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[IPr#–PEPPSI] – Well-Defined, Highly Hindered and Broadly Applicable Pd(II)–NHC (NHC = N-Heterocyclic Carbene) Precatalyst for Cross-Coupling Reactions

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Abstract: In this Special Issue on *Featured Papers in Organometallic Chemistry*, we report the synthesis and characterization of [IPr#–PEPPSI], a new, well-defined, highly-hindered Pd(II)–NHC precatalyst for cross-coupling reactions. The catalyst has been commercialized in collaboration with MilliporeSigma (no. 925489) to enable broad access of academic and industrial researchers for reaction screening and optimization. The broad activity of [IPr#–PEPPSI] in cross-coupling reactions in a range of bond activations by C–N, C–O, C–Cl, C–Br, C–S and C–H cleavage is presented. Comprehensive evaluation of steric and electronic properties is described. The facile access to [IPr#–PEPPSI] class of precatalysts based on the modular pyridine ligands together with steric impact of the IPr# peralkylation framework will facilitate the implementation of well-defined, air- and moisture-stable Pd(II)–NHC precatalysts in chemistry research.

Keywords: [IPr#–PEPPSI]; bulky-yet-flexible; palladium; air-stable catalysts; cross-coupling; chemoselective reactions.

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1. Introduction

Transition-metal-catalyzed cross-coupling reactions have been established as a transformative tool in organic synthesis in both academic and industrial research.[1] In particular, palladium-catalyzed cross-couplings have gained the essential status in modern organic synthesis due to versatility, broad functional group tolerance and predictability of Pd(0)/(II) cycle under functional group tolerant and ligand-controlled reaction conditions.[2-4] At present, in addition to everyday applications in academic research, Pd-catalyzed cross-coupling reactions are implemented on a ton-scale industrial processes and used by medicinal and materials chemists to develop more effective pharmaceuticals and new functional materials that are essential to the quality of life.[1,2]

Nucleophilic N-heterocyclic carbenes (NHCs) have been developed as a particularly attractive class of ligands for Pd-catalyzed cross-coupling reactions.[5-7] Principally, the strong σ-donation and variable steric-hindrance of N-Ar wingtips of the NHC scaffold permit to facilitate oxidative addition and reductive elimination steps of the catalytic cycle and enable new directions in cross-coupling research.[8,9] Furthermore, Pd–NHC catalysts have been also employed in other classes of Pd-catalyzed transformations, including oxidative couplings,[10] polymerizations[11] and radical couplings,[12] where the well-defined topology of NHC ligands enables specific control of the elementary steps and selectivity of the processes.

We recently reported a novel class of sterically-hindered NHC ligands obtained by modular peralkylation of aniline (Figure 1).[13,14] These ligands combine the steric

properties of sterically-demanding NHCs with facile multigram scale synthesis in a cost-effective manner utilizing feedstock aniline that is available in bulk. Furthermore, the para-substituent stabilizes the N-Ar group from rotation, enabling for an improved steric control of the ortho-substituents in the catalytic pocket. Our initial studies were performed using allyl-based catalysts, such as [(IPr#)Pd(cin)Cl] (MilliporeSigma, no. 919616).[13,15] Since it is well-established that Pd–PEPPSI complexes are complementary to Pd–allyl-based catalysts and should be screened together with Pd-allyl NHC complexes,[16] we now investigated [IPr#–PEPPSI] as readily prepared Pd(II)–NHC complex.

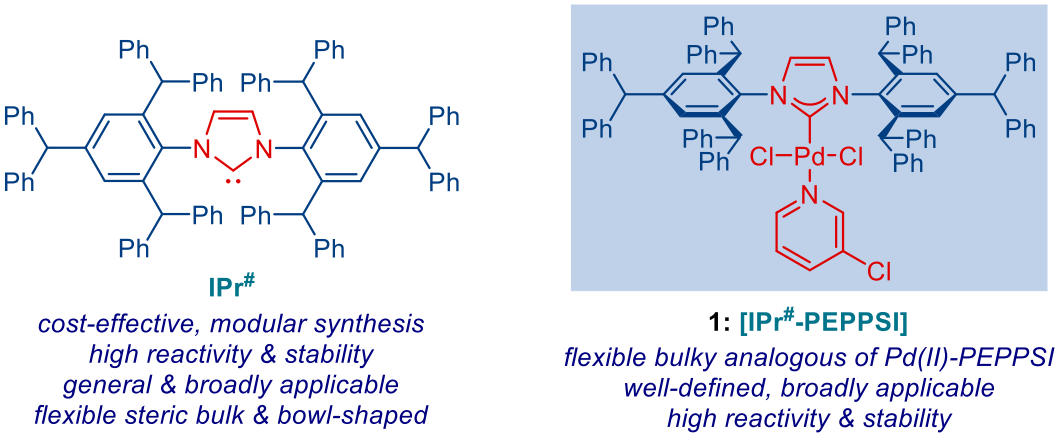
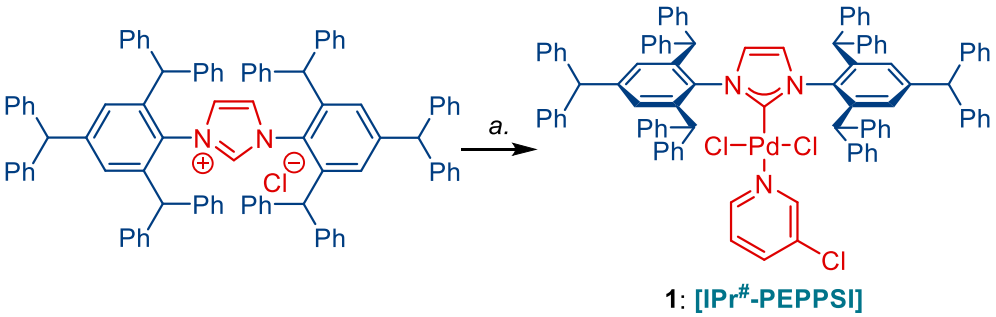


Figure 1. Sterically-demanding IPr# and [IPr#-PEPPSI].

