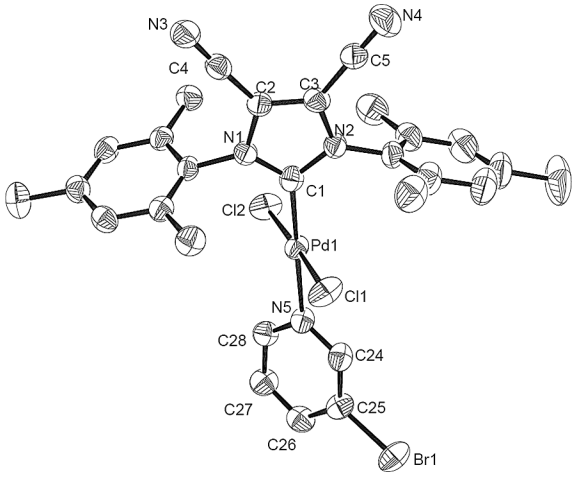


Figure 1. Molecular structure of **14**. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

$CHCl_3$ from a saturated solution containing **14**, or by slow evaporation of solvents from a saturated EtOH/$CHCl_3$ mixture (2:1) containing **15**, respectively. Single crystals of **1** were obtained by diffusion of hexane into a concentrated CH_2Cl_2 solution containing **1**. Selected bond lengths and angles of **1** and **14** and **15** are given in Table 1.

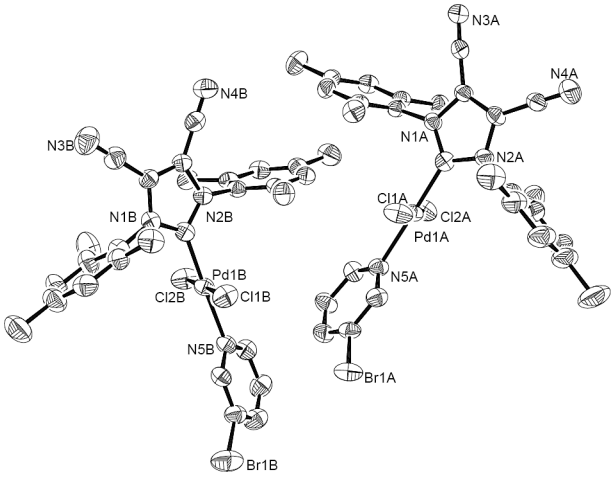


Figure 2. Asymmetric cell of **14** containing two molecules. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

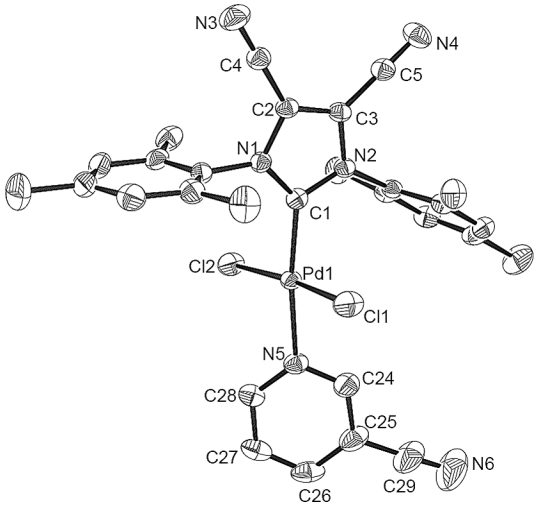


Figure 3. Molecular structure of **15**. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

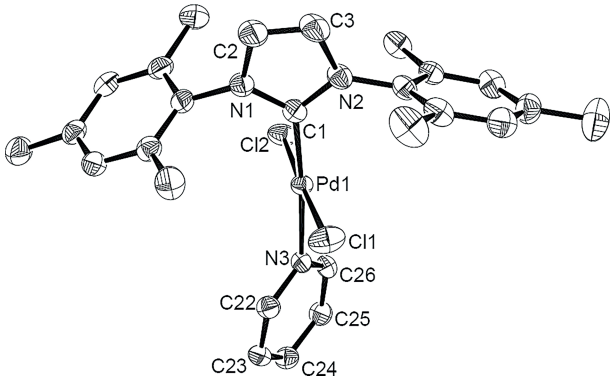


Figure 4. Molecular structure of **1**. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

Table 1. Selected bond lengths [Å], bond angles [°] and torsion angles [°] of **1**, **14** and **15**.

