Palladate pre-catalysts for the formation of C-N and C-C bonds

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Supporting Information Placeholder

ABSTRACT: A series of imidazolium-based palladate pre-catalysts has been synthesized and the catalytic activity of these air- and moisture-stable complexes evaluated as a function of the nature of the imidazolium counterion. These pre-catalysts can be converted under catalytic conditions to Pd-NHC species capable of enabling the Buchwald-Hartwig aryl amination and the α-arylation of ketones. Both reactions can be carried out efficiently under very mild operating conditions. The effectiveness of the protocol was tested on functionality-laden substrates.

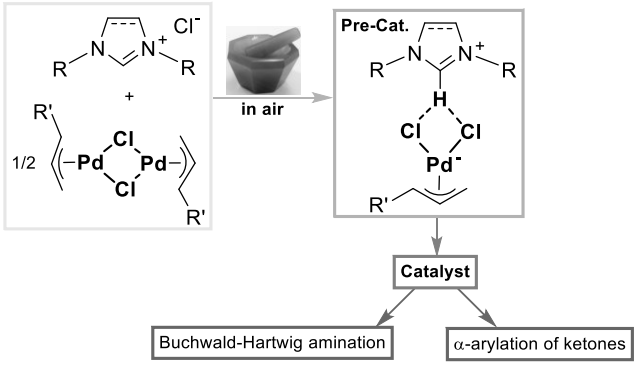
INTRODUCTION

The formation of carbon-heteroatom bonds is central to molecular assembly in its many incarnations.[1–3] In particular carbon-nitrogen bonds can be found in a plethora of molecules ranging from pharmaceutical agents, natural products to agrochemicals.[4–8] The Buchwald-Hartwig aryl amination reaction has become one of the most important cross-coupling reactions practiced in modern chemistry to achieve C-N bond formation. This protocol has led to a large variety of C-N containing molecules enabling a plethora of applications.[9–18] Due to its importance, various catalytic systems have been devised to the specific end of generating C-N bonds selectively.

The Buchwald-Hartwig reaction is principally mediated by palladium catalysts and operated through rapid and straightforward activation of well-defined complexes, leading to the putative Pd^0L species.[19-21] Our interest in this area has focused mainly on the use of N-heterocyclic carbenes (NHCs) as supporting ligands.[22,23] The difference in electronic and steric properties of NHCs compared to the traditionally used tertiary phosphine ligands has generated new possibilities and improved reaction conditions in catalysis.[24] The family of [Pd(NHC)(η^3-R-allyl)Cl] pre-catalysts has shown high catalytic activity in numerous cross-coupling reactions such as in carbon-carbon,[28,29] carbon-nitrogen[13,18,25-30] and carbon-sulfur[31, 32] bond formations as well as in the arylation of the ketones[33]. A main advantage of these pre-catalysts is their use at very low loadings under very mild reaction conditions and in environmentally friendly solvents.[34,35]

The efficacy of the bond-forming reaction is most often the focus of reports dealing with the Buchwald-Hartwig reaction and little attention is paid to the steps required to generate the pre-catalyst itself. In our search for increasingly user-friendly and greener catalytic systems, we recently reported on the use of a palladate pre-catalyst, [IPr·H][Pd(η^3-cin)Cl_2][36] (IPr = *N,N'*-bis-[2,6-(di-*iso*-propyl)phenyl]imidazol-2-ylidene;[37] cin = cinnamyl), that displays, in the Suzuki-Miyaura reaction, very high activity, a broad functional group tolerance while making use of a mild inorganic base and a green solvent.[38] Another important advantage of such systems is that they can be synthesized on gram-scale under solvent free conditions and without the need for any workup. Considering the importance of the C-N bond forming reaction and related α-arylation of ketone, we wished to explore whether the easily-prepared palladate pre-catalysts could display high efficacy in these two important reactions (Scheme 1).

Scheme 1. Palladate complexes as pre-catalysts in cross-coupling reactions.



RESULTS AND DISCUSSIONS

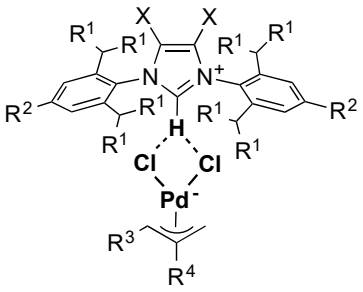
A number of [NHC·H][Pd(η^3-R-allyl)Cl_2] complexes were synthesized using the solvent-free method consisting of grinding the NHC salt with [Pd(η^3-cin)(μ-Cl)]$_2$.[38] In this manner, a number of palladates were obtained quantitatively in microan-

alytical purity (Scheme 2). The synthetic methodology was shown to be general, as variations of both NHC and allyl moieties are possible.

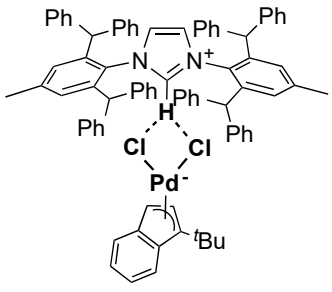
This new series of palladates was first tested in the Buchwald-Hartwig arylamination reaction involving 4-chloroanisole and 4-fluoroaniline. Early results revealed that complexes bearing $[IPr^*{\cdot}H]^+$ [*N*,*N'*-1,3-bis[2,6-bis(diphenylmethyl)-4-methyl phenyl)imidazolium] as counter cation (pre-ligand) lead to the best conversion. Furthermore the cinnamyl derivative $[IPr^*{\cdot}H][Pd(\eta^3\text{-cin})Cl_2]$ (**1**) was determined to be the optimum pre-catalyst (ESI, Table S1). Previous reports have shown that Ind^{tBu}-based Pd-NHC complexes exhibited higher activity than their allyl and cinnamyl counterparts.[39] Interestingly, under our conditions, this has been shown not to be the case as evidenced by the lower activity of the $[IPr^*{\cdot}H][Pd(\eta^3\text{-}Ind^{tBu})Cl_2]$ (only 56% conversion compared to 99% conversion when using **1**).

