DOI: 10.1002/adsc.201600480
Advanced Synthesis & Catalysis

Development of Structurally Diverse N-Heterocyclic Carbene Ligands *via* Palladium-Copper-Catalyzed Decarboxylative Arylation of Pyrazolo[1,5-*a*]pyridine-3-carboxylic Acid

Khyarul Alam,[+a] Seong Min Kim,[+a] Do Joong Kim,[a] and Jin Kyoon Park[a,*]

[a] Department of Chemistry and Institute of Functional Materials, Pusan National University, Busan 609-735, Korea
Fax: (+82)-51-510-7421; Phone: (+82)-51-510-2242
address:; e-mail: pjkyoon@pusan.ac.kr

[+] These authors contributed equally.

Received: May 5, 2016; Revised: June 4, 2016; Published online: ■■ ▮▮, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600480.

Abstract: A series of fused non-classical normal N-heterocyclic carbenes, Pyrpy-NHC precursors derived from pyrazolo[1,5-*a*]pyridines, has been prepared using palladium-copper-catalyzed decarboxylative arylation of pyrazolo[1,5-*a*]pyridine-3-carboxylic acid. Air-stable palladium and rhodium complexes of these ligands have been synthesized *via* mild transmetallation of Ag-Pyrpy-NHC. The structural properties of Rh(Pyrpy-NHC)(COD)Cl complexes were determined *via* X-ray analysis. The measurement of the CO stretching frequencies of dicarbonyl Rh-Pyrpy-NHC complexes revealed that the electron donating strength of Pyrpy-NHC could be tuned by varying the substituents of the aryl group. A catalytic study of the Pd-Pyrpy-NHC complexes revealed promising activity in the Suzuki–Miyaura reaction under ambient atmospheric conditions.

Keywords: carbenes; decarboxylative coupling; ligand design; palladium; rhodium

Introduction

N-Heterocyclic carbenes (NHCs) have been studied extensively in organometallic chemistry and there has been explosive development in the field of transition-metal-catalyzed reactions over the last decades.[1] Although phosphine-metal complexes have shown parallel unique reactivities and selectivities in many reactions, the preference for NHCs over phosphine ligands is due to the excellent stability of NHC-metal complexes towards air and moisture owing to the strong metal-carbene bond[2] as well as high reactivities.[3] Among the currently accepted NHC ligands, the two major classes are the normal NHCs (*n*NHCs), which have a resonance form with all-zero formal charges, and abnormal NHCs (*a*NHCs) or mesoionic carbenes (MICs), which should have a formal charge on the canonical structure.[4]

Since the introduction of the first example by the Crabtree group,[5] great progress has been made in the development of *a*NHCs/MICs[4a,6] because *a*NHCs/MICs, which have a carbon and a nitrogen adjacent to carbene carbon, are known to be stronger sigma donors and sometimes have better reactivity than classical *n*NHCs, which have two adjacent nitrogens.[7] The distinguishable features of *a*NHCs are also observed in the properties of coordinated metal centers, such as the coordination geometry and electron density.[8] Selected examples of *a*NHCs/MICs derived from imidazole (**A**),[9a] triazole (**B**),[9b] and imidazopyridine (**C** and **D**)[9c–d] are shown in Figure 1.

Recently, the Huynh group developed non-classical *n*NHC **E**, where the carbene carbon environment resembles that of *a*NHCs, derived from pyrazole and indazole.[10a–d] Interestingly, they found that Indy-NHC **E** has even more sigma-donating capability than some *a*NHCs. The Zhao group prepared a series of Indy-NHCs, such as **F**, by introducing various *N*-substituents for steric and electronic tuning and reported their catalytic activity in a Au-catalyzed reaction.[10e] Knowing these unique properties of non-classical *n*NHCs, we envisioned using pyrazolo[1,5-*a*]pyridine (Pyrpy) as a new backbone for a non-classical *n*NHC, Pyrpy-NHC (**G**) and surmised that varying *C*-substituents may lead to a wide range of novel properties, since most synthetic tools for NHCs focus only on introducing *N*-substituents for tunable electronic and steric properties. However, we found that having ster-