	1[a]	**14**	**15**
Pd1–C1	1.969(2)	1.953(4)/*1.962(5)*	1.968(2)
Pd1–Cl1	2.300(1)	2.292(1)/*2.289(1)*	2.291(1)
Pd1–Cl2	2.230(1)	2.296(1)/*2.292(1)*	2.296(1)
Pd1–N5[b]	2.093(2)	2.096(3)/*2.101(4)*	2.084(2)
C1–N1	1.353(3)	1.356(5)/*1.357(5)*	1.354(2)
C1–N2	1.354(3)	1.371(5)/*1.363(6)*	1.359(2)
N1–C2	1.391(3)	1.394(5)/*1.389(5)*	1.387(2)
N2–C3	1.388(3)	1.371(5)/*1.387(5)*	1.383(2)
C2–C3	1.330(4)	1.356(6)/*1.351(6)*	1.350(3)
C1–Pd1–Cl1	89.03(7)	88.23(12)/*88.60(12)*	88.72(5)
Cl2–Pd1–C1	91.87(6)	91.37(12)/*92.38(12)*	94.80(5)
N5–Pd1–Cl2[b]	89.71(5)	91.44(10)/*89.37(10)*	88.98(4)
Cl1–Pd1–N5[b]	89.58(5)	88.92(10)/*89.65(10)*	88.11(4)
Cl1–Pd1–Cl2	177.67(3)	176.97(5)/*178.98(5)*	173.83(2)
C1–Pd1–N5[b]	174.58(8)	177.11(16)/*177.94(15)*	172.51(7)
N1–C1–N2	105.28(19)	104.8(3)/*105.1(4)*	105.25(15)
N1–C2–C3	107.3(2)	106.6(4)/*106.5(4)*	106.99(15)
N2–C3–C2	107.0(2)	107.3(3)/*107.3(4)*	106.85(16)
C4–C2–C3–C5	/	–0.9(9)/*5.9(8)*	–1.1(3)
N2–C1–Pd1–Cl1	/	75.1(3)/*–71.5(4)*	76.3(1)
Cl1–Pd1–N5–C24	/	–33.8(3)/*41.0(3)*	55.8(2)

[a] Data for a second molecule in the asymmetric unit are given in italic letters. [b] In the case of **1**, it is N3 instead of N5.

Two independent molecules with a slightly distorted square-planar coordination geometry could be found in the asymmetric unit of **14**. The two molecules are twisted around the NHC-Pd-pyridine axis, as indicated by the location of the bromine atom of the pyridine ligand. One molecule is twisted clockwise (Figure 2, left molecule) whereas the other is twisted counterclockwise around the NHC-Pd-pyridine axis (Figure 2, right molecule). The NHC–Pd distance in **14** is 1.953(4)/*1.962(5) Å*, which is on par with the NHC–Pd distance of 1.962(4) Å in previously reported PEPPSI complex [$PdCl_2$(IMes)(3-Cl-py)] disclosed by Organ and co-workers.[10] The pyridine-Pd distance is 2.096(3)/*2.101(4) Å* and, therefore, shorter than the pyridine-Pd distance of 2.117(3) of [$PdCl_2$(IMes)(3-Cl-py)]. The slight differences of the Pd-pyridine distances between complexes bearing maleonitrile-based NHCs and complexes bearing analogous 4,5-unsubstituted imidazol-2-ylidenes occur due to the higher π-acceptor strength of $(CN)_2$IMes relative to IMes.[13]