Next, the conditions for pre-catalyst activation were investigated (ESI, Tables S2-S4). As expected, the activation temperature plays a more significant role than the operating temperature. 60 °C appears to be the ideal activation temperature as increasing the temperature further results in a decrease in conversion (see ESI for details).

Scheme 2. Imidazolium palladates used in this study.



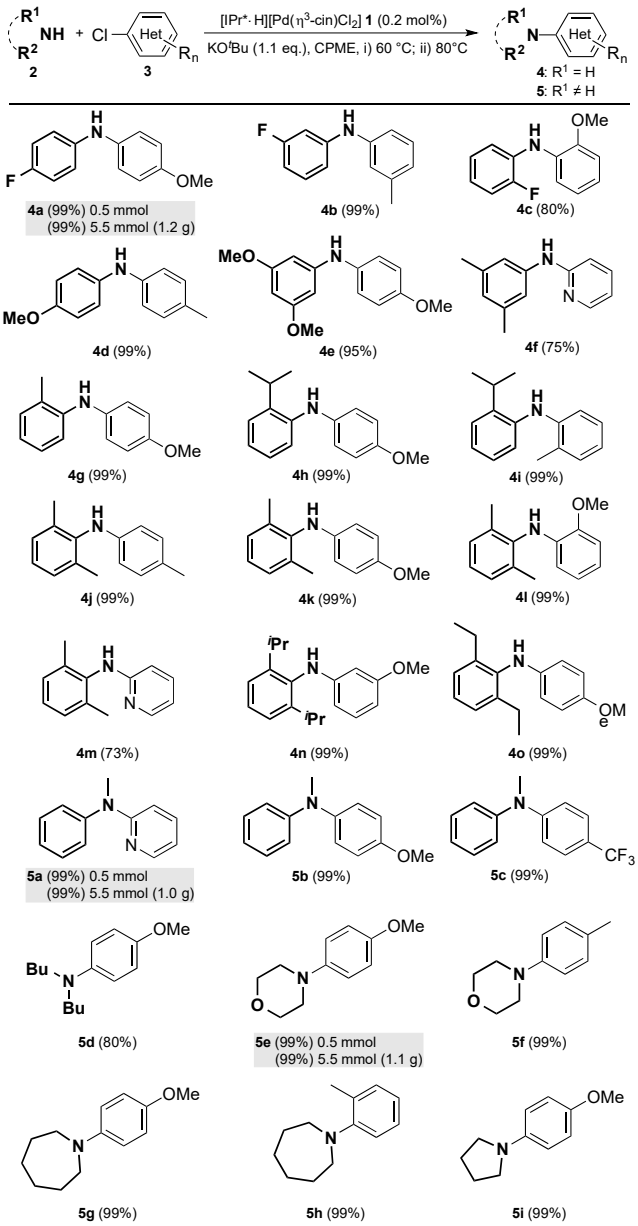
R^1	R^2	R^3	R^4	X	Palladate
Me	H	Ph	H	H	$[IPr{\cdot}H][Pd(\eta^3\text{-cin})Cl_2]$
Ph	Me	Ph	H	H	$[IPr^*{\cdot}H][Pd(\eta^3\text{-cin})Cl_2]$ **(1)**
Ph	OMe	Ph	H	H	$[IPr^{*OMe}{\cdot}H][Pd(\eta^3\text{-cin})Cl_2]$
Ph	Me	CH_3	H	H	$[IPr^*{\cdot}H][Pd(\eta^3\text{-crotyl})Cl_2]$
Ph	Me	H	Me	H	$[IPr^*{\cdot}H][Pd(\eta^3\text{-2-Me-allyl})Cl_2]$
Et	H	Ph	H	H	$[IPent{\cdot}H][Pd(\eta^3\text{-cin})Cl_2]$
Et	H	Ph	H	Cl	$[IPent^{Cl}{\cdot}H][Pd(\eta^3\text{-cin})Cl_2]$
^{n}Pr	H	Ph	H	H	$[IHept{\cdot}H][Pd(\eta^3\text{-cin})Cl_2]$
^{n}Bu	H	Ph	H	H	$[INon{\cdot}H][Pd(\eta^3\text{-cin})Cl_2]$



$[IPr^*{\cdot}H][Pd(\eta^3\text{-}Ind^tBu)Cl_2]$

We then focused on optimizing the reaction using green solvents.[40,41] In this context, cyclopentylmethyl ether (CPME) was chosen for its numerous advantages over other commonly employed ether solvents such as THF, diethyl ether or 1,4-dioxane. Indeed, in addition to its stability under acidic and basic conditions, CPME does not lead to formation of peroxides, thereby decreasing risks associated with this reaction.[42] In addition, the low miscibility of CPME with water allows efficient purification/separation and its use is therefore very attractive for large-scale industrial reactions.[42]

Scheme 3. Aryl amination of primary and secondary amines with aryl chlorides[a].



[a] **Reaction conditions**: $[IPr^*{\cdot}H][Pd(\eta^3\text{-cin})Cl_2]$ (1.2 mg, 0.2 mol%), KO^{t}Bu (62 mg, 0.55 mmol), CPME (1 mL); 1 h at 60 °C; then amine and aryl chloride in CPME (1 mL) added; 2 h at 80 °C. (Isolated yields, average of two reactions).