In this Special Issue on *Featured Papers in Organometallic Chemistry*, we report the synthesis and characterization of [IPr#–PEPPSI], a highly-hindered Pd(II)–NHC precatalyst for cross-coupling reactions (Figure 1).[17] More specifically, this complex features 3-Cl-py as an ancillary ligand, [(IPr#)Pd(3-Cl-py)Cl2] (**1**), and belongs to PEPPSI-type class of catalysts. The catalyst has been commercialized in collaboration with MilliporeSigma (no. 925489) to enable broad access of academic and industrial researchers for reaction screening and optimization. The broad activity of [IPr#–PEPPSI] in cross-coupling reactions as well as comprehensive evaluation of steric and electronic properties is presented.[17] The facile access to [IPr#–PEPPSI] based on the modular pyridine ligands together with steric impact of IPr# peralkylation framework will facilitate the implementation of well-defined Pd(II)–NHCs in chemistry research.

2. Results

Our studies commenced with the synthesis of [IPr#–PEPPSI] precatalyst. As shown in Scheme 1, the reaction of IPr#HCl, $PdCl_2$ and K_2CO_3 and 3-Cl-py at 80 °C for 24 h, afforded the desired complex [IPr#–PEPPSI] (**1**) in 82% yield.[18-19] Importantly, complex (**1**) was found to be stable to air and moisture.



Scheme 1. Synthesis of [IPr#–PEPPSI] Catalyst. Conditions: IPr#·HCl (1.1 equiv), $PdCl_2$ (1.0 equiv), K_2CO_3 (5.0 equiv), 3-Cl-py, 80 °C, 24 h, 82% yield.

The complex [IPr#–PEPPSI] (**1**) was fully characterized by x-ray crystallography (CCDC 2262376) (Figure 1). The single crystal was obtained by slow evaporation from dichloromethane from dilute solution. The complex crystalized with two molecules in the unit cell. Similar to other Pd(II)-Het complexes, [IPr#–PEPPSI] (**1**) features a square planar geometry at the Pd center (Figure 2, Table 1).[18-19] The bond angles between ligands on metal center in complex (**1**) (molecule-1: C–Pd–Cl, 88.8(1)°, 91.5(1)°; N–Pd–Cl, 90.6(1)°, 89.1(1)°; molecule-2: C–Pd–Cl, 89.8(1)°, 89.4(1)°; N–Pd–Cl, 90.4(1)°, 90.4(1)°) are consistent with the square planar geometry and in the range of Pd(II)–Het complexes bearing imidazol-2-ylidene ligands (e.g., [IPr–PEPPSI], C–Pd–Cl, 91.5(9)°, 87.2(9)°; N–Pd–Cl, 91.0(8)°, 90.4(7)°; [IPent–PEPPSI], C–Pd–Cl, 90.5(1)°, 90.3(1)°; N–Pd–Cl, 89.27(7)°, 89.90(7)°).[18-19] The metal-ligand bond lengths of [IPr#–PEPPSI] (**1**) (molecule-1: Pd–C, 1.978(4) Å; Pd–Cl, 2.285(1) Å, 2.300(1) Å; Pd–N, 2.119(4) Å; molecule-2: Pd–C, 1.965(4) Å; Pd–Cl, 2.301(1) Å, 2.302(1) Å; Pd–N, 2.114(4) Å) can be compared with Pd(II)–Het complexes, such as, [IPr–PEPPSI] (Pd–C, 1.969(3) Å; Pd–Cl, 1.290(9) Å, 1.298(7) Å; Pd–N, 2.137(3) Å) and [IPent–PEPPSI] (Pd–C, 1.975(3) Å; Pd–Cl, 2.2868(9) Å, 2.3033(9) Å; Pd–N, 2.097(2) Å).[18-19]

It should be noted that the unit cell contains 2 molecules, and they are independent. For clarity, both of the molecules were discussed in the same manner. The atoms corresponding to the second molecule show relatively larger ellipsoids than that of the first molecule, but the magnitude of the ellipsoids is very small. In the standard case, the anisotropic parameter for each atom is less than 0.2. There are two atoms (C198 and C174), in which their anisotropic parameter is slightly higher than 0.2. Despite our extensive attempts, the anisotropic parameter did not change.