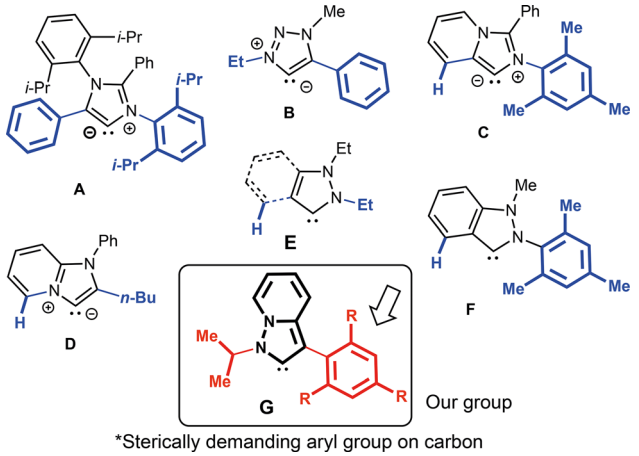


Figure 1. Selected examples of *a*NHCs/MICs (**A**–**D**) and non-classical *n*NHC (**E**–**G**) precursors.

ically demanding *C*-substituents on NHCs is rare owing to the lack of synthetic approaches.

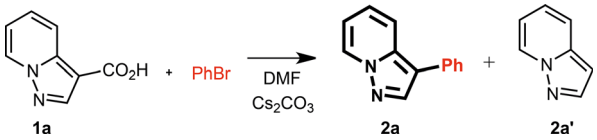
Since pyrazolo[1,5-*a*]pyridines are an important class of biologically active compounds[11] and are also used to develop luminescent compounds,[12] there are a number of reports that describe the facile synthesis of 2-substituted or 2,3-disubstituted pyrazolo[1,5-*a*]-pyridines,[13] but few synthetic methods for 3-substituted pyrazolo[1,5-*a*]pyridine derivatives have been reported (Scheme 1).[14] Conventional multistep coupling methods for the synthesis of 3-substituted derivatives suffer from limited scope, low yield, and use of expensive starting materials.[14a–b] Furthermore, recent direct C-3 arylations of pyrazolo[1,5-*a*]pyridines developed by the Wu group required four equivalents of aryl iodide with 30 h of reaction time.[14c] Regarding the development of pyrazolo[1,5-*a*]pyridine-based NHC ligands, a better synthetic method for sterically demanding 3-substituted pyrazolo[1,5-*a*]pyridines was needed. We surmised that decarboxylative arylations would be more flexible synthetic alternatives, because pyrazolo[1,5-*a*]pyridine-3-carboxylic acids are easy to access,[15] and utilizing aryl bromides as substrates in a short reaction time could be beneficial. Herein, we report the synthesis of 3-substituted pyrazolo[1,5-*a*]pyridines and Pyrpy-NHC precursors *via* decarboxylative coupling reactions and N-alkylations along with the characterizations of their metal complexes (Rh-Pyrpy-NHC and Pd-Pyrpy-NHC) and the catalytic activities of Pd-Pyrpy-NHC complexes.

