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Rational Exploration of N-Heterocyclic Carbene (NHC) Palladacycle Diversity: A Highly Active and Versatile Precatalyst for Suzuki–Miyaura Coupling Reactions of Deactivated Aryl and Alkyl Substrates

Guang-Rong Peh, Eric Assen B. Kantchev,* Jun-Cheng Er, and Jackie Y. Ying*[a]

Abstract: As less attention has been focussed on the design of highly efficient palladium precatalysts to ensure the smooth formation of the active catalyst for metal-mediated cross coupling reactions, we herein demonstrate that combining the bulky N-heterocyclic carbene (NHC) 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) with cyclopalladated acetanilide as the optimal palladium precatalyst leads to superior catalytic activity compared with the state-of-the-art NHC–Pd catalysts. The complex was discovered through the evaluation of a small, rationally designed library of NHC–palladacycles prepared by a novel, practical and atom-economic method, the direct reaction of IPr·HCl with palladacycle acetate dimers.

Keywords: carbenes · chemical library · cross-coupling · heterocycles · palladium

Introduction

A revolutionary development in organic synthesis took place in 1972–1977:[1] the discovery of nickel[2–4] and palladium[4–8] catalysts that allowed for the first time organic moieties in aryl or vinyl halides and aryl or vinyl organometallic derivatives to be joined by a single bond, a transformation that had been generally considered impossible. Palladium-mediated cross-coupling reactions[9,10] have since become a strategic class of transformations in modern organic synthesis, allowing an astonishing variety of complex molecules[11] to be prepared in a highly efficient manner. In the pharmaceutical industry, palladium-mediated coupling reactions are the single most employed C–C bond-forming reaction in the large-scale synthesis of drug candidates.[12] Since the 1970s the expansion of the scope of cross-coupling reactions to new classes of substrates has continued unabated. This has been enabled by the discovery of ever more active and specialised spectator ligands. In the mid 1990s amine cross-coupling (Buchwald–Hartwig amination) was discovered[13,14] and further developed as a process of major academic and industrial significance over the next decade. Aryl chlorides are another challenging but important class of substrates because they are more readily available and cheaper, but much less active than the traditional aryl bromides and iodides.[15,16] Today, palladium complexes of N-heterocyclic carbenes (NHC),[17–21] in particular, the bulky 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, **1**; Scheme 1),[22] trialkylphosphanes[23] or dialkyl(2-biaryl)phosphanes,[24–26] allow the coupling reactions of chloroarenes to proceed in high yields under mild conditions, even at room temperature. Similarly, the cross-coupling of alkyl halides is hampered by their low reactivity (relative to unsaturated substrates) and competition by β-hydride elimination.[27–29] These obstacles notwithstanding, the coupling of unactivated alkyl halides with palladium complexes of bulky trialkylphosphanes[30–38] or NHCs[39–48] has been successfully developed.

The nature of the palladium precatalyst, which is responsible for the smooth introduction of the active catalyst into the cycle, is as important as the nature of the spectator ligand for the success of a coupling reaction. A strong dependency on the palladium source has often been observed in many palladium-mediated cross-coupling reactions. However, the design of easy-to-activate palladium precatalysts lags behind spectator ligand design or discovery. Recently, Buchwald and co-workers elegantly showed that a six-membered palladacycle that was activated by a well-understood mechanism led to a significant improvement in the efficien-

[a] G.-R. Peh, Dr. E. A. B. Kantchev, J.-C. Er, Prof. J. Y. Ying
Institute of Bioengineering and Nanotechnology
31 Biopolis Way, The Nanos, Singapore 138669 (Singapore)
Fax: (+65)-6478-9020
E-mail: ekantchev@gmail.com
jyying@ibn.a-star.edu.sg

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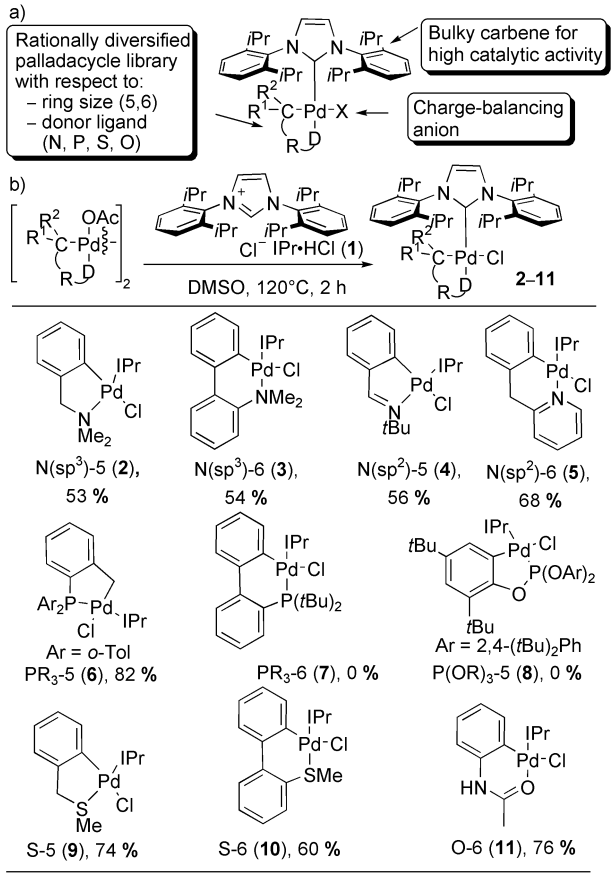


Scheme 1. Rationally diverse library of NHC–palladacycles (a) prepared by a novel, atom-economic method (b).