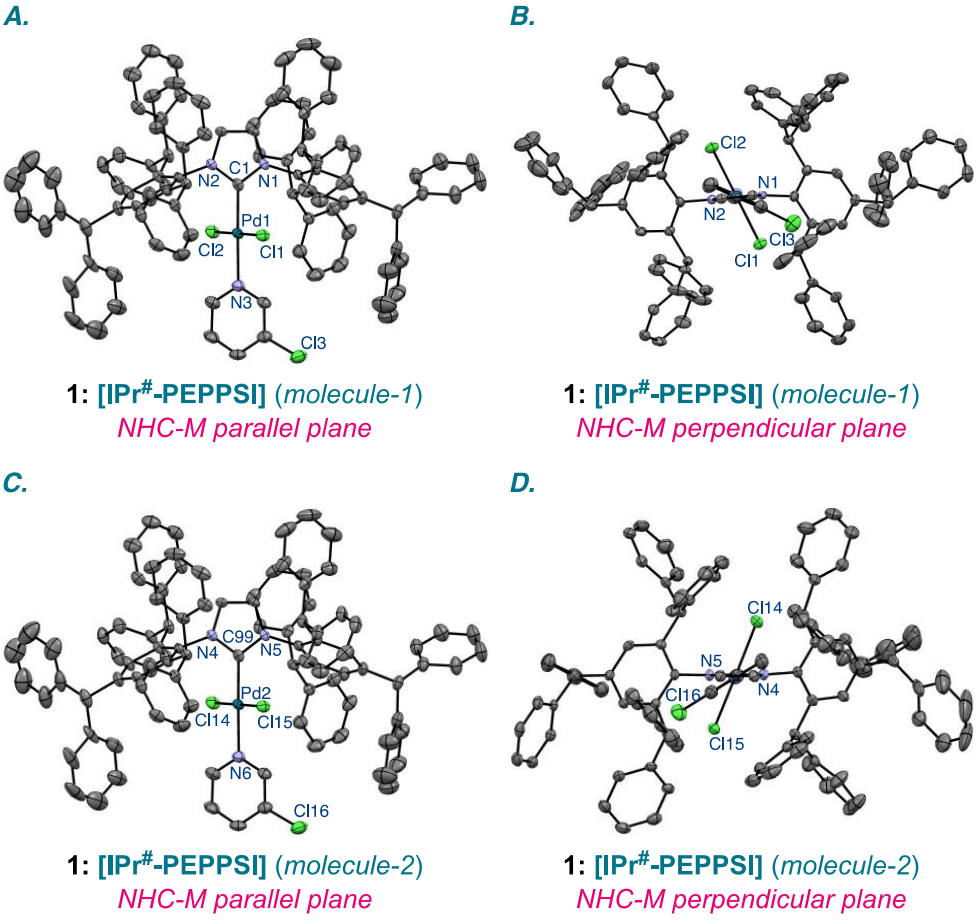


Figure 2. X-ray single crystal structure of complex [IPr#–PEPPSI] (**1**). Two molecules in the unit cell. (a) molecule-1: NHC–M parallel plane; (b) molecule-1: NHC–M perpendicular plane; (c) molecule-2: NHC–M parallel plane; (d) molecule-2: NHC–M perpendicular plane; Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: molecule-1: Pd1–C1, 1.978(4); Pd1–Cl1,

2.285(1); Pd1–Cl2, 2.300(1); Pd1–N3, 2.119(4); C1–N1, 1.353(6); C1–N2, 1.356(6); C1–Pd1–Cl1, 88.8(1); C1–Pd1–Cl2, 91.5(1); N3–Pd1–Cl1, 90.6(1); N3–Pd1–Cl2, 89.1(1); molecule-2: Pd2–C99, 1.965(4); Pd2–Cl14, 2.301(1); Pd2–Cl15, 2.302(1); Pd2–N6, 2.114(4); C99–N4, 1.365(6); C99–N5, 1.354(6); C99–Pd2–Cl14, 89.8(1); C99–Pd2–Cl15, 89.4(1); N6–Pd2–Cl14, 90.4(1); N6–Pd2–Cl15, 90.4(1). CCDC 2262376.

To further evaluate the steric impact of IPr# ligand on [IPr#-PEPPSI] (1) complex, the percent buried volumes (%V_{bur}) were calculated using the method by Cavallo (Figure 3).[20] The %V_{bur} values of the IPr# ligand in complex (**1**) are 40.2% (SW, 29.8%; NW, 54.8%; NE, 31.6%; SE, 44.7%) for molecule-1 and 38.2% (SW, 48.3%; NW, 30.2%; NE, 45.4%; SE, 28.6%) for molecule-2. These values can be compared with the %V_{bur} of Pd–PEPPSI complexes, for example, %V_{bur} of IPr (%V_{bur}, 34.8%; SW, 32.7%; NW, 40.7%; NE, 29.1%; SE, 36.7%) and IPent (%V_{bur}, 38.3%; SW, 47.4%%; NW, 30.3%%; NE, 45.2%; SE, 30.4%).[19] Interestingly, the average steric impact of IPr# ligand in [IPr#–PEPPSI] (**1**) is higher than that in both IPr and IPent congeners, however, lower than that in the allyl-congener [Pd(IPr#)(cin)Cl] (%V_{bur}, 44.7%; SW, 26.9%; NW, 63.7%; NE, 29.9%; SE, 58.2%).[13]

Table 1. Comparison of Percent Buried Volume (%V_{bur}) and Bond Lengths of [Pd-NHC] Complexes.[1]

Entry	Complexes	%V_{bur}	Pd–C_{NHC} [Å]	Pd–N_{py} [Å]	Pd–Cl [Å]
1	**[IPr#–PEPPSI]** (*molecule-1*)	40.2	1.978(4)	2.119(4)	2.285(1), 2.300(1)
2	**[IPr#–PEPPSI]** (*molecule-2*)	38.2	1.965(4)	2.114(4)	2.301(1), 2.302(1)
3	**[IPr–PEPPSI]**	34.8	1.969(3)	2.137(3)	2.290(9), 2.298(7)
4	**[IPent–PEPPSI]**	38.3	1.975(3)	2.097(2)	2.2868(9), 2.3033(9)
5	**[Pd(IPr#)(cin)Cl]**	44.7	2.046(4)	2.117(5), 2.133(6), 2.216(7)[a]	2.374(1)

[1]X-ray single crystal structure data. [a]Pd–cin bond lengths [Å].