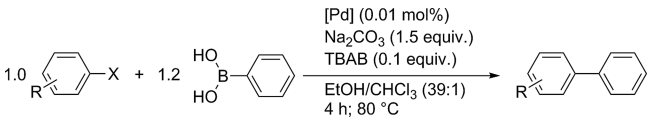
Complex **15** assumes a distorted square-planar coordination geometry. The NHC and the pyridine moiety are twisted clockwise around the NHC-Pd-pyridine axis. The NHC–Pd distance is 1.968(2) Å and, therefore, slightly longer than the NHC–Pd distance in **14**. The differences of the NHC–Pd bond lengths indicate higher π-backbonding of the 3-cyanopyridine in the *trans*-position to the NHC relative to the 3-bromopyridine in the analogous *trans*-position. The pyridine-Pd distance in **15** [2.084(2) Å] is slightly shorter than the pyridine-Pd in **14** [2.096(3)/*2.101(4) Å*]. The X-ray structure of complex **1** also shows a distorted square-planar coordination geometry. Bond lengths, angles

and torsions are in the range of those previously reported for the X-ray structure of [$PdCl_2$(IMes)(3-Cl-py)].[10]

The steric demands of NHC-ligands for **1**, **14** and **15** were determined by calculation of the percentage of the buried volume (%V_{bur}).[14,15] The %V_{bur} of a ligand is the occupied volume of a sphere around the metal center which is occupied by this ligand. For **1**, **14**, and **15**, %V_{bur} values of 32.5, 31.1 ± 0.4 and 31.8% were determined, respectively. The%V_{bur} for **1** is in the range of that for previously reported [$PdCl_2$(IMes)(3-Cl-py)] (32.4%).[10]

Catalytic Investigations

As the first step of catalytic investigations, the optimal reaction conditions (see Supporting Information) for the Suzuki–Miyaura reaction of 4-bromoacetophenone and phenylboronic acid were determined. Complex **4** was used as the precatalyst for optimization experiments. We found that the best results were achieved using 1.2 equiv. phenylboronic acid and 0.01 mol-% precatalyst loading at 80 °C over a reaction time of 4 h. Sodium carbonate (1.5 equiv.) was used as the base and tetra-*n*-butylammonium bromide (TBAB; 0.1 equiv.) was used as additive. The reagent ratios were based on 4-bromoacetophenone. These conditions were applied during substrate screening efforts unless noted otherwise. The screening was performed with precatalysts **1**, **4**, **5** and **12**–**15** for 23 different aryl- and heteroaryl bromides and three aryl chlorides with phenylboronic acid (Scheme 3).



Scheme 3. General reaction scheme for substrate screening efforts using various phenyl bromides, phenylboronic acid and precatalysts **1**, **4**, **5** and **12**–**15**.