cy of Buchwald–Hartwig amination when ligated with *S*-Phos compared with a similar catalyst prepared in situ from $[Pd_2(dba)_3]$ (dba: 1,3-dibenzylideneacetone).[49] The precatalyst allowed amination of non-activated aryl chlorides to be performed at temperatures as low as −10 °C. Another impressive report by Fairlamb et al. showed that the use of the more electron-rich 3,3′,5,5′-tetramethoxy analogue of dba (dmdba) instead of dba in the popular precatalyst $[Pd(dba)_2]$ facilitated the departure of disposable ligands, which resulted in an overall improvement in catalytic efficiency in the Suzuki–Miyaura reaction.[50] The importance of both discoveries is underscored by the fact that these catalysts were made commercially available within a very short time after publication. The problem of precatalyst design is especially acute in the field of NHC–Pd catalysis as a consequence of the non-trivial complexation of NHC to palladium. On one hand, in situ catalyst preparations are generally unsatisfactory, and on the other hand, well-defined precatalysts undergo activation at very different rates.[17,51,52] There is a similar dependence of the activation profile of NHC–Ru metathesis catalysts on the nature of the disposable ligand situated *anti* to the NHC,[53–56] which implies that this phenomenon might be general for NHC ligands. For this reason, the high-yielding synthesis, under optimised conditions, of well-defined complexes carrying additional ligands that are shed in the process of catalyst activation has become the dominant strategy in NHC–Pd catalyst development.[17,20] Nolan and co-workers showed that introducing a methyl or phenyl substituent at C-1 of the allyl moiety of [(IPr)Pd(π-allyl)Cl] complexes led to much faster activation in isopropanol/*t*BuOK.[57] Also, an IPr-ligated six-membered palladacycle (**3**; Scheme 1) was activated by this protocol highly efficiently.[51,58] Although NHC–palladacycles have been known since 1978,[59] the effect of the cyclometallated ligand on catalyst activation in the search for highly active catalysts has not been explored to date in a systematic manner, despite the promise of this class of complexes. Herein we present a highly active and easily prepared NHC–palladacycle catalyst for use in the Suzuki–Miyaura coupling reaction of aryl chlorides discovered through the exploration of a small, rationally designed NHC–palladacycle library prepared by a novel synthetic method.

Results and Discussion

Library design and synthesis—a new method for NHC–palladacycle preparation: Since the seminal work by the groups of Herrmann,[60] Beller[61] and Hartwig,[62] palladacycles[63] have become mainstream precatalysts[64,65] for cross-coupling reactions. In the presence of the nucleophilic coupling partner or a base, palladacycles release atomic Pd^0 by a σ-bond metathesis/reductive elimination sequence.[62,66] The corresponding hybrid NHC– (such as IPr, **1**; Scheme 1) or phosphane–palladacycles analogously form mono-ligated ligand–Pd species.[67] The highest catalytic activity is generally attained at a ligand/Pd ratio of 1:1 when the spectator ligand is either an NHC or a bulky trialkylphosphane or dialkyl(2-biaryl)phosphane.[68] Furthermore, the availability of a large number of diverse cyclopalladated compounds and spectator ligands opens the doors to the generation of a combinatorial library in the search for the most active precatalyst.[69] To explore the ability of various palladacycles to release Pd^0 under mild conditions, we considered a small palladacycle library that was rationally diverse with respect to the donor atom ($N(sp^3)$, $N(sp^2)$, P(phosphane), P(phosphite), S or O) and ring size (five or six) (Scheme 1a), carrying the highly active bulky carbene IPr and a chloride as the charge-balance anion. The current methods[67,70–72] for preparing NHC–palladacycles have not been deployed for combinatorial library generation due to the practical limitations associated with the handling of highly air-sensitive free NHCs, low yields and/or narrow substrate scope. Therefore, we sought a more "combinatorially friendly" NHC–palladacycle preparation protocol that could yield a wide range of NHC–palladacycles in an air- and moisture-tolerant manner, relying on easily accessible NHC precursors (imidazolium salts). Historically, the reaction of $Pd(OAc)_2$ and imidazolium salts to form NHC–Pd^{II} halide complexes has paved the way for the current surge in NHC catalysis.[60] We surmised that palladacycle-bound acetates would retain this reactivity. This was proven to be the case: heating IPr·HCl (**1**)[22] with pre-

formed palladacycle acetates (easily prepared by *o*-palladation of the required heteroatom-containing aromatic compounds with $Pd(OAc)_2$) in dimethyl sulfoxide (DMSO) led to the expedient formation of IPr-ligated palladacycles (**2**–**11**) in yields of 53–82% (Scheme 1b) with a success rate of 80% (attempts at the synthesis of compounds **7** and **8** failed). The reaction has a wide scope, affording the first examples of NHC-ligated κ^2C,S-palladacycles **9** and **10** and a κ^2C,O-palladacycle **11** in good yields (60–76%). Compounds **9** and **11** exhibit the same structural pattern as observed in known *C*,*P*- and *C*,*N*-palladacycles,[67,70–72] that is, a slightly distorted square-planar Pd^{II} centre with the planes of the imidazole and palladacycle rings almost, but not exactly, perpendicular and the carbene carbon and the neutral donor ligand mutually *trans* (Figure 1). For comparison, when IPr·HCl (**1**) reacts with $Pd(OAc)_2$ in a 2:1 ratio, a $PdCl_2$ complex containing one IPr ligand bound to palladium through C1 (normal mode) and one through C4 (abnormal mode) is formed.[52] Our repeated experiments aimed at preparing IPr–Pd complexes from IPr·HCl (**1**) and $Pd(OAc)_2$ in a 1:1 ratio only resulted in decomposition.