Results and Discussion

Decarboxylative arylation of pyrazolo[1,5-*a*]pyridine-3-carboxylic acid

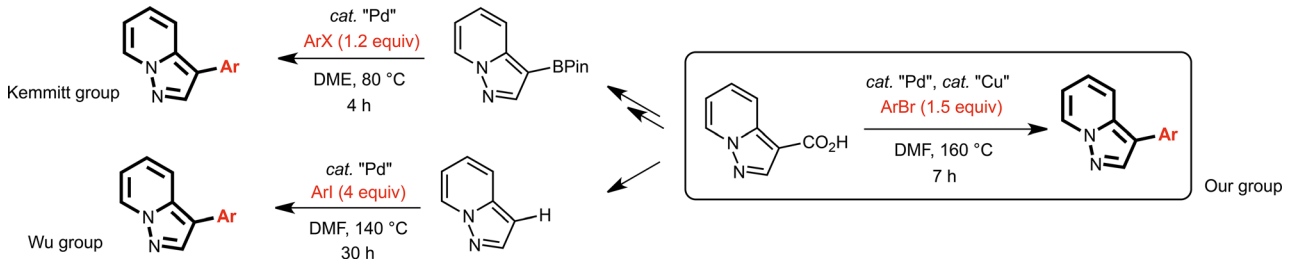
Since the Nilsson group introduced the decarboxylative Ullmann reaction,[16] many practical methods have been developed.[17] We began by testing the typical conditions developed by the Forgione and Bilodeau group (Table 1).[18] In the presence of Bu_4NCl, we obtained arylated product **2a** in 52% yield and protodecarboxylated product **2a'** in 47% yield

Table 1. Screening of decarboxylative coupling using Pd catalysts.[a]



Entry	Catalyst	Additive	Yield [%] of **2a**/**2a'**[b]
1	$Pd[P(tBu)_3]_2$	Bu_4NCl	52/47
2	$Pd[P(tBu)_3]_2$	–	56/26
3[c]	$Pd(OAc)_2 + P(tBu)_3$	Bu_4NCl	29/28(43)[d]
4[c]	$Pd(OAc)_2 + P(tBu)_3$	–	31/0
5[e]	$Pd[P(tBu)_3]_2$	–	<5/95
6[f]	$Pd[P(tBu)_3]_2$	–	0/100

[a] Conditions: pyrazolo[1,5-*a*]pyridine-3-carboxylic acid, **1a** (1.0 equiv), bromobenzene (2.0 equiv), Pd catalyst (5 mol%), Cs_2CO_3 (1.5 equiv), additive (1.0 equiv), DMF (0.1 M), 160 °C.
[b] Yield based on ^1H NMR using dibromomethane as an internal standard.
[c] $P(tBu)_3 \cdot HBF_4$ (5 mol%) was used.
[d] Isolated yield of butyl ester is shown in parentheses.
[e] In toluene.
[f] In dioxane.

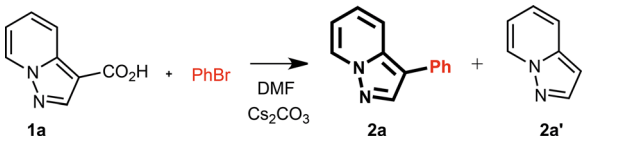


Scheme 1. Synthesis of 3-substituted pyrazolo[1,5-*a*]pyridines.

(entry 1).[19] Although protodecarboxylation decreased in the absence of Bu_4NCl, the amount of the arylated product did not increase (entry 2). Interestingly, when we added $Pd(OAc)_2$ and $P(tBu)_3{\cdot}HBF_4$ in the presence of Bu_4NCl, butyl ester was isolated in 43% yield from the reaction of **1a** with Bu_4NCl before the decarboxylative coupling (entry 3). We obtained the arylated product in 31% yield with no formation of the protodecarboxylated product in the absence of Bu_4NCl (entry 4). Non-polar solvents, toluene and 1,4-dioxane, gave little or no desired product but mostly protodecarboxylated product (entries 5 and 6).

After we found that the Pd-only conditions did not work well, we decided to test the Pd/Cu bimetallic system developed by the Goossen group (Table 2).[20] Under these conditions (5 mol% of $Pd[P(tBu)_3]_2$, 10 mol% of Cu_2O, and 10 mol% of 1,10-phenanthroline), we obtained the arylated product in 87% yield with 9% of **2a'** (entry 1). Bidentate dppf (1,1′-bis(diphenylphosphino)ferrocene) ligand did not increase the yield of **2a,** but the yield of **2a'** increased (entry 2). Adding $Pd_2(dba)_3$ (dba = dibenzylideneacetone) without using a phosphine ligand gave **2a** and **2a'** in 84% and 10% yields, respectively (entry 3).