The use of precatalyst **5** led to the lowest product yields relative to precatalysts **1**, **4** or PEPPSI precatalysts **12**–**15**. Acyclic precatalyst **4** and PEPPSI precatalysts **12**–**15** promoted efficient Suzuki–Miyaura reactions when *para*-substituted aryl bromides were deployed. The use of aryl bromides bearing electron-withdrawing *para*-substituents lead to almost quantitative yields, when **12**–**15** were used. Application of precatalyst **4** afforded lower, but still good, product yields (Table 2, Entries 2, 3 and 5–7). The use of aryl bromides bearing electron-donating groups led to moderate to high yields (Table 2, Entry 10). Precatalyst **4** seemed preferable for these substrates, as it outperformed PEPPSI precatalysts **12**–**15**. This is displayed most clearly with 2-bromomesitylene as the aryl bromide (Table 2, Entry 14). Deployment of precatalyst **4** led to a 23% yield of desired 2-phenylmesitylene. Using PEPPSI precatalysts **12**–**15**, yields of only less than 10% could be achieved. Increased steric hindrance of the aryl bromide led to much lower yields, as was seen when 4-bromoanisole, 3-bromoanisole and 2-bromoanisole were used as the aryl bromide (Table 2, Entries 11–13). Only bromophenols could clearly not be tolerated by the catalytic system; resulting putative hydroxybiphenyls completely eluded detection (Table 2, Entries 18–20). The precatalysts failed to enable reactions with chlorobenzene or 4-chloroanisole. Only when using 4-chloroacetophenone, could traces of the desired coupling product be detected (Table 2, Entries 21–23). Prolonged reaction times and higher precatalyst loadings translated to increased product yields with chlorobenzene or 4-chloroanisole (Table 2, Entries 24, 25). The yield of 4-acetylbiphenyl could be increased to a maximum of 26% with precatalyst **12** (Table 2, Entry 26). Comparisons to results obtained with precatalyst **1**, the literature known analogous complex to **12**, reveal that no reaction improvement could be achieved by simply using a stronger σ-donor NHC-ligand under the reaction conditions deployed in this study. Only with 1-bromo-5-nitroanisole (Table 2, Entry 4), could **1** be used to attain product yields significantly greater than those encountered using precatalysts bearing the maleonitrile-based NHC $(CN)_2$IMes.

Table 2. Substrate scope of the Suzuki–Miyaura reaction of phenylboronic acid and phenyl halides using precatalysts **1**, **4**, **5** and **12**–**15**.[a]

			Yield[b]						
	R	X	**1**	**4**	**5**	**12**	**13**	**14**	**15**
1	4-H	Br	76	47	18	84	67	82	79
2	4-Ac	Br	100	100	45	100	99	97	96
3	4-NO_2	Br	98	100	52	100	99	100	87
4	2-OMe-4-NO_2	Br	60	49	11	33	40	43	33
5	4-CHO	Br	100	98	70	97	100	100	100
6	4-CN	Br	80	79	33	100	93	99	100
7	4-CO_2Me	Br	94	100	44	100	100	99	99
8	2-F	Br	19	83	4	51	64	27	33
9	4-F	Br	77	71	20	99	92	93	79
10	4-Me	Br	63	88	3	56	63	74	76
11	2-OMe	Br	6	40	2	28	29	16	17
12	3-OMe	Br	39	52	7	45	49	50	50
13	4-OMe	Br	30	81	13	65	58	50	45
14	2,4,6-Me	Br	6	23	<1	4	9	4	4
15	2-Ph	Br	83	60	55	79	69	67	66
16	4-NH_2	Br	21	53	15	37	50	36	35
17	4-Br[c]	Br	43	62	5	76	57	44	53
18	2-OH	Br	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
19	3-OH	Br	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
20	4-OH	Br	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
21	4-H	Cl	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
22	4-Ac	Cl	<1	3	n.d.	<1	<1	<1	<1
23	4-OMe	Cl	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
24	4-H[d]	Cl	2	2	n.d.	1	1	1	1
25	4-OMe[d]	Cl	<1	n.d.	n.d.	<1	<1	n.d.	n.d.
26	4-Ac[d]	Cl	5	4	n.d.	26	15	14	15

[a] Reagents and conditions: 4-bromoacetophenone (126 µmol; 1.0 equiv.), phenylboronic acid (1.2 equiv.), sodium carbonate (1.5 equiv.), TBAB (0.1 equiv.), precatalyst (0.01 mol-%); EtOH/$CHCl_3$, 39:1 (0.5 mL), 4 h, 80 °C (oil bath temperature). [b] GC yield average yield of independent runs using 1,3,5-trimethoxybenzene as an internal standard. [c] Product is *p*-terphenyl. [d] Reaction time: 16 h, precatalyst loading: 1 mol-%.