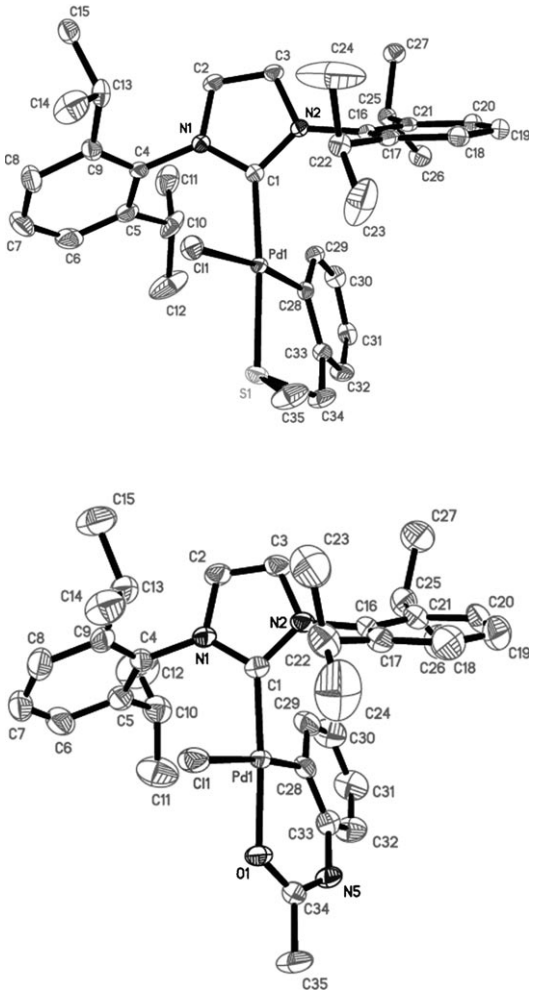
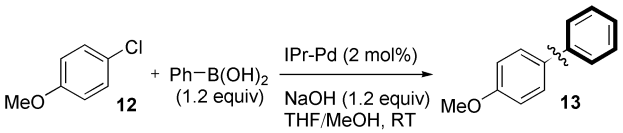


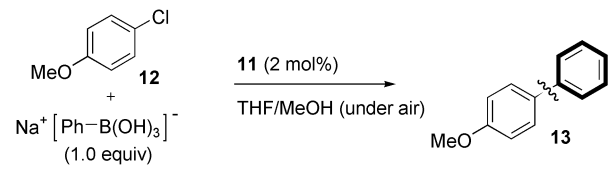
Figure 1. ORTEP representation of the single-crystal X-ray structures of complexes **9** (upper) and **11** (lower). The thermal ellipsoids were drawn at the 30% probability level and the hydrogen atoms and co-crystallising solvent molecules (for complex **11**) have been omitted for clarity.

Catalytic activity evaluation: Palladacycles release Pd^0 in a manner that is dependent on temperature, co-reactant and the nature of the cyclometallated framework.[62,66,69] High temperatures or strongly basic/nucleophilic co-reactants are generally necessary. We sought cyclopalladated ligand(s) that would allow the active IPr–Pd catalyst to be released efficiently at room temperature under mild, non-basic conditions. To achieve this, a model Suzuki–Miyaura reaction with a deactivated aryl chloride (**12**) was performed with the exact amount of NaOH necessary to neutralise the boronic acid before the injection of the precatalyst stock solution, creating only a mildly basic medium (Scheme 2). We discovered that acetanilide-derived palladacycle **11** (O-6) was highly active under these conditions (yield of 86% after 30 min; Figure 2). None of the other NHC–palladacycles screened was active under these conditions.[73] Complex **11** also outperformed the other known IPr–Pd precatalysts carrying other precatalyst-stabilising disposable ligands: acetylacetonate (**14**),[74] π-allyl (**15**),[75] π-cinnamyl (**16**),[57] 3-chloropyridine (PEPPSI-IPr, **17**)[42] and naphthoquinone (**18**).[76] Only precatalysts **16** and **17** led to moderate cross-coupling yields (yields of 8.5% for **16** and 40% for **17** vs. 88% for **11** after 2 h; Figure 2).



Scheme 2. Cross-coupling reaction of a deactivated substrate, *p*-chloroanisole (**12**), and pre-activated phenylboronic acid under non-basic conditions at room temperature mediated by the IPr-Pd precatalyst with various disposable ligands.

A calorimetric experiment using the preformed sodium phenyltrihydroxyborate (a commercial, convenient and active Suzuki–Miyaura substrate[77]) and *p*-chloroanisole (**12**; Scheme 3) revealed that the activation of the catalyst was fast at room temperature, resulting in a very short induction time (~1.5 min, Figure 3). Thereupon a highly exothermic reaction ensued, with the temperature of the reaction mixture reaching 38.0 °C within 7.5 min, and the reaction was complete within 20–25 min. Notably, this experiment was performed by dispensing a solution of **11** in methanol in air without the use of anhydrous and air-free solvents, which



Scheme 3. Cross-coupling reaction of a deactivated substrate, *p*-chloroanisole (**12**), and sodium phenyltrihydroxyborate mediated by complex **11** in air.

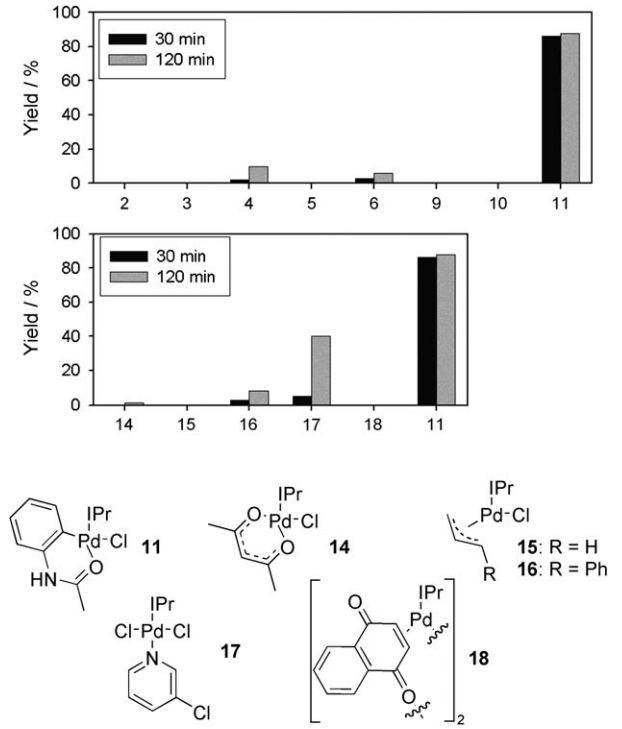


Figure 2. Evaluation of the catalytic activity of the NHC–palladacycle library (upper panel) and comparison of the catalytic activity of IPr-cyclopalladated acetanilide complex **11** with popular, commercially available IPr-Pd precatalysts (lower panel) in the model reaction (Scheme 2).