Table 2. Decarboxylative coupling under Goossen's conditions.[a]



1a 2a 2a'

Entry	Pd	Cu/Ligand[b]	Yield [%] of **2a**/**2a'**[c]
1	$Pd[P(tBu)_3]_2$	Cu_2O/phen	87/9
2	$Pd(dppf)Cl_2$	Cu_2O/phen	81/16
3	$Pd_2(dba)_3$	Cu_2O/phen	84/10
4	$Pd(PPh_3)_4$	Cu_2O/phen	92/6
5[d]	$Pd(PPh_3)_4$	Cu_2O/phen	58/36
6[e]	$Pd(PPh_3)_4$	Cu_2O/phen	15/74
7	$Pd(PPh_3)_4$	Cu_2O/bipy	30/62
8	$Pd(PPh_3)_4$	CuI/phen	79/11
9	$Pd(PPh_3)_4$	CuCl/phen	97/-
10[f]	$Pd(PPh_3)_4$	CuCl/phen	97/–
11	$Pd(PPh_3)_4$	–	62/26

[a] Conditions: pyrazolo[1,5-*a*]pyridine-3-carboxylic acid, **1a** (1.0 equiv), bromobenzene (2.0 equiv), Pd catalyst (5 mol%), Cu catalyst (10 mol%), ligand (10 mol%), Cs_2CO_3 (1.5 equiv), DMF (0.1 M), 160 °C.
[b] Phen = 1,10-phenanthroline, bipy = 2,2′-bipyridine.
[c] Yield based on ^{1}H NMR using dibromomethane as an internal standard.
[d] K_2CO_3 was used
[e] Ag_2CO_3 was used
[f] Bromobenzene (1.5 equiv) was used.

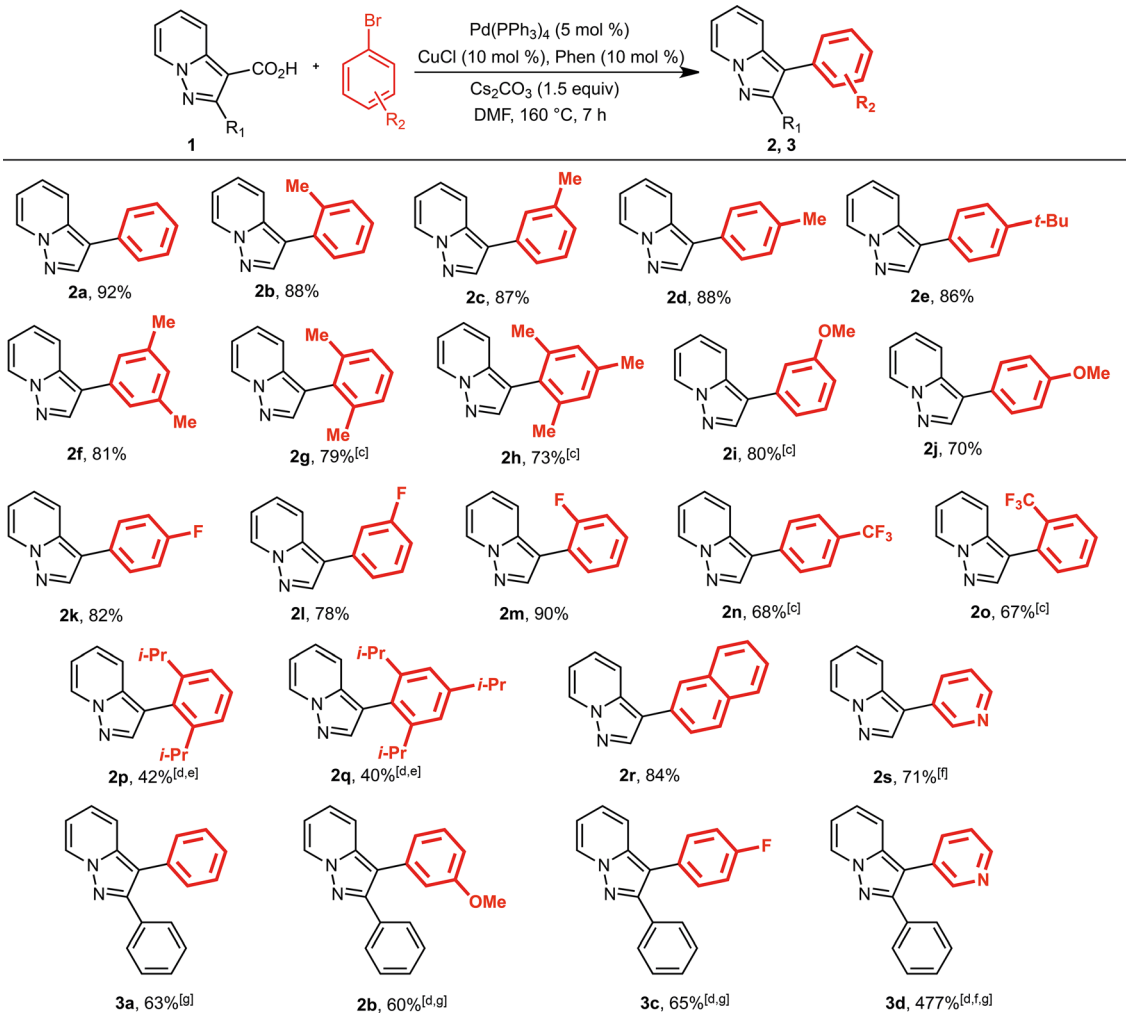
The yield of **2a** increased to 92% with lesser amount of **2a'** using $Pd(PPh_3)_4$ (entry 4). After screening the bases by using K_2CO_3 and Ag_2CO_3, Cs_2CO_3 turned out to be the best (entry 4 vs. 5 and 6). Bipyridine had a detrimental effect, affording **2a'** in 62% yield (entry 7). To our delight, CuCl gave the highest yield (97%) with almost no formation of **2a'** among the copper sources (entry 9 vs. 4 and 8). The amount of bromobenzene could be further reduced without decreasing the yield (entry 10). In the absence of CuCl and 1,10-phenanthroline, the yield of **2a** decreased to 62% with 26% of **2a'** (entry 11).