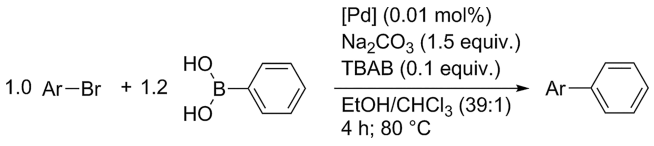
1-Bromonaphthalene and 9-bromoanthracene could also be converted to corresponding desired coupling products in good to excellent yields (Table 3, Entries 1, 2). Catalyst poison 3-bromopyridine could also be used successfully as a

coupling substrate, but yields were rather poor (Table 3, Entry 3) (Scheme 4).

Table 3. Substrate scope of the Suzuki–Miyaura reaction of phenylboronic acid and aryl bromides (Ar-Br) using precatalysts **1**, **4**, **5** and **12**–**15**.[a]

		Yield[b]						
	Ar	**1**	**4**	**5**	**12**	**13**	**14**	**15**
1	1-naphthyl	76	100	18	94	82	73	96
2	9-anthryl	73	44	7	76	84	61	34
3	3-pyridyl	11	15	8	22	17	20	32

[a] Reagents and conditions: 4-bromoacetophenone (126 µmol; 1.0 equiv.), phenylboronic acid (1.2 equiv.), sodium carbonate (1.5 equiv.), TBAB (0.1 equiv.), precatalyst (0.01 mol-%); EtOH/$CHCl_3$, 39:1 (0.5 mL), 4 h, 80 °C (oil bath temperature). [b] GC yield average yield of independent runs using 1,3,5-trimethoxybenzene as internal standard.



Scheme 4. General reaction scheme for the substrate screening using aryl bromides and phenylboronic acid.

To explain the differences in reactivity of precatalysts **1**, **4**, **5** and **12**–**15**, reaction rate experiments were conducted. Figure 5 depicts the yield/time curves of the Suzuki–Miyaura reaction using 4-bromoacetophenone and phenylboronic acid and precatalysts **1**, **4**, **5** and **12**–**15**. The data for **14** and **15** conform to the data of **13** and were thus omitted for clarity (for all yield/time curves see the Supporting Information). The PEPPSI precatalysts were found to initiate reactions with the highest rates and with only slight differences among them. Precatalyst **12**, bearing the unsubstituted pyridine correlated to a slightly higher reaction rate than **13**, **14** or **15**. Using **12**, full conversion to the desired product was achieved after 75 min. It took 90 min with pre-

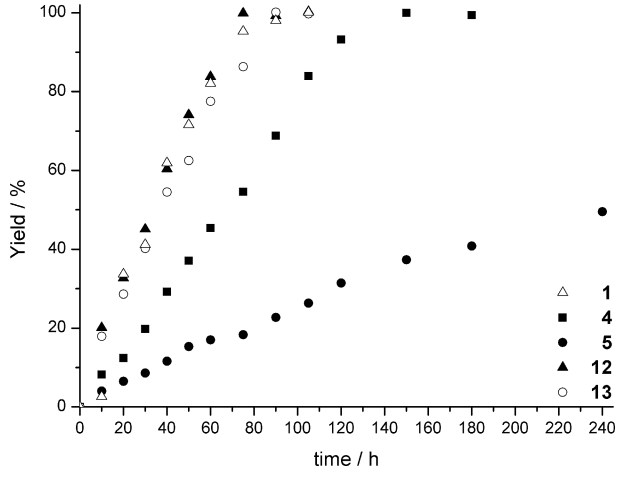


Figure 5. Reaction rate experiments of the Suzuki–Miyaura reaction using 4-bromoacetophenone and phenylboronic acid. **1** (Δ), **4** (■), **5** (●), **12** (▲) and **13** (○): precatalyst loading 0.01 mol-%. Reactions were performed in duplicate, yields were determined by GC-FID.

catalysts **13**–**15** to achieve full conversion. This is in agreement with the results for IPr-bearing PEPPSI complexes presented by Organ [IPr: 1,3-di(bisisopropylphenyl)-imidazol-2-ylidene].[10] For precatalyst **1**, an initiation phase of 10 min with almost no product formation was detected. After 10 min, the reaction appeared to proceed rapidly and full conversion to the desired product was achieved after 90 min.