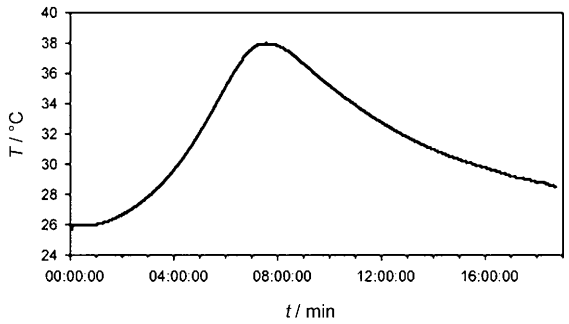


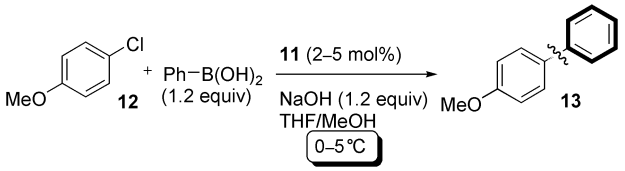
Figure 3. Thermal profile of the reaction of *p*-chloroanisole (**12**) and sodium phenyltrihydroxyborate in air mediated by complex **11** (Scheme 3).

demonstrates the potential of this complex for practical Suzuki–Miyaura coupling reactions in the context of automated parallel synthesis.[78]

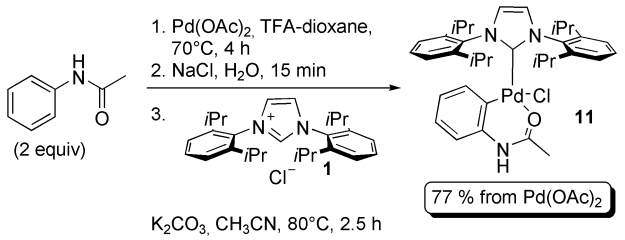
Moreover, the active catalyst from **11** was produced at 0 °C, even though the Suzuki–Miyaura coupling was considerably slower at that temperature. At 2 mol % and 30 min reaction time, almost no product was obtained at 0 °C. A longer reaction time (4 h) and higher catalyst loading (5 mol %) resulted in a practically quantitative yield (Table 1). To the best of our knowledge, this is the first example of a palladium-catalysed Suzuki–Miyaura coupling reaction below room temperature.

IPr-cyclopalladated acetanilide complex as a practical Suzuki–Miyaura precatalyst: To explore the scope of substrates, complex **11** was resynthesised on a gram scale by a modified method as we found that the method for cyclopalladation of acetanilide we originally employed[79] during the palladacycle library synthesis did not work reproducibly on a large scale in our hands. Cyclopalladation in the presence of trifluoroacetic acid (TFA) furnished the corresponding TFA–palladacycle.[80] Considering TFA to be insufficiently basic to deprotonate an imidazolium salt, we converted it into a chloride and introduced the carbene by a method recently developed in our laboratory (K_2CO_3 in acetonitrile at reflux, yield of 77 % from $Pd(OAc)_2$ on a 1.5 g scale; Scheme 4).[70]

Table 1. Cross-coupling reaction of a deactivated substrate, *p*-chloroanisole (**12**), and pre-activated phenylboronic acid under non-basic conditions at 0 °C mediated by **11**.