With the optimized conditions in hand, we investigated the substrate scope with a variety of aryl bromides, and the results are summarized in Table 3. The aryl bromides with a methyl group at the *ortho*, *para*, and *meta* positions reacted smoothly and afforded coupling products **2b–d** in 87–88% yields. A bulky substituent at the *para* position did not affect the yield of product **2e** (86% yield). However, di- and trimethyl-substituted derivatives gave slightly lower yields, especially with substituents at the *ortho* position (**2f–h**). Although aryl bromides with both electron-donating and withdrawing groups were well tolerated to give **2i–m** in 70–90% yields, the CF_3 group resulted in moderate yields for **2n–o** (68% and 67%, respectively). Despite low yields, highly sterically demanding aryl bromides, such as those with a diisopropyl group at the 2 and 4 positions, gave desired products **2p–q** in 42% and 40% yields, respectively. 2-Bromonaphthalene also readily reacted to give **2r** in 84% yield. 3-Bromopyridine was also tolerated, giving 71% yield of **2s.** 2-Substituted pyrazolo[1,5-*a*]pyridine-3-carboxylic acid was also tolerated with 15 mol% of $Pd(PPh_3)_4$. 2,3-Diphenylpyrazolo[1,5-*a*]pyridine **3a** was obtained in 63% yield and the aryl bromide with electron donating and withdrawing group gave moderate yields of **3b** (60%) and **3c** (65%). 3-Bromopyridine gave 47% yield of **3d**.