Precatalyst **4** also enabled complete substrate conversion to 4-acetylbiphenyl, but required a reaction time twice as long as for the comparable reaction containing **12**. The reaction rate of the reaction catalyzed by **5** was much lower than that of the reaction catalyzed by **4**, and the product yield was found to still be increasing after 240 min, indicating that the catalyst was still active. Reactions requiring more than 240 min are not sensible, thus, reactions were terminated after 240 min.

It is known from recent studies concerning the Mizoroki–Heck reaction that the catalytically active species derived from **4** and **5** are palladium nanoparticles.[11] To obtain information about the nature of the catalytically active species under milder conditions of the Suzuki–Miyaura reaction, poisoning experiments were performed, using elemental Hg (10000 equiv., based upon the precatalyst loading). It is known that mercury forms an amalgam with heterogeneous palladium and can adsorb palladium at the mercury surface. Consequently, Hg can be used to remove heterogeneous palladium from reaction mixtures.[9,16] Upon addition of Hg at the start of the reaction, no conversion to the desired 4-acetylbiphenyl was detected. Poisoning occurred with all precatalysts. In a second experiment, Hg was added 1 h after the coupling reactions were started. At the same time, a sample of the reaction mixture was taken and the product yield determined. After 4 h, reactions were terminated and product yields were determined. No further conversion to the desired 4-acetylbiphenyl took place after the addition of mercury. These results indicate that coupling reactions using all seven precatalysts, are catalyzed by palladium nanoparticles and not by monoligated [Pd^0(NHC)] species.

Conclusions

Four PEPPSI precatalysts **12**–**15**, bearing π-acidic 4,5-dicyano-1,3-dimesitylimidazol-2-ylidene were prepared and characterized. X-ray structures of complexes **1**, **14** and **15** could be determined and compared to previously known complexes. The reactivity of PEPPSI complexes **12**–**15** were compared to established precatalysts **1**, **4** and **5** in an extensive substrate screening employing the Suzuki–Miyaura reaction. All seven precatalysts are suitable for the Suzuki–Miyaura reaction when aryl bromides are deployed. Precatalyst **12** exerted the highest initiation rates of the precatalysts presented in this study, but recently presented precatalyst **4** displayed the best overall activity. It could be shown that, relative to precatalyst **1** bearing the stronger σ-donor IMes, precatalysts characterized by the stronger π-acceptor

$(CN)_2$IMes do not inhibit product formation under the deployed conditions; instead they lead to comparable or even higher yields than those using the IMes-bearing precatalyst **1**. Unfortunately, poisoning experiments showed that palladium nanoparticles are responsible for the catalytic activity of precatalysts studied herein.

Experimental Section

General Information: All synthetic manipulations were conducted under argon or nitrogen atmosphere using standard Schlenk techniques. Dry solvents were used for all manipulations. Solvents were dried after literature procedures.[17] Compounds **1**,[8a] **4**,[11] **5**,[11] **7**,[13] **8**,[18a] **9**,[18a] **10**,[18b] **11**,[18c] were synthesized as described in the literature. Other chemicals were purchased from commercial sources and used for the reactions as received. Elemental analyses (C, H, N) were performed with an Elementar Vario EL elemental analyzer. NMR spectra were recorded with a Bruker Avance 300 or 500 spectrometer. Resonances for NMR spectra are reported relative to Me_4Si (δ = 0.0 ppm) and calibrated based on the solvent signal for ^1H and ^{13}C.[19] Spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant [Hz] and integration. Mass spectra were recorded with a Micromass Q-TOFmicro (ESI) or with a Thermo Quest SSQ 710 (70 eV) (EI). IR Spectra were recorded with a Thermo Nicolet NEXUS FTIR in a KBr disk between 400 and 4000 cm^{-1} using a resolution of 4 cm^{-1}. Background measurement was performed before measuring the samples with a bare KBr disc. Single crystal intensity data were collected with a STOE IPDS 2 at 293 K using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Solutions of the crystal structure were performed by direct methods and refinements were performed by full-matrix least square methods on F^2 by the SHELX-97 software package.[20] Non-hydrogen atoms were refined with anisotropic temperature factors. The deposited atom data (CIF) as well as the data in Table 2 reflect only the known cell content.