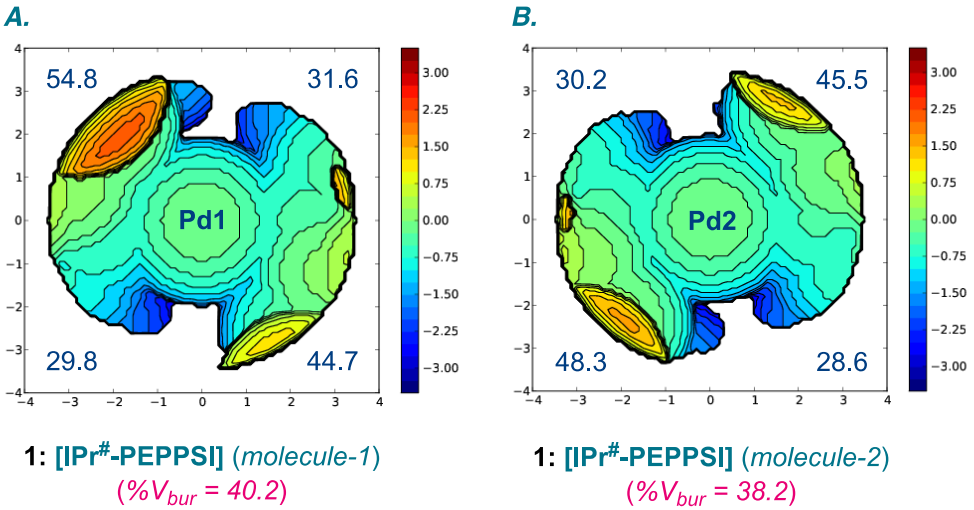
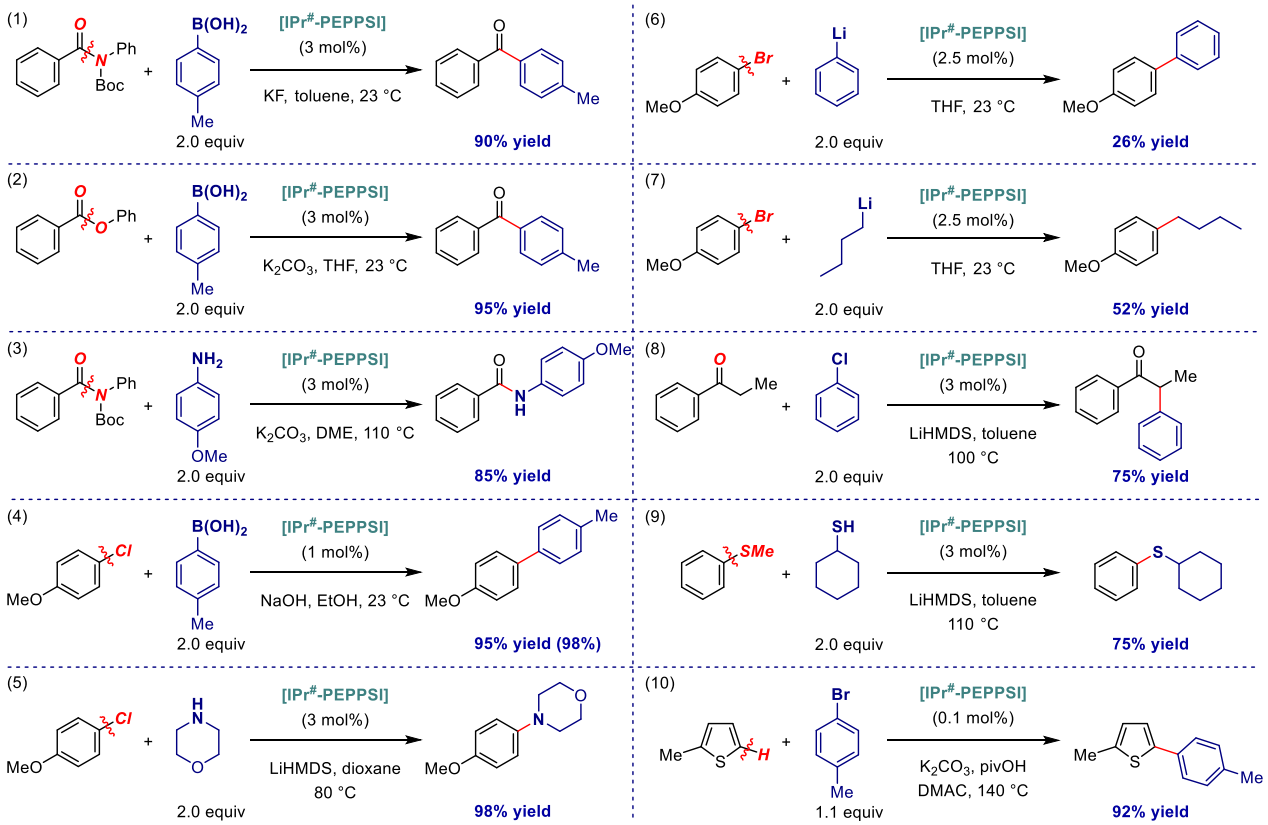


Figure 3. Topographical steric map of [IPr#–PEPPSI] (**1**) showing % V_{bur} per quadrant calculated from X-ray single crystal structure. (a) molecule-1; (b) molecule-2. See SI for additional details.