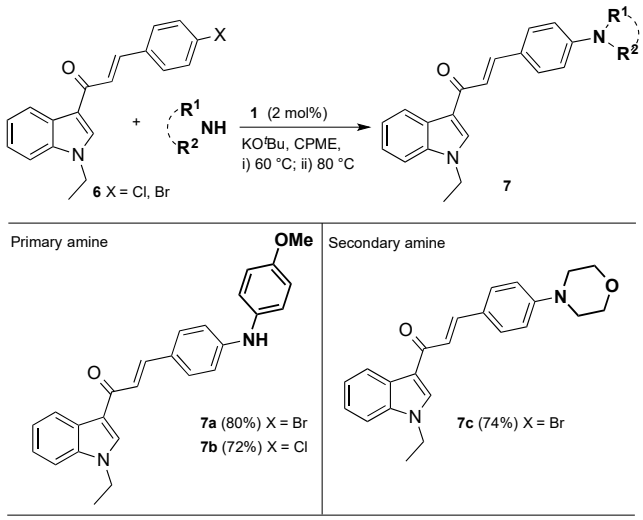
The scope of the newly established catalytic system was next explored using a variation of primary amines with aryl chlorides (Scheme 3, **4a**-**o**). It was possible to couple substrates with substituents at *para*, *meta* or *ortho* positions without loss of reactivity (Scheme 3). The use of sterically hindered anilines such as 2-tolylaniline (**4g**), 2-isopropylaniline (**4h** and **4i**), 2,6-diisopropylaniline (entry **4n**) and 2,6-diethylaniline (**4o**) resulted in excellent isolated yields.[43] As all reactions proceed in high yield, the product purification was

achieved by using a simple filtration through silica to remove impurities and catalyst residues. The use of flash column chromatography proved unnecessary. A series of secondary amines (aliphatic and aromatic) was also successfully coupled using this methodology (Scheme 3, **5a**-**i**).

As proof of the robustness of the procedure and of the catalysts, three compounds were scaled to 5.5 mmol (≥ 1g) (**4a**, **5a** and **5e**). In all cases, no loss of reactivity was observed. Seven-membered ring, azepane (**5g** and **5h**) as well as four-membered ring pyrrolidine (**5f**) were coupled successfully in excellent yields.

We then turned our attention to more complex structures, and targeted a motif present in anti-cancer agents.[44] The specific architecture of *N*-ethylindolylphenylpropenone was selected as it brings multiple challenges in the form of numerous functional groups (2 heteroatoms and an alkene moiety), that have the ability to inhibit catalysts (Scheme 4). [12,25,45-47] Both primary and secondary amines were coupled successfully, leading to the formation of **7a-c** in good isolated yields, after flash column chromatography. The involvement of more complex and functionalized substrates showcases the potential use of this simple methodology and of these simple catalysts to enable the generation of complex molecules using a late-functionalisation strategy. This greener approach generates molecular diversity in a very rapid and efficient manner.

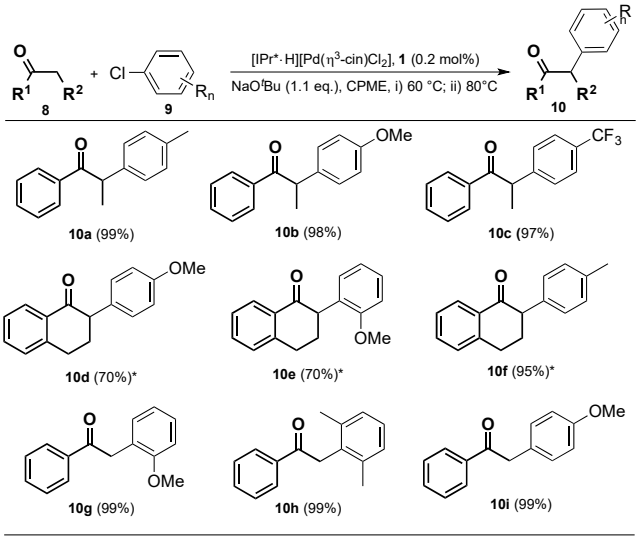
Scheme 4. Aryl amination of more elaborated substrates[a].



[a] **Reaction conditions**: [IPr*·H][Pd(η³-cin)Cl₂] (12 mg, 2 mol%), KO^{t}Bu (62 mg, 0.55 mmol), CPME (1 mL); 1 h at 60 °C; then amine and aryl halide in CPME (1 mL) added; 2 h at 80 °C. (Isolated yields, average of two reactions).

The coupling of enolizable ketones and aryl chlorides finds its importance in the synthesis of natural products and synthetic intermediates found in pharmaceuticals. First reported by Hartwig,[48] Buchwald[49] and Miura,[50] the α-arylation of ketones is now a powerful and widely used tool in synthetic chemistry. Since the arylation of ketones and aryl amination reactions proceed through closely related mechanisms, we studied our palladate catalytic strategy in the α-arylation of a range of ketones (Scheme 5). Conveniently by changing the base from KO^{t}Bu to NaO^{t}Bu, the optimized conditions were established for the present ketone functionalization protocol (See supporting information). The reaction was carried out in air with no need for dry solvent using low catalyst loading (0.2 mol% Pd). Propiophenone was successfully coupled with neutral (**10a**), electron-donating (**10b**) and electron-withdrawing (**10c**) aryl chlorides, in high isolated yields. Sterically hindered aryl chlorides were successfully coupled with the more challenging α-tetralone (**10e**) and acetophenone (**10g** and **10h**).

Scheme 5. Scope of the ketone arylation reaction[a].



[a] **Reaction conditions**: [IPr*·H][Pd(η³-cin)Cl₂] (**1**) (1.2 mg, 0.2 mol%),NaO^{t}Bu (53 mg, 0.55 mmol), CPME (1 mL); 1 h at 60 °C; then ketone and aryl chloride in CPME (1 mL) added; 1 h (*3 h) at 80 °C. (Isolated yields, average of two reactions).

CONCLUSIONS

A range of palladate pre-catalysts was synthesized following a facile and environmentally-friendly synthetic protocol. The pre-catalysts were tested in the aryl amination and the α-arylation ketone reactions. A highly efficient protocol was established for both reactions using low catalyst loading and a green solvent (CPME). Highly functionalized and biologically relevant substrates have been coupled using the aryl amination reaction protocol highlighting the compatibility of the present protocol with late-stage functionalization synthetic strategies. Ongoing studies aimed at expanding the role of these palladates in related reactions are currently being examined in our laboratories.

EXPERIMENTAL SECTION

General procedure for the synthesis of [NHC·H][Pd(η³-R-allyl)Cl₂] complexes: In air, the NHC·HCl and [Pd(η³-R-allyl)(μ-Cl)]₂ were added to a mortar. The two solids were mixed and grinded using a pestle for 5 min. A crystalline solid was obtained.