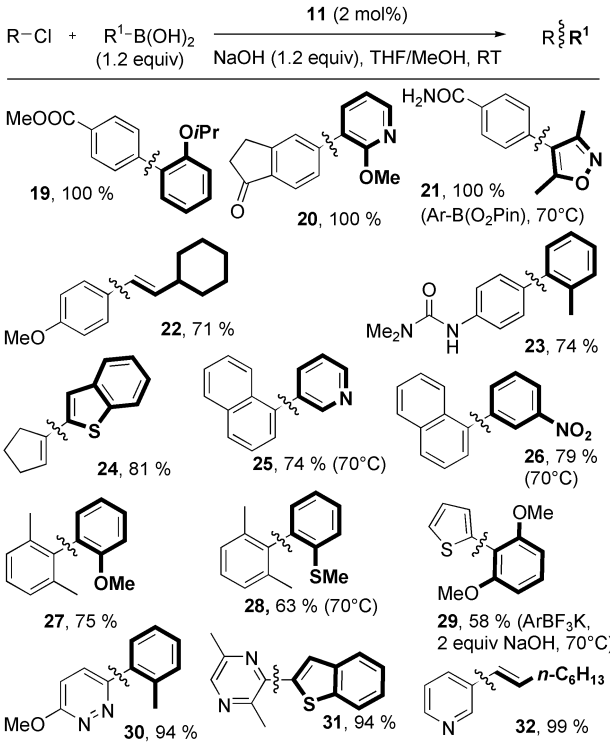


11 [mol %]	time [h]	yield of **13** [%]
2	0.5	0.46
2	2	23
5	4	97

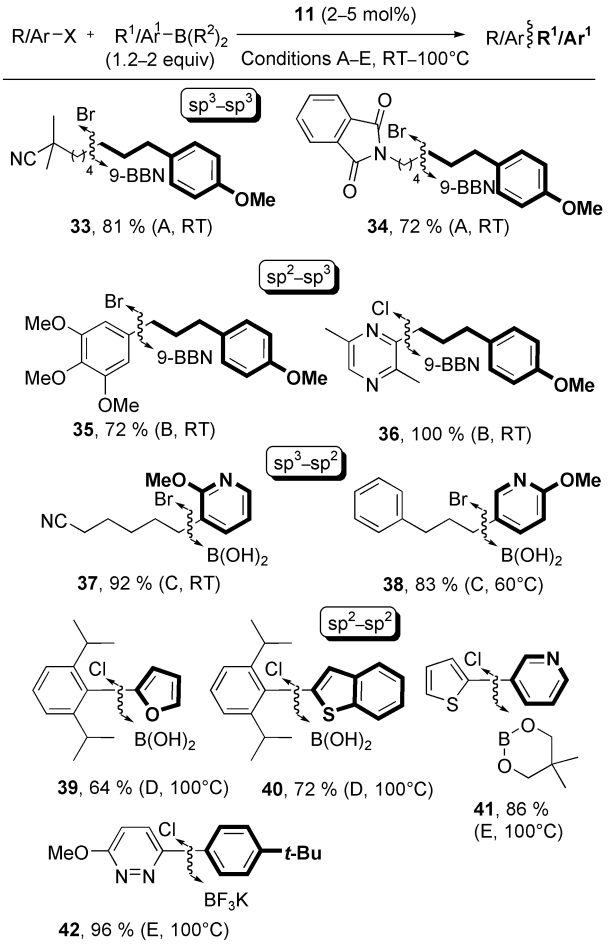


Scheme 4. Preparative synthesis of **11** on a 1.5 g scale.

We next investigated the coupling reactions of aryl and vinyl chlorides and aryl- and vinylboronic acids (Scheme 5) under the conditions of our screening protocol. Complex **11** (2 mol %) mediated the Suzuki–Miyaura reaction of an array of electron-poor (activated), electron-rich, doubly *ortho*-substituted and heterocyclic (all deactivated) aryl and vinyl chlorides with electron-rich or non-hindered arylboronic acids in good to excellent yields at room temperature. The reaction took place under practically non-basic conditions, which allowed base-sensitive substrates to be used. For instance, the coupling of methyl 4-chlorobenzoate (product **19**, 100 %) proceeded in quantitative yield without any competing ester hydrolysis. Generally we found that the performance of the catalyst was much more sensitive to the substituents in the boronic acids than in the aryl chlorides; hindered or electron-poor arylboronic acids only activated the catalyst reliably at 70 °C. At room temperature, only low yields were observed for these more challenging coupling partners. Whether this difference in performance is due to



Scheme 5. Cross-coupling reactions of aryl and vinyl chlorides with aryl- and vinylboronic acids, pinacol esters and potassium trifluoroborates under non-basic conditions mediated by **11**. The yields are of isolated chromatographically homogeneous materials (average from two runs), non-optimised for time and catalyst loading.



Scheme 6. Cross-coupling reactions of aryl and alkyl chlorides and bromides with alkyl bromides and arylboronic acids, esters and potassium trifluoroborates in various possible combinations mediated by **11**. The yields are of isolated chromatographically homogeneous materials (average from two runs), non-optimised for time and catalyst loading. Conditions: A) 4 mol% **11**, $K_3PO_4 \cdot H_2O$, dioxane; B) 4 mol% **11**, K_3PO_4, THF/H_2O; C) 4 mol% **11**, *t*BuOK, dioxane/MeOH; D) 5 mol% **11**, K_3PO_4, dioxane/H_2O; E) 2 mol% **11**, K_3PO_4, dioxane/H_2O.

the inability of the less active boronic acids to activate the precatalyst at room temperature or the active catalyst (IPr–Pd^0) did not attain sufficiently high turnover is unclear at this point. Synthetically important congeners of arylboronic acid, pinacol boronic esters or potassium trifluoroborates, also reacted under these conditions (products **21** and **29** prepared in yields of 100 and 58%, respectively).

IPr–Pd^0 (the active catalyst released upon activation of **11**) has been shown to mediate cross-coupling reactions of the much more challenging sp^3 carbon centres[40,42–47] in addition to the more traditional sp^2 centres. In the case of organozinc reagents (Negishi coupling), coupling reactions for various possible combinations have been demonstrated.[43] The scope of the Suzuki–Miyaura coupling reactions mediated by complex **11** was significantly expanded to include alkyl halides and alkyl boron reagents when K_3PO_4 or *tert*-BuOK were used as the base at room temperature and up to 100°C (Scheme 6). Gratifyingly, complex **11** was also readily activated under conditions suitable for the coupling of these more challenging substrate combinations even though each combination required a specific solvent, base and temperature to take place. 9-Alkyl-9-BBN (9-alkyl-9-borabicyclo[2.2.1]nonane) derivatives reacted smoothly with alkyl bromides (products **33** and **34** in yields of 81 and 72%, respectively) and aryl halides (halide = Br, Cl; **35** and **36** in yields of 72 and 100%, respectively) with K_3PO_4 as the base. On the other hand, the first (to the best of our knowledge) reaction of alkyl halides and arylboronic acids mediated by NHC–Pd complexes required the use of *tert*-BuOK (**37** and **38** in yields of 92 and 83%, respectively), which also demonstrates the coupling reactions of sp^3 and sp^2 carbon centres in various possible combinations with IPr–Pd in the case of organoboron nucleophiles. In this case, K_3PO_4 and NaOH were ineffective. We further endeavoured to test the limits of the catalytic activity of complex **11** by employing a very sterically hindered aryl chloride, 2-chloro-1,3-diisopropylbenzene. At 100°C, the coupling reactions of boronic acids derived from five-membered heterocycles gave good yields (**39** and **40** in yields of 64 and 72%, respectively) in the presence of K_3PO_4 at 5 mol% **11**. Remarkably, numerous attempts to couple phenylboronic acids to this aryl chloride with or without additional substituents were unsatisfactory, generally producing low yields and inseparable mixtures. Therefore, we believe this substrate can serve as a suitable 'benchmark' for future catalyst development in the

field of cross-coupling reactions. Finally, the coupling reactions of boronic esters and potassium trifluoroborates (**41** and **42** in yields of 86 and 96%, respectively) were demonstrated to proceed well in the presence of K_3PO_4 at a lower catalyst loading (2 mol%).