Next, we evaluated the activity of [IPr#–PEPPSI] (**1**) in a range of cross-coupling reactions (Scheme 2).[13] As shown, [IPr#–PEPPSI] (**1**) is a highly effective catalyst in acyl N–C(O) amide Suzuki cross-coupling (entry 1),[21] acyl O–C(O) ester Suzuki cross-coupling (entry 2),[22] transamidation of acyl N–C(O) (entry 3),[23] C–Cl Suzuki (entry 4)[24]

and C–Cl Buchwald-Hartwig cross-coupling (entry 5),[25] C–Br Murahashi-Feringa cross-coupling (entry 7),[26] ketone α-arylation (entry 8),[27] Morandi C–S sulfur cross-coupling (entry 9)[28] and C–H arylation (entry 10).[29] It is now well-established that the selectivity of different Pd–NHCs depends on the stabilizing ancillary ligand, and it is generally recommended that Pd–NHCs with various ancillary ligands should be screened in order to identify the optimal catalyst for a given reaction. Importantly, the results demonstrate that [IPr#–PEPPSI] (**1**) is effective in a range of N–C, O–C, C–Cl, C–Br, C–S and C–H activations using different organometallic reagents (organoboron, amide, organolithium, enolate, sulfide) for cross-coupling reactions that are among the most common in industrial and academic settings.[1–4] Considering the availability of [IPr#–PEPPSI] (MilliporeSigma no. 925489) and its broad reactivity, this catalyst offers an important addition to the cross-coupling toolbox.[30]



Scheme 2. Activity of [IPr#–PEPPSI] in Cross-Coupling Reactions.

It should be noted that steric flexibility is critical to stabilize different intermediates in the catalytic cycles. For example, it is well-known that less steric hindrance is better for OA and more steric hindrance is beneficial for RE[1-3]. The steric flexibility of IPr# ligand has the capacity to adjust to the required steric environment in the key catalytic steps. The asymmetric steric distribution is likely to contribute to the flexibility of the ligand.[5] Regarding the turnover limiting steps, it is generally accepted that oxidative addition is the rate-limiting step for less reactive electrophiles, while reductive elimination is limiting for substrates that undergo facile oxidative addition.[1-3] To demonstrate the generality of the catalyst, the catalyst has been tested in a variety of different types of reactions, including electrophiles and nucleophiles that are characterized by distinct mechanism.

In a broader sense, the present catalyst should be benchmarked against its closest analogue, [PdCl(IPr#)(cin)], which features the cinnamyl group instead of 3-chloro-pyridine as an ancillary ligand. The [PdCl(IPr#)(cin)] catalyst leads to the formation of the products in Scheme 2 in the following yields: 95% (entry 1), 40% (entry 2), 75% (entry 3),

98% (entry 4), 98% (entry 5), 96% (entry 6), 82% (entry 7), 90% (entry 8), 80% (entry 9), 95% (entry 10). Thus, [IPr#–PEPPSI] is more effective than its allyl-congener, [(IPr#)Pd(cin)Cl], in O–C(O) cross-coupling (entry 2), but less effective in C–Br Murahashi-Feringa cross-coupling (entries 6-7), while the reactivity in other reactions is comparable (entries 1, 3-5, 8-10). In general, it is now well-established that the selectivity of different Pd–NHCs depends on the stabilizing ancillary ligand, and it is generally recommended that Pd–NHCs with various ancillary ligands should be screened in order to identify the optimal catalyst for a given reaction. It should be noted that the PEPPSI-type complexes are a distinct class of Pd-NHC catalysts than (NHC)Pd(R-allyl)Cl and other classes of Pd-NHC complexes, offering prospects for the development of cross-coupling reactions through ancillary ligand design. The synthesis of PEPPSI type catalysts is generally more straightforward, which is important for their use by a range of interested chemists. Furthermore, PEPPSI type complexes are typically more cost-effective to prepare than other classes of Pd-NHC complexes, making them advantageous from a synthetic standpoint. Furthermore, the activation to active Pd(0)-NHC species follows different mechanisms for PEPPSI type complexes, which provides different class of sterically-hindered complexes for cross-coupling reactions. Importantly, the present study demonstrates that the [IPr#–PEPPSI] complex can be employed for a range of N–C, O–C, C–Cl, C–Br, C–S and C–H bond activations.

To gain insight into the origin of high catalytic reactivity of complex [IPr#–PEPPSI] (**1**), electronic and steric properties were determined at the B3LYP 6-311++g(d,p) level.

First, to gain insight into the electronic properties of [IPr#–PEPPSI] (**1**), frontier molecular orbitals were calculated (Figure 4). The HOMO of [IPr#–PEPPSI] (**1**) (-6.26 eV) is located within Pd–Cl bonds. The energy HOMO of [IPr#–PEPPSI] (**1**) can be compared with the prototypical less sterically-demanding [IPr–PEPPSI] (-6.06 eV). Furthermore, the LUMO (-2.01 eV) and LUMO+1 (-1.81 eV) of [IPr#–PEPPSI] (**1**) catalyst are lobed within Pd–N_{py} and Pd–C_{NHC} bonds, respectively. These values can be compared with the corresponding orbitals for [IPr–PEPPSI] (LUMO, -1.87 eV; LUMO+1, -1.63 eV). Overall, the HOMO and LUMO orbitals indicate a relative strength of Pd–C_{NHC} bond cf. Pd–N_{py} bond, and comparable levels of energy to the IPr–PEPPSI despite much higher steric demand.