[IHept·H][Pd(η³-cin)Cl₂]: Following the general procedure from IHept·HCl (50.0 mg, 0.08 mmol) and [Pd(η³-cin)(μ-Cl)]₂ (20.0 mg, 0.04 mmol), the product was obtained as a yellow powder in 96% yield (67.0 mg).^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.51 (s, 2H, CH_{Imid}), 7.95 (s, 1H, C_{NCHN}), 7.60 (t, J = 7.8 Hz, 2H, CH_{Ar}), 7.49 (d, J = 9.1 Hz, 2H, $CH_{Ar(cin)}$), 7.27-7.25 (m, 4H, CH_{Ar}), 7.21-7.19 (m, 3H, $CH_{Ar(cin)}$), 5.68 (br. s, 1H, $CH_{(cin)}$), 4.47 (br. s, 1H, $CH_{2(cin)}$), 3.88 (d, J = 6.0 Hz, 1H, $CH_{2(cin)}$), 2.94 (d, J = 11.6 Hz, 1H, $CH_{(cin)}$), 2.08 (m, 4H, $CH_{(IHept)}$), 1.65-1.49 (m, 16H, $CH_{2(IPent)}$), 1.34-1.25 (m, 4H, $CH_{2(IHept)}$), 1.11-0.95 (m, 12H, $CH_{2(IHept)}$), 0.89-0.81 (m, 24H, $CH_{3(IHept)}$).^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 143.1 (C_{Ar}), 134.2 (CH_{NCN}), 132.0 (CH_{Ar} + C_{Ar}), 129.3 (CH_{imid}), 128.6 (CH_{cin}), 128.0 (CH_{cin}), 125.3 (CH_{Ar}), 105.1 (CH_{cin}), 68.9 (CH_{cin}), 58.1 ($CH_{2(cin)}$), 40.5 ($CH_{(IHept)}$), 39.5 ($CH_{2(IHept)}$), 38.3 ($CH_{2(IHept)}$), 21.4 ($CH_{2(IHept)}$), 21.0 ($CH_{2(IHept)}$), 14.5 ($CH_{3(IHept)}$), 14.2 ($CH_{3(IHept)}$). Anal. Calcd.

for $C_{52}H_{78}Cl_2N_2Pd$ C 68.75, H 8.65, N 3.08. Found: C 68.75, H 9.03, N 2.96.

[INon·H][Pd(η³-cin)Cl₂]: Following the general procedure from INon·HCl (50.0 mg, 0.06 mmol) and $[Pd(\eta^3\text{-cin})(\mu\text{-Cl})]_2$ (17.0mg, 0.03 mmol), the product was obtained as a yellow powder in 99% yield (70.0 mg).^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.45 (s, 2H, CH_{Imid}), 7.94 (s, 1H, C_{NCHN}), 7.61 (t, J = 7.8 Hz, 2H, CH_{Ar}), 7.47 (d, J = 7.6 Hz, 2H, $CH_{Ar(cin)}$), 7.27 (d, J = 7.9 Hz, 4H, CH_{Ar}), 7.20 (d, J = 7.2 Hz, 3H, $CH_{Ar(cin)}$), 5.65 (br. s, 1H, $CH_{(cin)}$), 4.46 (br. s, 1H, $CH_{(cin)}$), 3.84 (br. s, 1H, $CH_{(cin)}$), 2.88 (br. s, 1H, $CH_{(cin)}$), 2.03 (m, 4H, $CH_{(INon)}$), 1.67-1.52 (m, 16H, $CH_{2(INon)}$), 1.28 (m, 20H, $CH_{2(INon)}$), 1.10-0.91 (m, 12H, $CH_{2(INon)}$), 0.87 (t, J = 7.1 Hz, 12H, $CH_{3(INon)}$), 0.79 (t, J =7.3 Hz, 12H, $CH_{3(INon)}$).^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 143.1 (C_{Ar}), 134.3 (CH_{NCN}), 132.2 (CH_{Ar}), 132.0 (C_{Ar}), 129.1 (CH_{imid}), 128.6 (CH_{cin}), 128.0 (CH_{cin}), 125.4 (CH_{Ar}), 105.2 (CH_{cin}), 68.9 (CH_{cin}), 58.0 ($CH_{2(cin)}$), 40.7 (CH_{cin}), 37.0 ($CH_{2(INon)}$), 35.6 ($CH_{2(INon)}$), 30.2 ($CH_{2(INon)}$), 30.0 ($CH_{2(INon)}$), 23.1 ($CH_{2(INon)}$), 22.8 ($CH_{2(INon)}$), 14.1 ($CH_{3(INon)}$), 13.9 ($CH_{3(INon)}$). Anal. Calcd. for $C_{60}H_{94}Cl_2N_2Pd$ C 70.60, H 9.28, N 2.74. Found: C 70.42, H 9.48, N 2.81.

[Pr^{OMe}·H][Pd(η³-cin)Cl₂]:* Following the general procedure from IPr*^{OMe}·HCl (50.0 mg, 0.05 mmol) and $[Pd(\eta^3\text{-cin})(\mu\text{-Cl})]_2$ (13.0 mg, 0.02 mmol), the product was obtained as a yellow powder in 99% yield (63.0 mg).^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.29 (s, 1H, C_{NCHN}), 7.34-7.08 (m, 35H, CH_{Ar}), 6.79 (d, J = 7.2 Hz, 10H, CH_{Ar}), 6.46 (s, 4H, CH_{Ar}), 5.80-5.60 (br. m, 1H, $CH_{(cin)}$), 5.45 (s, 4H, $CH_{(IPr*OMe)}$), 5.23 (s, 2H, CH_{Imid}), 3.85 (br. s, 1H, $CH_{(cin)}$), 3.76 (br. s, 1H, $CH_{(cin)}$), 3.51 (s, 6H, $CH_{3(IPr*OMe)}$), 2.87 (br. s, 1H, $CH_{(cin)}$).^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 160.5 (C_{Ar}), 143.2 (CH_{NCN}), 143.0 (C_{Ar}), 142.7 (C_{Ar}), 142.2 (C_{Ar}), 130.4 (CH_{Ar}), 129.3 (CH_{Ar}), 128.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.2 (CH_{Ar}), 127.0 (CH_{Ar}), 126.9 (CH_{Ar}), 125.8 (CH), 123.1 (CH_{imid}), 115.7 (CH_{Ar}), 105.7 (CH_{cin}), 69.0 (CH_{cin}), 55.2 ($OCH_{3(IPr*OMe)}$), 51.5 ($CH_{(IPr*OMe)}$). Anal. Calcd. for $C_{78}H_{66}Cl_2N_2O_2Pd$ C 75.51, H 5.36, N 2.26. Found: C 75.33, H 5.64, N 2.32.