Conclusion

We have discovered a novel, highly active precatalyst for the coupling of deactivated aryl chlorides and phenylboronic acid at room temperature under very mild, weakly basic conditions through the evaluation of a small, rationally diverse library of NHC–palladacycles. The NHC–palladacycles were synthesised by a novel method involving the heating of easily accessible palladacycle acetates with an imidazolium salt. NHC-ligated *o*-palladated acetanilide mediated the sp^2 (electrophile)–sp^2 (organoboron compound), sp^2–sp^3, sp^3–sp^2 and sp^3–sp^3 Suzuki–Miyaura coupling reactions of challenging substrates in good-to-excellent yields. As a case in point, the coupling reactions of an extremely sterically hindered aryl chloride, 1-chloro-2,6-diisopropylbenzene, were conducted for the first time. Representatives of all major classes of organoboron compounds (boronic acids and esters, potassium trifluoroborates and 9-BBN derivatives) were found to be suitable. Remarkably, this catalyst also allowed the first palladium-mediated Suzuki–Miyaura coupling at 0°C to be achieved. The precatalyst could be synthesised in air on a gram scale in good yields. The Suzuki–Miyaura reactions can also be performed by using non-anhydrous solvents in air.

Experimental Section

General: All reagents, catalysts and solvents were purchased from commercial sources and used without further purification, unless otherwise indicated. Deuterated solvents were purchased from Sigma–Aldrich. TLC plates and reaction vials (screw-cap threaded, caps attached, 17 × 60 mm) were purchased from VWR. ^{1}H and ^{13}C NMR data were acquired at 25°C on a Bruker AV400 spectrometer. The elemental analyses were performed at the National University of Singapore. Prior to the analysis, the samples were dissolved in CH_2Cl_2 and filtered; the solvent was removed under reduced pressure, and the neat compounds were dried at 56°C, 5 torr over P_2O_5 for 18 h. HRMS (FAB and EI) were performed at the National University of Singapore. Flash chromatography was conducted on a CombiFlash Rx16 or CombiFlash Companion by using normal-phase silica-gel cartridges with hexane (solvent A)/ethyl acetate (solvent B) gradients, unless otherwise specified. All preparative Suzuki–Miyaura cross-coupling reaction runs were performed in duplicate and combined before purification; the amounts and yields indicated below were for a single run.

Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene][2-(methylthiomethyl)phenyl-*C*^{1},*S*)palladium(II) (9): Cyclopalladated benzyl methyl thioether acetate (151 mg, 0.5 mmol) and IPr·HCl[22] (**1**; 213 mg, 0.5 mmol) were dissolved in DMSO (2.5 mL) in a Radley carousel tube and heated at 120°C with stirring for 1 h. After cooling, H_2O (25 mL) was added and the off-white or grey precipitate was filtered through a pad of Celite and washed with copious amounts of water. After removing most of the water by air suction for 10 min, the filter cake was dissolved completely in CH_2Cl_2 (20–50 mL) and the product solution was dried ($MgSO_4$) and filtered into a 100 mL pear-shaped flask. Silica gel (3–5 g) was added and the solvent was removed under reduced pressure. The free-flowing powder was transferred into an empty CombiFlash solid-loading cartridge and the product was purified by flash chromatography (CombiFlash 12 g cartridge, gradient (% B, time): 0 to 60, 30 min); **9** (176 mg, 74%) was isolated as an off-white solid. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 7.80 (s, 2H), 7.42 (t, J = 7.9 Hz, 2H), 7.29 (dd, J = 7.6, 1.2 Hz, 2H), 7.21 (br s, 2H), 6.85 (dd, J = 7.2, 1.2 Hz, 1H), 6.77 (td, J = 7.2, 1.2 Hz, 1H), 6.75 (td, J = 7.6, 1.4 Hz, 1H), 6.55 (d, J = 7.2 Hz, 1H), 3.98–3.44 (br s, 2H), 3.35–2.90 (br s, 4H), 1.33 (d, J = 6.4 Hz, 6H), 1.11 (d, J = 6.4 Hz, 6H), 0.97 (d, J = 6.4 Hz, 6H), 0.89–0.42 ppm (br s, 6H); ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 178.8, 151.2, 149.7, 147.6, 145.2, 138.7, 137.3, 136.5, 130.0, 126.3, 125.7, 124.1, 123.7, 123.4, 46.8, 28.8, 28.6, 26.7, 23.5, 21.2, 20.9 ppm; elemental analysis calcd. (%) for $C_{35}H_{45}ClN_2PdS$ (667.68): C 62.96, H 6.79, N 4.20; found: C 62.72, H 6.63, N 3.94.

Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene][2-(*N*-acetylamino)phenyl-*C*^{1},*O*]palladium(II) (11): A 100 mL round-bottomed flask was charged with $Pd(OAc)_2$ (674 mg, 3 mmol), acetanilide (810 mg, 6 mmol) and an egg-shaped magnetic stirrer bar in air. Anhydrous dioxane (12 mL) and TFA (1.2 mL, 16 mmol) were added with stirring. The reaction mixture was heated at 70°C for 2.5 h. While hot, the greenish-yellow solution was diluted with brine (50 mL) and stirred for 30 min. The precipitate formed was filtered and washed sequentially with H_2O (50 mL), Et_2O (25 mL) and CH_2Cl_2 (25 mL). After drying, cyclopalladated acetanilide chloride (713 mg, 2.58 mmol) was obtained as a canary yellow solid. IPr·HCl (**1**; 1.15 g, 2.71 mmol), K_2CO_3 (430 mg, 3.10 mmol) and an egg-shaped magnetic stirrer bar were added to this solid in a 50 mL round-bottomed flask in air. CH_3CN (13 mL) was added and the reaction mixture was heated at reflux with vigorous stirring for 2.5 h. The mixture was cooled to room temperature and filtered through a pad of Celite with copious amounts of CH_2Cl_2. Complex **11** (1.53 g, 77% from $Pd(OAc)_2$) was obtained as an off-white solid after flash chromatography (CombiFlash 24 g cartridge; solvent A: hexane/CH_2Cl_2 (1:1, v/v); solvent B: ethyl acetate; gradient (% B, time): 0 to 5, 30 min). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.72 (br s, 1H), 7.33 (t, J = 7.7 Hz, 2H), 7.20 (br s, 2H), 7.09–7.14 (m, 4H), 6.77–6.85 (m, 2H), 6.54–6.58 (m, 1H), 6.35 (br d, J = 7.5 Hz, 1H), 3.26 (quint., J = 6.4 Hz, 2H), 3.06 (quint., J = 6.4 Hz, 2H), 2.01 (br s, 3H), 1.39 (d, J = 6.5 Hz, 6H), 1.10 (d, J = 6.7 Hz, 6H), 0.97 (d, J = 6.8 Hz, 6H), 0.58 ppm (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.5, 166.9, 165.4, 147.8, 145.1, 141.6, 140.1, 136.0, 134.8, 130.0, 127.4, 125.1, 124.2, 124.1, 124.1, 122.8, 117.8, 29.0, 28.5, 26.7, 26.2, 23.1, 22.9, 21.9 ppm; HRMS (FAB): calcd. for $C_{35}H_{44}ON_3{}^{106}Pd$ $[M-Cl]^+$: 628.2514; found: 628.2526 (δ = 1.96 ppm); $C_{35}H_{44}ON_3{}^{108}Pd$ $[M-Cl]^+$: 630.2518; found: 630.2517 (δ = −0.09 ppm).

***N*-[4-(*o*-Tolyl)phenyl]-*N*′,*N*′-dimethylurea (23)**

Stock solution A: Complex **11** (111 mg mL^{-1}) was placed in a pear-shaped flask, which was capped with a rubber septum, and the flask was backfilled with Ar (3×). The complex was then dissolved in the desired volume of dry, oxygen-free THF (Note: The stock solution could be stored for at least 2 weeks without loss of activity).

Stock solution B: NaOH (40 mg mL^{-1}) was gently shaken in MeOH until complete dissolution and then degassed by bubbling a gentle stream of Ar for at least 15 min.

Reaction procedure: A Pyrex glass tube was charged with a magnetic stirrer bar, *N*-(4-chlorophenyl)-*N*′,*N*′-dimethylurea (199 mg, 1 mmol) and *o*-tolylboronic acid (163 mg, 1.2 mmol). The tube was sealed with a septum and backfilled with Ar (3×). An aliquot (1.2 mL) of the stock solution A (13.3 mg **11**, 2 mol%) was then added and the mixture was stirred for 5 min. Next an aliquot (1.2 mL) of the stock solution B (48 mg NaOH, 1.2 mmol) was added and the reaction mixture was stirred at the desired temperature for 18 h. The reactions were carried out in duplicate and the mixtures were then combined by quantitative transfer (CH_2Cl_2) to a 100 mL pear-shaped flask. Silica gel (1.5–2.5 g) was added and the solvent was removed in vacuo. The free-flowing powder was transferred into an empty CombiFlash solid-loading cartridge and **23** (188 mg, 74%) was obtained as a white solid after flash chromatography (CombiFlash 12 g cartridge; gradient (% B, time): 0 to 10, 1 min; 10 to 50, 20 min). ^{1}H NMR

($CDCl_3$, 400 MHz): $\delta = 7.43$ (d, $J = 8.6$ Hz, 2H), 7.23–7.28 (m, 6H), 3.07 (s, 6H), 2.29 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 155.8$, 141.5, 137.9, 136.6, 135.5, 130.3, 129.9, 129.7, 127.1, 125.8, 119.5, 36.5, 20.6 ppm; HRMS (FAB): calcd. for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255.1497; found: 255.1492 ($\delta = 2.19$ ppm).

9-(4-Methoxyphenyl)-2,2-dimethylnonanenitrile (33)

Hydroboration of 4-allylanisole in dioxane: A 50 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with 9-BBN dimer (1.74 g, 7.15 mmol) in a glove box. The flask was capped with a rubber septum and removed from the glove box. Anhydrous 1,4-dioxane (5 mL) was added followed by 4-allylanisole (2.0 mL, 1.93 g, 13 mmol). Additional anhydrous dioxane (5 mL) was added to give a final concentration of 1.3 M based on 4-allylanisole. The reaction was stirred overnight at room temperature to give a clear homogeneous 9-[3-(4-methoxyphenyl)propyl]-9-BBN solution.

Reaction procedure: A 10 mL vial was charged with **11** (27 mg, 0.04 mmol), finely ground $K_3PO_4 \cdot H_2O$ (369 mg, 1.6 mmol) and a magnetic stirrer bar. The vial was sealed with a rubber septum and backfilled with Ar (3×). 6-Bromo-2,2-dimethylhexanenitrile (170 μL, 204 mg, 1.0 mmol) was added through a syringe followed by a solution of 9-[3-(4-methoxyphenyl)propyl]-9-BBN (1.3 M in dioxane; 1.25 mL, 1.6 mmol). The reaction was carried out in duplicate and after 18 h, the reaction mixtures were combined by quantitative transfer (CH_2Cl_2) to a 100 mL pear-shaped flask. Silica gel (1.5–2.5 g) was added and the solvent was removed in vacuo. The free-flowing powder was transferred into an empty CombiFlash solid-loading cartridge and **33** (220 mg, 81%) was obtained after flash chromatography (CombiFlash 12 g cartridge; gradient (% B, time): 0 to 5, 20 min). ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.11$ (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 3.80 (s, 3H), 2.54–2.58 (m, 2H), 1.58–1.67 (m, 3H), 1.42–1.55 (m, 4H), 1.34 ppm (br s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 157.6$, 134.9, 129.3, 125.3, 113.6, 55.2, 41.1, 35.0, 32.4, 31.7, 29.5, 29.3, 29.1, 26.7, 25.3; HRMS (EI): calcd. for $C_{18}H_{27}NO$ $[M]^+$: 273.2087; found: 273.2096 ($\delta = 3.22$ ppm).