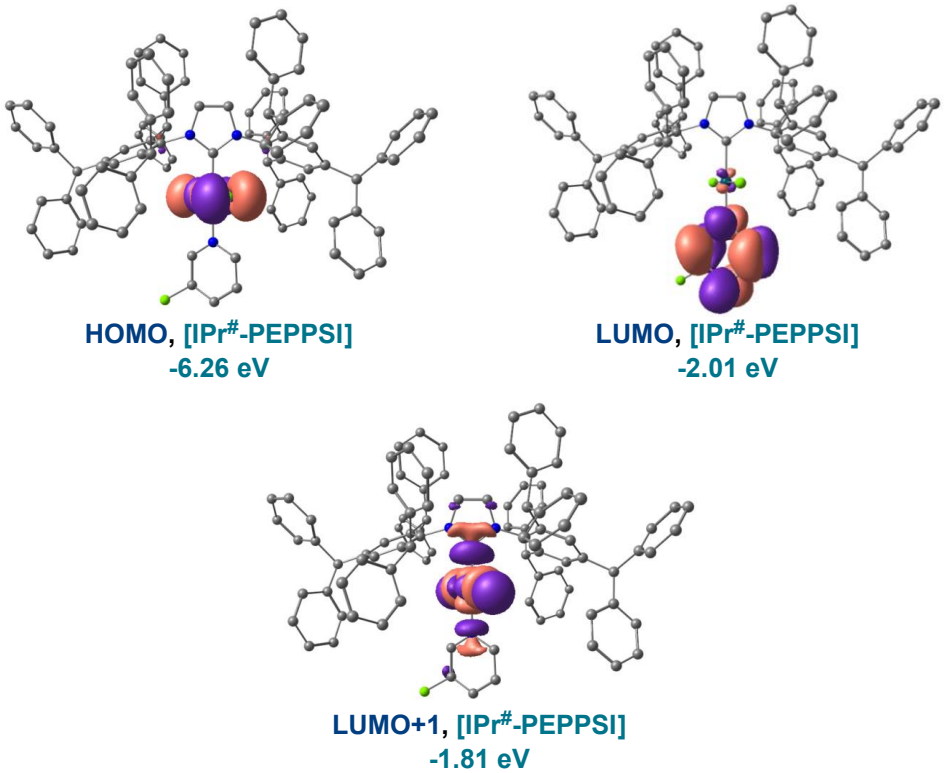


Figure 4. Frontier orbitals and energies (eV) of [IPr#–PEPPSI] (**1**) calculated at B3LYP 6-311++g(d,p). See SI for details.

To gain further insight into the relative bond strengths, the Wiberg bond orders were determined (Table 2). The Wiberg bond orders of Pd–C_{NHC} (0.6801) and Pd–N_{py} (0.3099) for [IPr#–PEPPSI] (**1**) indicate much stronger Pd–$C_{(carbene)}$ bond vs. Pd–N_{py}, which can be compared with [IPr–PEPPSI] of 0.6871 and 0.3267, respectively. Furthermore, the Pd–Cl1 (0.6062) and Pd–Cl2 (0.6032) bond orders in [IPr#–PEPPSI] (**1**) can be compared with [IPr–PEPPSI] of 0.6278, 0.6302. Overall, the data shows strong Pd–$C_{(carbene)}$ bond and capacity for facile dissociation of ancillary and halide ligands in [IPr#–PEPPSI] (**1**).

Finally, to eliminate impact from steric packing, the $\%V_{bur}$ was calculated from the optimized structure of complex (1) at B3LYP 6-311++g(d,p) level (Figure 5). The $\%V_{bur}$ for [IPr#–PEPPSI] (**1**) is 38.9% (SW, 27.6%; NW, 49.4%; NE, 28.2%; SE, 50.4%), which can be com-pared with [IPr–PEPPSI], $\%V_{bur}$ of 33.7% (SW, 37.4%; NW, 30.0%; NE, 37.4%; SE, 29.9%). The data indicates much larger steric impact of [IPr#–PEPPSI] (**1**) than the classical IPr congener. Interestingly, [IPr#–PEPPSI] (**1**) features an asymmetrical distribution of the N-Ar wingtips, which is important in cross-coupling catalysis to promote oxidative addition and reductive elimination steps. It should be noted that the steric map in Figure 3 is based on the crystal structure, and the steric map on Figure 5 is based on the computation. The steric distribution in Figure 3 is affected by crystal packing. The steric map in Figure 5 shows C2 symmetry during the $\%V_{bur}$ calculation. The entire molecule is not C2 symmetric because we have non-symmetric 3-Cl-py on the trans side.

Typically, large steric $\%V_{bur}$ of NHC ligands is required for effective cross-coupling reactions.[6] In general, ligands with $\%V_{bur}$ of less than 40% are less efficient in the cross-coupling due to slower reductive elimination steps. Furthermore, it is interesting to note that ring expanded NHCs show similar profiles to the present catalysts. For example, the 6-membered analogue of IPr is characterized by the $\%V_{bur}$ of 50.9% and the 7-membered ring expanded analogue of IPr is characterized by the $\%V_{bur}$ of 52.7%.[31]

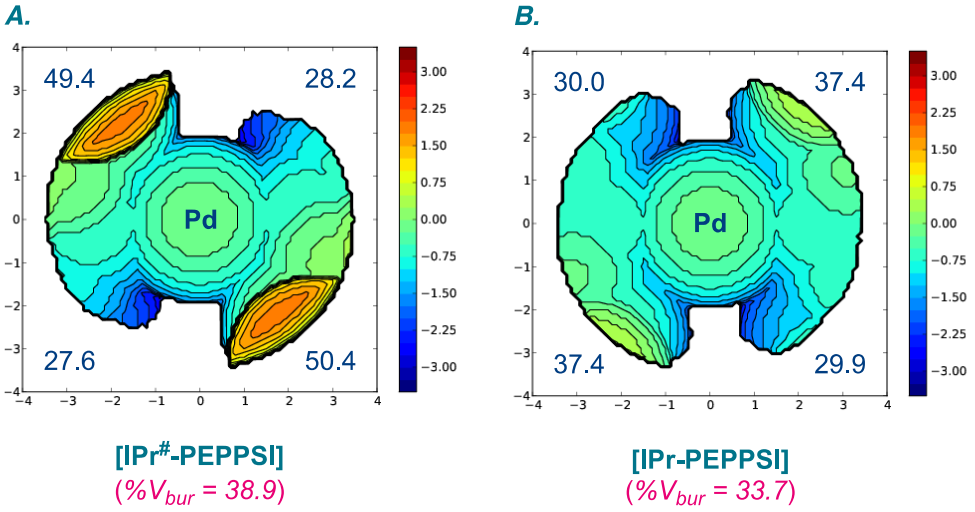


Figure 5. Topographical steric maps of [IPr#–PEPPSI] (**1**) and [IPr-PEPPSI] calculated at B3LYP 6-311++g(d,p). See SI for details.