[IPent^{Cl}·H][Pd(η³-cin)Cl₂]: Following the general procedure from IPent^{Cl}·HCl (50.0 mg, 0.08 mmol) and $[Pd(\eta^3\text{-cin})(\mu\text{-Cl})]_2$ (21.0 mg, 0.04 mmol), the product was obtained as a yellow powder in 99% yield (71.0 mg).^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.41 (s, 1H, C_{NCHN}), 7.60 (t, J = 7.7 Hz, 2H, CH_{Ar}), 7.48 (d, J = 7.3 Hz, 2H, $CH_{Ar(cin)}$), 7.29 (d, J = 7.7 Hz, 4H), 7.24-7.23 (m, 3H, $CH_{Ar(cin)}$), 5.74 (br. s, 1H, $CH_{(cin)}$), 4.56 (br. s, 1H, $CH_{2(cin)}$), 3.92 (br. s, 1H, $CH_{2(cin)}$), 2.97 (br. s, 1H, $CH_{(cin)}$), 1.96-1.95 (m, 4H, $CH_{(IPentCl)}$), 1.86-1.78 (m, 8H, $CH_{2(IPentCl)}$), 1.69-1.63 (m, 8H, $CH_{2(IPentCl)}$), 0.89-0.84 (m, 24H, $CH_{3(IPentCl)}$).^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 143.4 (C_{Ar}), 142.8 (CCl_{imid}), 137.3 (CH_{NCN}), 132.2 (CH_{Ar}), 129.6 (CH_{Ar}), 128.1 (CH_{Ar}), 126.1 (CH_{Ar}), 121.1 (C_{Ar}), 105.9 (CH_{cin}), 81.9 (CH_{cin}), 59.2 ($CH_{2(cin)}$), 43.4 ($CH_{(IPentCl)}$), 29.3 ($CH_{2(IPentCl)}$), 27.2 ($CH_{2(IPentCl)}$), 12.4 ($CH_{3(IPentCl)}$), 11.9 ($CH_{3(IPentCl)}$). Anal. Calcd. for $C_{44}H_{60}Cl_4N_2Pd$ C 61.08, H 6.99, N 3.24. Found: C 60.90, H 6.78, N 3.14.

[IPr·H][Pd(η³-crotyl)Cl₂]*: Following the general procedure from IPr*·HCl (50.0 mg, 0.05 mmol) and $[Pd(\eta^3\text{-crotyl})(\mu\text{-Cl})]_2$ (10.3 mg, 0.03 mmol), the product was obtained as a yellow powder in 99% yield (60.0 mg).^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.60 (s, 1H, C_{NCHN}), 7.30-7.27 (m, 16H, CH_{Ar}), 7.16-7.10 (m, 16H, CH_{Ar}), 6.79-6.77 (m, 12H, CH_{Ar}), 5.43 (s, 6H$_{IPr*}$,), 5.04 (br.s. 1H, CH_{crotyl}), 3.71 (m, 2H, $CH_{2(crotyl)}$), 2.56 (br. s, 1H, CH_{crotyl}), 2.14 (s, 6H, $CH_{3(IPr*)}$), 1.29 (d, J = 5.6 Hz, 3H, $CH_{3(crotyl)}$).^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 142.6 (C_{Ar}), 142.2 (CH_{NCN}), 141.4 (C_{Ar}), 141.0 (C_{Ar}), 130.9 (C_{Ar}), 130.3 (CH_{Ar}), 129.2 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 126.9 (CH_{Ar}), 126.7 (CH_{Ar}), 110.3 (CH_{imid}), 79.6 (CH_{crotyl}), 57.3.0 (CH_{crotyl}), 51.1 ($CH_{2(crotyl)}$), 21.8 ($CH_{3(IPr*)}$), 18.1 ($CH_{3(crotyl)}$). Anal. Calcd. for $C_{73}H_{64}Cl_2N_2Pd$. C 76.47, H 5.63, N 2.44. Found: C 76.23, H 5.49, N 2.42.

[IPr·H][Pd(η³-2-Me-allyl)Cl₂]*: Following the general procedure from IPr*·HCl (50.0 mg, 0.05 mmol) and $[Pd(\eta^3\text{-2-Me-allyl})(\mu\text{-Cl})]_2$ (10.3 mg, 0.03 mmol), the product was obtained as a yellow powder in 99% yield (61.0 mg).^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.89 (s, 1H, C_{NCHN}), 7.29-7.03 (m, 32H, CH_{Ar}), 6.77-6.76 (m, 8H, CH_{Ar}), 6.71 (s, 4H, CH_{Ar}), 5.44 (s, 4H, $CH_{(IPr*)}$), 5.37 (s, 2H, CH_{Imid}), 3.85 (br. s, 2H, $CH_{2(allyl)}$), 2.81 (br. s, 1H, CH_{allyl}), 2.53 (br. s, 1H, CH_{allyl}), 2.16 (s, 6H, $CH_{3(IPr*)}$), 2.08 (br. s, 3H, $CH_{3(allyl)}$).^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 142.9 (C_{Ar}), 142.3 (C_{NCN}), 141.9 (C_{Ar}), 141.1 (C_{Ar}), 140.7 (C_{Ar}), 131.1 (CH_{Ar}), 130.5 (CH_{Ar}), 129.4 (CH_{Ar}), 128.7 (CH_{Ar}), 128.2 (CH_{Ar}), 126.9 (CH_{Ar}), 126.8 (CH_{Ar}), 123.3 (CH_{imid}), 105.9 (CH_{allyl}), 60.5 (CH_{allyl}), 59.5 (CH_{allyl}), 51.3 ($CH_{(IPr*)}$), 22.0 ($CH_{3(IPr*)}$), 14.3 ($CH_{3(allyl)}$). Anal. Calcd. for $C_{73}H_{64}Cl_2N_2Pd$ $2CH_2Cl_2$ C 67.49 H 5.59 N 2.14 Found: C 67.88 H 5.30 N 2.47.