CCDC-1042289 (for **1**), CCDC-1042287 (for **14**) and CCDC-1042288 (for **15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthetic Procedures

General Synthesis of the PEPPSI Precatalysts 12–15: To a 50 mL to round-bottomed flask equipped with a reflux condenser and a magnetic stirrer, 4,5-dicano-1,3-dimesityl-2(pentafluorophenyl)-imidazoline and the $[PdCl_2(3\text{-R-py})_2]$ complex were suspended in toluene (20 mL). The mixture was refluxed for 16 h. After cooling to room temperature, the volatiles were removed under vacuum and the crude product was purified by liquid column chromatography on silica with $CHCl_3$:*n*-hexane as eluent.

Analytical Data

$[PdCl_2\{(CN)_2IMes\}(py)]$ (12): Yield 88%. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, J = 5.1 Hz, 2 H), 7.60 (t, J = 7.8 Hz, 1 H), 7.17–7.10 (m, 6 H), 2.41 (s, 6 H), 2.38 (s, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 151.6, 141.6, 138.1, 136.2, 131.5, 130.2, 124.4, 117.2, 105.8, 21.5, 19.1 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3024, 2952, 2921, 2861, 2245, 1607, 1480, 1449, 1382, 1346, 1301, 1217, 1155, 1073, 1035, 1019, 856, 756, 693, 562, 496 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{27}Cl_2N_5Pd$ 609.0678 $[M]^+$, found 574.1022 $[M - Cl]^+$. $C_{28}H_{27}Cl_2N_5Pd$ (610.88): calcd. C 55.05, H 4.46, N 11.46; found C 54.95, H 4.42, N 11.39.

$[PdCl_2\{(CN)_2IMes\}(3\text{-Cl-py})]$ (13): Yield 81%. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.50 (d, J = 2.1 Hz, 1 H), 8.42 (dd, J = 5.7, 1.2 Hz, 1 H), 7.62 (d, J = 8.4 Hz, 1 H), 7.16–7.06 (m, 6 H), 2.41 (s, 6 H), 2.37 (s, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 150.6, 149.6, 141.8, 138.2, 136.1, 132.4, 131.4, 130.3, 125.7, 117.3, 106.7, 21.5, 19.1 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3095, 3029, 2952, 2921, 2861, 2245, 1608, 1567, 1475, 1421, 1382, 1347, 1302, 1200, 1122, 1101, 1055, 1034, 854, 791, 750, 690, 562, 497 cm^{-1}. $C_{28}H_{26}Cl_3N_5$ (645.32): calcd. C 52.11 H 4.06 N 10.85; found C 51.83 H 4.05 N 10.79.

$[PdCl_2\{(CN)_2IMes\}(3\text{-Br-py})]$ (14): Yield 85%. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, J = 1.8 Hz, 1 H), 8.46 (d, J = 6.6 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 1 H), 7.13 (s, 4 H), 7.05 (dd, J = 8.1, 5.7 Hz, 1 H), 2.41 (s, 6 H), 2.37 (s, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 152.5, 150.0, 141.8, 141.1, 136.1, 131.4, 130.3, 129.2, 128.4, 125.1, 120.4, 117.3, 105.7, 21.5, 19.1 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3089, 3027, 2922, 2859, 2244, 1607, 1559, 1470, 1420, 1385, 1348, 1302, 1198, 1096, 2059, 1033, 858, 788, 719, 690, 562, 497 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{26}BrCl_2N_5Pd$ 686.9783 $[M]^+$, found 652.0081 $[M - Cl]^+$. $C_{28}H_{26}BrCl_2N_5$ (689.77): calcd. C 48.76, H 3.80, N 10.15; found C 49.09, H 3.77, N 10.08.