Table 2. Bond Orders of [IPr#-PEPPSI] (**1**) and [IPr–PEPPSI] Complexes.[1]

Entry	Complexes	Pd–C_{NHC}	Pd–N_{py}	Pd–Cl
1	**[IPr#–PEPPSI]**	0.6801	0.3099	0.6062, 0.6032
2	**[IPr–PEPPSI]**	0.6871	0.3267	0.6278, 0.6302

[1]Calculated at B3LYP 6-311++g(d,p).

3. Discussion

In conclusion, we have reported the synthesis, characterization and reactivity of [IPr#–PEPPSI]. This well-defined, air- and moisture-stable catalyst is based on the sterically-demanding IPr# framework obtained by modular peralkylation of anilines. The broad activity of [IPr#–PEPPSI] in cross-coupling reactions by N–C, O–C, C–Cl, C–Br, C–S and C–H activations has been demonstrated. Comprehensive evaluation of steric and electronic properties provided further insight into the properties of [IPr#–PEPPSI]. Considering the facile access to [IPr#–PEPPSI], its commercial availability (MilliporeSigma, 925489), and promising reactivity in a range of cross-coupling reactions, we expect that this class of catalysts will facilitate the broad use of Pd(II)–NHCs in catalysis research.[30]

4. Materials and Methods

General Procedure for the preparation of [IPr#-PEPPSI] (1). An oven-dried 10 mL vial equipped with a stir bar was charged with IPr#HCl (552 mg, 0.44 mmol, 1.1 equiv), $PdCl_2$ (71 mg, 0.4 mmol, 1.0 equiv), K_2CO_3 (276 mg, 2.0 mmol, 5.0 equiv). 3-Chloropyridine (2.0 ml) was added, and the reaction was stirred at 80 °C for 24 h. After cooling to room temperature, the mixture was diluted with DCM and filtered out the solid. The solution was collected and concentrated by evaporation and high vacuum to remove the 3-Chloropyridine. The pure product was obtained by recrystallization in DCM/hexane as a white solid. Yield 82% (494 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.81 (d, *J* = 5.5 Hz, 1 H), 7.83 (d, *J* = 8.2 Hz, 1 H), 7.27 (m, 8 H), 7.15 (m, 12 H), 7.10-7.05 (m, 16 H), 7.00 (dd, *J* = 19.7, 7.4 Hz, 16 H), 6.78 (s, 4 H), 6.69 (d, *J* = 7.5 Hz, 8 H), 6.32 (s, 4 H), 5.38 (s, 2 H), 4.98 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.85, 149.93, 144.16, 144.04, 143.61, 141.79, 138.01, 135.88, 132.61, 131.42, 130.27, 129.47, 129.36, 128.27, 127.83, 126.23, 126.14, 126.06, 124.81, 124.14, 56.30, 51.09. HRMS (ESI) m/z: [M – Cl]+ Calcd for $C_{98}H_{76}N_3Cl_2Pd$ 1472.4452, found 1472.4450. Crystallographic data has been deposited with the Cambridge Crystallographic Data Center (CCDC 2262376).

Activity of [Pd#-PEPPSI] in Cross-Coupling Reactions. All cross-coupling reactions were carried out according to the procedures previously described. [13] For comparison purposes, all products were identified by ^{1}H NMR (500 MHz, $CDCl_3$) and GC-MS using internal standard and comparison with authentic samples. All yields correspond to yields determined by ^{1}HNMR.

N–C(O) Cleavage: Suzuki–Miyaura Amide Cross-Coupling. An oven dried vial equipped with a stir bar was charged with an amide substrate (29.7 mg, 0.10 mmol, 1.0 equiv), boronic acid (27.2 mg, 0.20 mmol, 2.0 equiv), potassium fluoride (17.4 mg, 0.30 mmol, 3.0 equiv), [IPr#-PEPPSI] (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (0.40 mL, 0.25 M) and water (0.50 mmol, 5.0 equiv) were added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 16 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

O–C(O) Cleavage: Buchwald-Hartwig Ester Cross-Coupling. An oven dried vial equipped with a stir bar was charged with an ester substrate (19.8 mg, 0.10 mmol, 1.0 equiv), boronic acid (27.2 mg, 0.20 mmol, 2.0 equiv), potassium fluoride (17.4 mg, 0.30 mmol, 3.0 equiv), [IPr#-PEPPSI] (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (0.40 mL, 0.25 M) and water (0.50 mmol, 5.0 equiv) were added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 16 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain

conversion, selectivity and yield using internal standard and comparison with authentic samples.