[IPr·H][Pd(Ind^{tBu})Cl₂]*: Following the general procedure from IPr*·HCl (50.0 mg, 0.05 mmol) and $[Pd(Ind^{tBu})(\mu\text{-Cl})]_2$ (16.3 mg, 0.03 mmol), the product was obtained as a brown powder in 99% yield (67.0 mg).^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.02 (s, 1H,C_{NCHN}), 7.26-7.09 (m, 34H, CH_{Ar}), 6.91-6.75 (m, 15H, 10 CH_{Ar} + 5 CH_{Ind}), 5.53 (m, 1H, CH_{Ind}), 5.42 (s, 2H, CH_{Imid}), 5.38 (s, 4, $CH_{(IPr*)}$) 2.16 (s, 6H, $CH_{3(IPr*)}$), 1.39-1.27 (m, 9H, $CH_{3(Ind)}$).^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) = 142.0 (C_{Ar}), 142.3 (CH_{NCN}), 142.1 (C_{Ar}), 141.1 (C_{Ar}), 140.6 (C_{Ar}), 131.1 (CH_{Ar}), 130.4 (CH_{Ar}), 129.4 (CH_{Ar}), 128.6 (CH_{Ar}), 127.6 (CH_{Ind}), 127.3 (CH_{Ind}), 126.9 (CH_{Ar}), 126.8 (CH_{Ar}), 125.4 (CH_{Ind}), 123.2 (CH_{imid}), 120.2 (CH_{Ind}), 118.8 (CH_{Ind}), 118.7 (CH_{Ind}), 107.6 (CH_{Ind}), 73.4 (CH_{Ind}), 51.2 (CH_2), 34.3 ($CH_{(Ind)}$), 29.0 ($CH_{3(Ind)}$), 28.8 ($CH_{3(Ind)}$), 22.0 ($CH_{3(IPr*)}$). Anal. Calcd. for $C_{82}H_{72}Cl_2N_2Pd$ C 77.99 H 5.75 N 2.22 Found: C 77.86 H 5.60 N 2.42.

General procedure for the Buchwald-Hartwig reactions: A vial was charged with $[IPr^*\cdot H][Pd(\eta^3\text{-cin})Cl_2]$ (1.2 mg, 0.2 mol%), KO^{t}Bu (62 mg, 0.55 mmol), CPME (1 mL) and a magnetic stir bar and sealed with a screw cap. The mixture was stirred at 60 °C for 1 h. The vial was removed from the heating block and the corresponding solution of aniline and aryl chloride in CPME (1 mL) was added. The reaction was stirred (910 rpm) for 2 h at 80 °C. After this time, the crude mixture was purified by filtration through silica gel and the product isolated by removal of volatiles under reduced pressure.

General procedure for the α-arylation of ketones: A vial was charged with $[IPr^*\cdot H][Pd(\eta^3\text{-cin})Cl_2]$ (1.2 mg, 0.2 mol%), NaO^{t}Bu (53 mg, 0.55 mmol), CPME (1 mL) and a magnetic stir bar and sealed with a screw cap. The mixture was left stirring at 60 °C for 1 h. The vial was removed from the heating block and the corresponding solution of aryl ketone and aryl chloride in CPME (1 mL) was added. The reaction was stirred (910 rpm) for 2 h at 80 °C. Volatiles were removed under reduced pressure and the crude product was purified using flash chromatography (5:95 ethyl acetate/petroleum ether).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Materials, methods, optimization data, detailed synthetic procedures and spectroscopic data and spectra (PDF).

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Notes

The authors declare no conflict of interest.