$[PdCl_2\{(CN)_2IMes\}(3\text{-CN-py})]$ (15): Yield 76%. ^1H NMR (300 MHz, CD_2Cl_2): δ = 8.90 (d, J = 1.5 Hz, 1 H), 8.81 (dd, J = 5.7, 1.5 Hz, 1 H), 7.97 (dt, J = 5.1, 1.8 Hz, 1 H), 7.37 (dd, J = 7.8, 5.7 Hz, 1 H) 7.17 (s, 4 H), 2.43 (s, 6 H), 2.36 (s, 12 H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 167.4, 155.0, 154.4, 142.2, 141.9, 136.6, 131.8, 130.4, 125.0, 117.8, 115.3, 111.2, 106.1, 21.5, 19.2 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3064, 3034, 2921, 2857, 2250, 2240, 1602, 1475, 1418, 1388, 1346, 1302, 1195, 1112, 1072, 1033, 865, 853, 811, 690, 562, 496 cm^{-1}. $C_{29}H_{26}Cl_2N_6$ (635.89): calcd. C 54.78 H 4.12 N 13.22; found C 54.58 H 4.03 N 13.06.

Representative Procedure for the Suzuki–Miyaura Reaction: Sodium carbonate (100.1 mg, 945 µmol, 1.5 equiv., relative to the aryl halide) and TBAB (20.3 mg, 63 µmol, 0.1 equiv.) were added to a Schlenk tube fitted with a magnetic stirrer. 4-Bromoacetophenone (125.3 mg, 630 µmol) and a solution containing phenylboronic acid (92.1 mg, 756 µmol, 1.2 equiv.) in technical ethanol (975 µL) were added. A solution containing precatalyst **4** (50 µg, 63 nmol, 0.01 mol-%) in $CHCl_3$ (25 µL) was added and the mixture was stirred. The flask was flushed with argon and placed in a preheated oil bath at 80 °C and stirred at this temperature for 4 h. After 4 h, the flask was immediately cooled to 0 °C in an ice bath. The cold mixture was hydrolyzed with 1N hydrochloric acid (2 mL). $CHCl_3$ (2 mL) was then added and the mixture was poured into water (2 mL). The phases were separated aqueous phase was extracted three times with $CHCl_3$ (2 mL). The organic phases were collected, dried with $MgSO_4$ and concentrated in vacuo. For the catalytic screening, the crude product was then dissolved in a solution of the internal standard 1,3,5-trimethoxybenzene (10.5 mg, 12.6 µmol, 0.1 equiv.) in $CHCl_3$ (2.0 mL, GC grade from Merck) and the GC yield determined by using a Perkin–Elmer Clarus 580 instrument equipped with a Perkin–Elmer Elite 5 MS column (length: 30 m, diameter: 0.25 mm). Signals were detected using an FID detector.

For the calibration of the GC, the cross-coupling products were isolated by flash chromatography on silica (height: 460 mm, diameter: 15 mm) with hexane/ethyl acetate mixtures as eluent and afterwards analyzed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. The spectroscopic data of already known products are in agreement with literature data.[21]

The hitherto not reported analytical data for 5-nitro-2-phenylanisole (Table 2, Entry 4) are presented here:

5-Nitro-2-phenylanisole: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (dd, J = 8.1, 2.1 Hz, 1 H), 7.84 (d, J = 2.1 Hz, 1 H), 7.56–7.50 (m, 2 H) 7.48–7.38 (m, 4 H), 3.92 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 157.0, 148.2, 137.5, 136.5, 131.2, 129.5, 128.4, 116.2, 106.3, 56.2 ppm. HRMS (EI): calcd. For $C_{13}H_{11}NO_3$ 229.0739 $[M]^+$, found 229.0745.

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