N–C(O) Cleavage: Buchwald-Hartwig Amide Cross-Coupling (Transamidation). An oven dried vial equipped with a stir bar was charged with an amide substrate (29.7 mg, 0.10 mmol, 1.0 equiv), amine (24.6 mg, 0.20 mmol, 2.0 equiv), potassium carbonate (41.4 mg, 0.30 mmol, 3.0 equiv), [IPr#-PEPPSI] (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. DME (0.40 mL, 0.25 M) was added with vigorous stirring and the reaction mixture was stirred at 110 °C for 16 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

C–Cl Cleavage: Suzuki–Miyaura Cross-Coupling. An oven dried vial equipped with a stir bar was charged with an aryl chloride substrate (14.2 mg, 0.10 mmol, 1.0 equiv), boronic acid (27.2 mg, 0.20 mmol, 2.0 equiv), NaOH (12 mg, 0.30 mmol, 3.0 equiv), [IPr#-PEPPSI] (1.0 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. EtOH (0.40 mL, 0.25 M) was added with vigorous stirring at room temperature and the reaction mixture was stirred at room temperature for 16 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

C–Cl Cleavage: Buchwald-Hartwig Cross-Coupling. An oven dried vial equipped with a stir bar was charged with an aryl chloride substrate (14.2 mg, 0.10 mmol, 1.0 equiv), morpholine (17.4 mg, 0.20 mmol, 2.0 equiv), [IPr#-PEPPSI] (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.40 mL, 0.25 M) was added and LiHMDS (1.0 M in THF, 0.30 mmol, 3.0 equiv) were added with vigorous stirring at room temperature and the reaction was stirred at 80 °C for 16 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (1 x 10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

C–Br Cleavage: Feringa Cross-Coupling with Aryllithium. An oven dried vial equipped with a stir bar was charged with an aryl bromide substrate (187 mg, 1.0 mmol, 1.0 equiv), PhLi (1.9 M in Bu_2O, 2.0 mmol, 2.0 equiv) and [IPr#-PEPPSI] (2.5 mol%) at room temperature under argon and stirred for 10 min. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (1 x 10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

C–Br Cleavage: Feringa Cross-Coupling with Alkyllithium. An oven dried vial equipped with a stir bar was charged with an aryl bromide substrate (187 mg, 1.0 mmol, 1.0 equiv), *n*BuLi (2.5 M in hexanes, 2.0 mmol, 2.0 equiv) and [IPr#-PEPPSI] (2.5 mol%) at room temperature under argon and stirred for 10 min. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (1 x 10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

C–Cl Cleavage: α-Ketone Arylation. An oven dried vial equipped with a stir bar was charged with a ketone substrate (13.4 mg, 0.10 mmol, 1.0 equiv), chlorobenzene (22.4

mg, 0.20 mmol, 2.0 equiv), [IPr#-PEPPSI] (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (0.40 mL, 0.25 M) and LiHMDS (1.0 M in THF, 0.20 mmol, 2.0 equiv) were added with vigorous stirring at room temperature and the reaction mixture was stirred at 100 °C for 24 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (1 x 10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

C–S Cleavage: Carbon–Sulfur Bond Metathesis. An oven dried vial equipped with a stir bar was charged with a thioether substrate (12.4 mg, 0.10 mmol, 1.0 equiv), cyclohexanethiol (26.0 mg, 0.20 mmol, 2.0 equiv), [IPr#-PEPPSI] (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (0.10 mL, 1.0 M) and LiHMDS (1.0 M in THF, 0.26 mmol, 2.6 equiv) were added with vigorous stirring at room temperature and the reaction mixture was stirred at 110 °C for 16 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (1 x 10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

C–H Cleavage: Direct C–H Arylation. An oven dried vial equipped with a stir bar was charged with a thiophene substrate (9.8 mg, 0.10 mmol, 1.0 equiv), 1-bromo-4-methylbenzene (18.8 mg, 0.11 mmol, 1.1 equiv), potassium carbonate (20.7 mg, 0.15 mmol, 1.5 equiv), PivOH (3.1 mg, 0.03 mmol, 0.30 equiv), [IPr#-PEPPSI] (0.1 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. DMA (0.40 mL, 0.25 M) was added with vigorous stirring at room temperature and the reaction mixture was stirred at 140 °C for 16 h. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (1 x 10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The sample was analyzed by ^{1}HNMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

Crystallographic Analysis. Crystal Data and Structure Refinement Summaries for [IPr#-PEPPSI] are included in Table S1 in the Supplementary Materials. Supplementary Material also include large ORTEP structures of [IPr#-PEPPSI] (50% ellipsoids) in NHC–M parallel plane and NHC–M perpendicular plane.

Computational Methods. All the calculations were performed using Gaussian 09 suite of programs. All of the geometry optimizations were performed at the B3LYP level of theory in the gas phase with the QZVP basis set for palladium and the 6-311++G(d,p) basis set for the other atoms. For geometry optimizations, we employed the X-ray structure of [IPr#–PEPPSI] as the starting geometry and performed full optimization. The absence of imaginary frequencies was used to characterize the structures as minima on the potential energy surface. All of the optimized geometries were verified as minima (no imaginary frequencies). NBO calculations were performed at the DFT/B3LYP level using NBO program implemented in Gaussian software package. Wiberg bond indices were calculated by the NBO method. Energetic parameters were calculated under standard conditions (298.15 K and 1 atm). Structural representations were generated using CYLview software (Legault, C. Y. CYL view version 1.0 BETA, University of Sherbrooke). All other representations were generated using Gauss View (GaussView, version 5, Dennington, R.; Keith, T.; Millam, J. Semichem Inc., Shawnee Mission, KS, 2009) or ChemCraft software (Andrienko, G. L. ChemCraft version b562a, https://www.chemcraftprog.com/).

Supplementary Materials: Procedures and computational data are available online at www.mdpi.com/xxx/s1.

Author Contributions: M.M.R., Q.Z., G.M., R.L., R.S. conducted experimental work and analyzed the data. M.S. initiated the project, designed experiments to develop this reaction, and wrote the paper.

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Conflicts of Interest: The authors declare the following competing financial interest(s): Rutgers University has filed patent(s) on ligands and precatalysts described in this manuscript (US 62/958,565, Jan 8, 2020).

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