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REFERENCES

(1) Corbet, J. P.; Mignani, G. Selected Patented Cross-Coupling Reaction Technologies. *Chem. Rev.* **2006**, *106*, 2651–2710.
(2) Johansson Seechurn, C.C.C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.
(3) Colacot, T. J.; Matthey, J. The 2010 Nobel Prize in Chemistry: Palladium-Catalysed Cross-Coupling. *Platinum. Met. Rev.* **2011**, *55*, 84–90.
(4) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.
(5) Magano, J.; Dunetz, J. R. Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of Pharmaceuticals. *Chem. Rev.* **2011**, *111*, 2177–2250.
(6) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564–12649.
(7) Würtz, S.; Glorius, F. Surveying Sterically Demanding N-Heterocyclic Carbene Ligands with Restricted Flexibility for Palladium-catalyzed Cross-Coupling Reactions. *Acc. Chem. Res.* **2008**, *41*, 1523–1533.
(8) Hazari, N.; Melvin, P. R.; Beromi, M. M. Well-defined nickel and palladium precatalysts for cross-coupling. *Nat. Rev. Chem.* **2017**, *1*, 0025.
(9) Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. New Insights into Xantphos/Pd-Catalyzed C−N Bond Forming Reactions: A Structural and Kinetic Study. *Organometallics* **2006**, *25*, 82–91.
(10) Surry, D. S.; Buchwald, S. L. Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361.
(11) Fors, B. P.; Davis, N. R.; Buchwald, S. L. An Efficient Process for Pd-Catalyzed C−N Cross-Coupling Reactions of Aryl Iodides: Insight Into Controlling Factors. *J. Am. Chem. Soc.* **2009**, *131*, 5766–5768.
(12) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Design and preparation of new palladium precatalysts for C–C and C–N cross-coupling reactions. *Chem. Sci.* **2013**, *4*, 916–920.
(13) Pommella, A.; Tomaiuolo, G.; Chartoire, A.; Caserta, S.; Toscano, G.; Nolan, S. P.; Guido, S. Palladium-N-heterocyclic carbene (NHC) catalyzed C–N bond formation in a continuous flow microreactor. Effect of process parameters and comparison with batch operation. *Chem. Eng. J.* **2013**, *223*, 578–583.
(14) Chartoire, A.; Boreux, A.; Martin, A. R.; Nolan, S. P. Solvent-free aryl amination catalysed by [Pd(NHC)] complexes. *RSC Adv.* **2013**, *3*, 3840-3843.
(15) Sunesson, Y.; Lime, E.; Lill, S. O. N.; Meadows, R. E.; Norrby, P. Role of the Base in Buchwald–Hartwig Amination. *J. Org. Chem.* **2014**, *79*, 11961–11969.
(16) Zhang, Y.; César, V.; Storch, G.; Lugan, N.; Lavigne, G. Skeleton Decoration of NHCs by Amino Groups and its Sequential Booster Effect on the Palladium-Catalyzed Buchwald–Hartwig Amination. *Angew. Chem. Int. Ed.* **2014**, *53*, 6482–6486.
(17) Le Duc, G.; Meiries, S.; Nolan, S. P. Effect of Electronic Enrichment of NHCs on the Catalytic Activity of [Pd(NHC)(acac)Cl] in Buchwald–Hartwig Coupling. *Organometallics* **2013**, *32*, 7547–7551.
(18) Marelli, E.; Chartoire, A.; Le Duc, G.; Nolan, S. P. Arylation of Amines in Alkane Solvents by using Well-Defined Palladium–N-Heterocyclic Carbene Complexes. *ChemCatChem* **2015**, *7*, 4021–4024.
(19) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. Modified (NHC)Pd(allyl)Cl (NHC = N-Heterocyclic Carbene) Complexes for Room-Temperature Suzuki−Miyaura and Buchwald−Hartwig Reactions. *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.
(20) Marion, N.; Navarro, O.; Stevens, E. D.; Ecarnot, E. C.; Bell, A.; Amoroso, D.; Nolan, S. P. Modified [(IPr)Pd(R-acac)Cl] Complexes: Influence of the acac Substitution on the Catalytic Activity in Aryl Amination. *Chem. Asian J.* **2010**, *5*, 841–846.
(21) Cawley, M. J.; Cloke, F. G. N.; Fitzmaurice, R. J.; Pearson, S. E.; Scott, J. S.; Caddick, S. Development of a practical Buchwald–Hartwig amine arylation protocol using a conveniently prepared [Pd(NHC)(R-allyl)Cl] catalyst. *Org. Biomol. Chem.* **2008**, *6*, 2820–2825.
(22) *Science of Synthesis: N-Heterocyclic Carbenes in Catalytic Organic Synthesis*, vol 1 & 2 (Nolan, S. P.; Cazin, C. S. J.; Eds.) Thieme, Stuttgart, **2016**.
(23) (a) Herrmann, W. A. N-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309; (b) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An overview of N-heterocyclic carbenes. *Nature* **2014**, *510*, 485–496; (c) Froese, R. D. J.; Lombardi, C.; Pompeo, M.; Rucker, R. P.; Organ, M. G. Designing Pd–N-Heterocyclic Carbene Complexes for High Reactivity and Selectivity for Cross-Coupling Applications. *Acc. Chem. Res.* **2017**, *50*, 2244–2253.
(24) For recent overview of electronic and steric properties, see: (a) Nelson, D. J.; Nolan, S. P. Quantifying and understanding the electronic properties of N-heterocyclic carbenes. *Chem. Soc. Rev.* **2013**, *42*, 6723–6753; (b) Gómez-Suárez, A.; Nelson, D. J.; Nolan, S. P. Quantifying and understanding the steric properties of N-heterocyclic carbenes. *Chem. Commun.* **2017**, *53*, 2650-2660; (c) Huynh, H. V. Electronic Properties of N-Heterocyclic Carbenes and Their Experimental Determination. *Chem. Rev.* **2018**, *118*, 9457–9492.
(25) Chartoire, A.; Lesieur, M.; Falivene, L.; Slawin, A. M. Z.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P. [Pd(IPr*)(cinnamyl)Cl]: An Efficient Pre-catalyst for the Preparation of Tetra-ortho-substituted Biaryls by Suzuki–Miyaura Cross-Coupling. *Chem. Eur. J.* **2012**, *18*, 4517–4521.
(26) Martin, A. R.; Chartoire, A.; Slawin, A. M. Z.; Nolan, S. P. Extending the utility of [Pd(NHC)(cinnamyl)Cl] precatalysts: Direct arylation of heterocycles. *Beilstein J. Org. Chem.* **2012**, *8*, 1637–1643.
(27) Chartoire, A.; Lesieur, M.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. Highly Active Well-Defined Palladium Precatalysts for the Efficient Amination of Aryl Chlorides. *Organometallics* **2011**, *30*, 4432–4436.
(28) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. Rapid Room Temperature Buchwald–Hartwig and Suzuki–Miyaura Couplings of Heteroaromatic Compounds Employing Low Catalyst Loadings. *Chem. Eur. J.* **2006**, *12*, 5142–5148.
(29) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. Cross-Coupling and Dehalogenation Reactions Catalyzed by (N-Heterocyclic carbene)Pd(allyl)Cl Complexes. *J. Org. Chem.* **2004**, *69*, 3173–3180.
(30) Chartoire, A.; Claver, C.; Corpet, M.; Krinsky, J.; Mayen, J.; Nelson, D. J.; Nolan, S. P.; Pen Afiel, I.; Woodward, R.; Meadows, R. E. Recyclable NHC Catalyst for the Development of a Generalized Approach to Continuous Buchwald–Hartwig