1,2,3-Trimethoxy-5-(3-(4-methoxyphenyl)propyl)benzene (35)

Hydroboration of 4-allylanisole in THF: A solution of 9-BBN (0.5 M in THF, 39 mL, 19.5 mmol) followed by 4-allylanisole (2.0 mL, 1.93 g, 13 mmol) was injected into an oven-dried 100 mL round-bottomed flask equipped with a magnetic stirrer bar. The reaction was stirred overnight at room temperature and the 9-[3-(4-methoxyphenyl)propyl]-9-BBN solution formed (0.32 M in THF) was used directly.

Reaction procedure: A 10 mL vial was charged with **11** (27 mg, 0.04 mmol) followed by finely ground anhydrous K_3PO_4 (340 mg, 1.6 mmol) and a magnetic stirrer bar. The vial was sealed with a rubber septum and backfilled with Ar (3×). 5-Bromo-1,2,3-trimethoxybenzene (340 mg, 1.0 mmol) was added and 9-[3-(4-methoxyphenyl)propyl]-9-BBN solution (0.32 M in THF, 5.0 mL, 1.6 mmol) and H_2O (1.0 mL) were injected through a syringe in succession with vigorous stirring. The reaction was carried out in duplicate and after 18 h, the reaction mixtures were combined by quantitative transfer (CH_2Cl_2) to a 100 mL pear-shaped flask. Silica gel (1.5–2.5 g) was added and the solvent was removed in vacuo. The free-flowing powder was transferred into an empty CombiFlash solid-loading cartridge and **35** (229 mg, 72%) was obtained after flash chromatography (CombiFlash 12 g cartridge; gradient (% B, time): 0 to 20, 25 min). ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.13$ (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.42 (s, 2H), 3.86 (s, 6H), 3.85 (s, 3H), 3.81 (s, 1H), 2.59–2.65 (m, 4H), 1.90–2.00 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 157.7$, 153.0, 138.2, 134.2, 129.4, 113.7, 105.2, 60.9, 56.0, 55.3, 35.8, 34.6, 33.3 ppm; HRMS (EI): calcd. for $C_{19}H_{24}O_4$ $[M]^+$: 316.1669; found: 316.1670 ($\delta = 0.40$ ppm).

6-(2-Methoxypyridin-3-yl)hexanenitrile (37): A 10 mL vial was charged with **11** (27 mg, 0.04 mmol), 2-methoxy-3-pyridineboronic acid (230 mg, 1.5 mmol), *t*BuOK (168 mg, 1.5 mmol) and a magnetic stirrer bar. The vial was sealed with a rubber septum and backfilled with Ar (3×). Anhydrous dioxane (1.2 mL) and anhydrous methanol (1.2 mL) were added in succession through a syringe. After stirring for 15 s, 3-bromohexanenitrile (140 μL, 176 mg, 1.0 mmol) was added through a syringe. The reaction mixture was stirred at room temperature. The reaction was carried out in duplicate and after 18 h, the reaction mixtures were combined by quantitative transfer (CH_2Cl_2) to a 100 mL pear-shaped flask. Silica gel (2.5–4 g) was added and the solvent was removed under reduced pressure on a rotary evaporator equipped with a bump trap fitted with a glass filter. The free-flowing powder was transferred quantitatively into an empty CombiFlash solid-loading cartridge and **37** (201 mg, 92%) was obtained after flash chromatography (CombiFlash 12 g cartridge; gradient (% B, time): 0 to 20, 25 min). ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.02$ (dd, $J = 1.9$, 5.1 Hz, 1H), 7.37 (dd, $J = 1.9$, 7.2 Hz, 1H), 6.82 (dd, $J = 5.0$, 7.1 Hz, 1H), 6.82 (dd, $J = 5.0$, 7.1 Hz, 1H), 3.95 (s, 3H), 2.56–2.60 (m, 2H), 2.35 (t, $J = 7.1$ Hz, 1H), 1.66–1.75 (m, 2H), 1.58–1.65 (m, 2H), 1.46–1.55 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 162.1$, 144.3, 137.6, 124.5, 119.8, 116.7, 53.3, 29.6, 28.4, 28.2, 25.2, 17.1 ppm; HRMS (FAB): calcd. for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.1335; found: 205.1341 ($\delta = 2.55$ ppm).

2-(2,6-Diisopropylphenyl)furan (39): A 10 mL reaction vial was charged with **11** (0.02 mmol, 14 mg), furan-2-boronic acid (244 mg, 2.0 mmol), finely ground K_3PO_4 (2.0 mmol, 425 mg) and a magnetic stirrer bar. It was sealed with a rubber septum and purged with Ar (3×). 2-Chloro-1,3-diisopropylbenzene (197 mg, 1.0 mmol) was added through a preweighed syringe and 1,4-dioxane (2.5 mL) and H_2O (1.0 mL) were injected in succession with vigorous stirring. The reaction was carried out in duplicate and stirred overnight at 100 °C, after which time the reactions were combined, diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered through a Celite pad and quantitatively transferred into a 100 mL pear-shaped flask. Silica gel (2–3 g) was added and the solvent was removed in vacuo. The free-flowing powder was transferred into an empty CombiFlash solid-loading cartridge and **39** (147 mg, 64%) was obtained after flash chromatography (CombiFlash 12 g cartridge; gradient (% B, time): 0, 30 min). ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.56$ (br s, 1H), 7.42–7.46 (m, 1H), 7.24–7.27 (m, 2H), 6.53–6.54 (m, 1H), 6.31–6.33 (m, 1H), 2.71–2.78 (m, 2H), 1.20 ppm (dd, $J = 6.9$, 1.6 Hz, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 151.8$, 141.6, 129.7, 129.1, 122.6, 110.3, 109.3, 30.8, 24.3 ppm; HRMS (EI): calcd. for $C_{16}H_{20}O$ $[M]^+$: 228.1514; found: 228.1509 ($\delta = -2.22$ ppm).

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