Reaction and Workup. *Org. Process Res. Dev.* **2016**, *20*, 551–557.
(31) Bastug, G.; Nolan, S. P. Carbon–Sulfur Bond Formation Catalyzed by [Pd(IPr*OMe)(cin)Cl] (cin = cinnamyl). *J. Org. Chem.* **2013**, *78*, 9303-9308.
(32) Izquierdo, F.; Chartoire, A.; Nolan, S. P. Direct S-Arylation of Unactivated Arylsulfoxides Using [Pd(IPr*)(cin)Cl]. *ACS Catal.* **2013**, *3*, 2190–2193.
(33) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. Well-Defined, Air-Stable (NHC)Pd(Allyl)Cl (NHC = N-Heterocyclic Carbene) Catalysts for the Arylation of Ketones. *Org. Lett.* **2002**, *4*, 4053–4055.
(34) Izquierdo, F.; Corpet, M.; Nolan, S. P. The Suzuki–Miyaura Reaction Performed Using a Palladium–N-Heterocyclic Carbene Catalyst and a Weak Inorganic Base. *Eur. J. Org. Chem.* **2015**, 1920–1924.
(35) Hruszkewycz, D. P.; Balcells, D.; Guard, L. M.; Hazari, N.; Tilset, M. Insight into the Efficiency of Cinnamyl-Supported Precatalysts for the Suzuki–Miyaura Reaction: Observation of Pd(I) Dimers with Bridging Allyl Ligands During Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 7300–7316.
(36) Zinser, C. M.; Nahra, F.; Brill, M.; Meadows, R. E.; Cordes, D. B.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. A simple synthetic entryway into palladium cross-coupling catalysis. *Chem. Commun.* **2017**, *53*, 7990–7993.
(37) For the first reported synthesis and use of IPr and IPr•HCl see: Huang, J.; Nolan, S. P. Efficient Cross-Coupling of Aryl Chlorides with Aryl Grignard Reagents (Kumada Reaction) Mediated by a Palladium/Imidazolium Chloride System. *J. Am. Chem. Soc.* **1999**, *121*, 9889-9890.
(38) Zinser, C. M.; Warren, K. G.; Meadows, R. E.; Nahra, F.; Al-Majid, A. M.; Barakat, A. M.; Islam, M. S.; Nolan, S. P.; Cazin, C. S. J. Towards environmentally friendlier Suzuki–Miyaura reactions with precursors of Pd-NHC (NHC = N-heterocyclic carbene) complexes. *Green Chem.* **2018**, *20*, 3246-3252. In this report, [IPr·H][Pd(η^3-cin)Cl_2], [IPr*·H][Pd(η^3-cin)Cl_2] and [IPent·H][Pd(η^3-cin)Cl_2] have been previously described. For synthesis and characterization data, see Supporting information.
(39) Melvin, P. R.; Balcells, D.; Hazari, N.; Nova, A. Understanding Precatalyst Activation in Cross-Coupling Reactions: Alcohol Facilitated Reduction from Pd(II) to Pd(0) in Precatalysts of the Type (η3-allyl)Pd(L)(Cl) and (η3-indenyl)Pd(L)(Cl). *ACS Catal.*, **2015**, *5*, 5596–5606.
(40) Slater, C. S.; Savelski, M. A method to characterize the greenness of solvents used in pharmaceutical manufacture. *J. Environ. Sci. Heal. Part A* **2007**, *42*, 1595–1605.
(41) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. Expanding GSK's solvent selection guide – embedding sustainability into solvent selection starting at medicinal chemistry. *Green Chem.* **2011**, *13*, 854–862.
(42) Watanabe, K.; Yamagiwa, N.; Torisawa, Y. Cyclopentyl Methyl Ether as a New and Alternative Process Solvent. *Org. Process Res. Dev.* **2007**, *11*, 251–258.
(43) A recent report makes use of a well-defined Ni system to enable the Buchwald-Hartwig reaction of sterically demanding amines: (a) Tassone, J. P.; England, E. V.; MacQueen, P. M.; Ferguson, M. J.; Stradiotto, M. PhPAd-DalPhos: Ligand-Enabled, Nickel-Catalyzed Cross-Coupling of (Hetero)aryl Electrophiles with Bulky Primary Alkylamines. *Angew. Chem. Int. Ed.* **2019**, 58, 2485–2489. Note these couplings at rt have been achieved with Pd-NHC complexes: (b) Marion, N. M.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. Modified (NHC)Pd(allyl)Cl (NHC = N-Heterocyclic Carbene) Complexes for Room-Temperature Suzuki−Miyaura and Buchwald−Hartwig Reactions. *J. Am. Chem. Soc*. **2006**, *128*, 4101–4111.
(44) Martel-Frachet, V.; Kadri, M.; Boumendjel, A.; Ronot, X. Structural requirement of arylindolylpropenones as anti-bladder carcinoma cells agents. *Bioorganic Med. Chem.* **2011**, *19*, 6143-6148.
(45) Zhang, Y.; Lavigne, G.; César, V. Buchwald–Hartwig Amination of (Hetero)Aryl Tosylates Using a Well-Defined N-Heterocyclic Carbene/Palladium(II) Precatalyst. *J. Org. Chem.* **2015**, *80*, 7666–7673.
(46) Brusoe, A. T.; Hartwig, J. F. Palladium-Catalyzed Arylation of Fluoroalkylamines. *J. Am. Chem. Soc.* **2015**, *137*, 8460–8468.
(47) Ge, S.; Green, R. A.; Hartwig, J. F. Controlling First-Row Catalysts: Amination of Aryl and Heteroaryl Chlorides and Bromides with Primary Aliphatic Amines Catalyzed by a BINAP-Ligated Single-Component Ni(0) Complex. *J. Am. Chem. Soc.* **2014**, *136*, 1617-1627.
(48) Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Direct α-Arylation of Ketones. Rate Acceleration by Sterically Hindered Chelating Ligands and Reductive Elimination from a Transition Metal Enolate Complex. *J. Am. Chem. Soc.* **1997**, *119*, 12382-12383.
(49) Palucki, M.; Buchwald, S. L. Palladium-Catalyzed α-Arylation of Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 11108-11109.
(50) Tetsuya, S.; Kawamura, Y.; Miura, M.; Nomura, M. Palladium-Catalyzed Regioselective Mono- and Diarylation Reactions of 2-Phenylphenols and Naphthols with Aryl Halides. *Angew. Chem. Int. Ed.* **1997**, *36*, 1740-1742.

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