Synthesis of Pyrpy-NHC ligand precursors

The synthetic pathway for Pyrpy-NHC ligand precursors **4a–g** is outlined in Scheme 2. Treatment of pyrazolo[1,5-*a*]pyridine derivatives with 2-iodopropane at 120 °C led to the formation of pyrazolo[1,5-*a*]pyridinium iodides in good yields. Anion exchange of iodide with chloride was performed simply by passing the solution through a column of ion exchange resin Dowex 1×8 chloride form, and compounds **4a–g** were obtained in quantitative yields. The ^{1}H NMR spectra of compounds **4a–g** showed the characteristic singlet peak at $\delta \approx$ 7.98–9.14 ppm arising from the C-2 proton of pyrazolo[1,5-*a*]pyridinium chloride salt.[22]

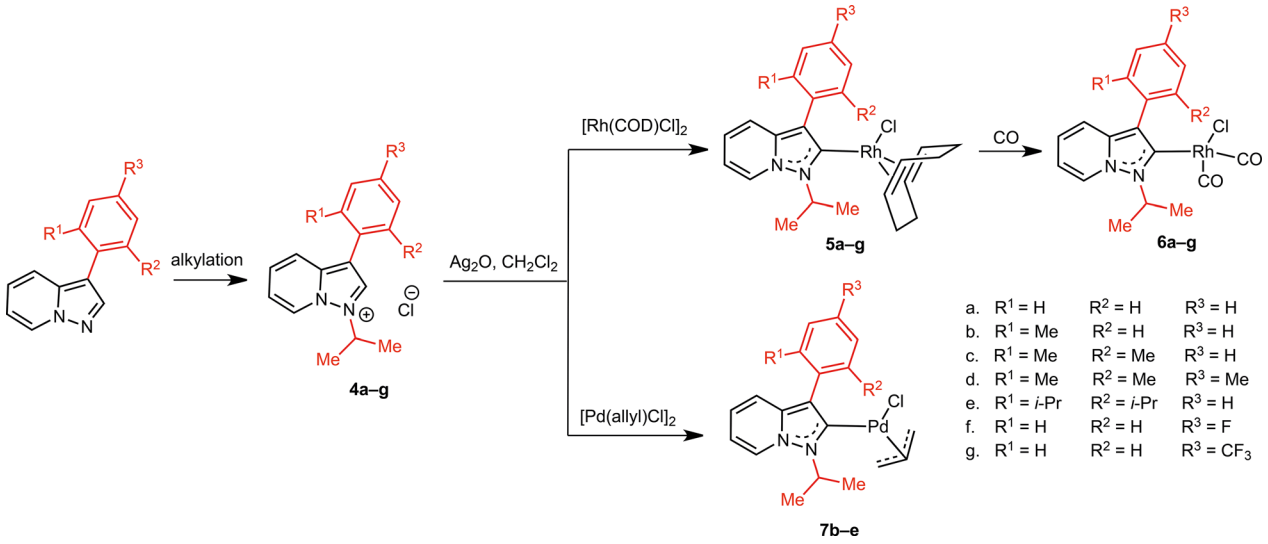
Table 3. Decarboxylative arylations with various aryl bromides.[a,b]



[a] Conditions: pyrazolo[1,5-*a*]pyridine-3-carboxylic acid, **1** (1.0 equiv), aryl bromide (1.5 equiv), Pd catalyst (5 mol%), Cu catalyst (10 mol%), ligand (10 mol%), Cs_2CO_3 (1.5 equiv), DMF (0.1 M), 160 °C, 7 h.
[b] Isolated yield.
[c] Reaction time was 8 h.
[d] Reaction time was 12 h.
[e] Aryl bromide (2.0 equiv) was used.
[f] $Pd[P(tBu)_3]_2$ was used instead because triphenylphosphine oxide was inseparable in the case of $Pd(PPh_3)_4$.
[g] Pd catalyst (15 mol%) was used.

Synthesis and structures of Rh-Pyrpy-NHC complexes

Since silver transmetallation is a well-established method for the synthesis of NHC-metal complexes,[23] we treated **4a–g** with Ag_2O (0.5 equiv) in CH_2Cl_2 to obtain the corresponding Ag-Pyrpy-NHC complexes. In situ addition of $[Rh(COD)Cl]_2$ (0.5 equiv) (COD = 1,5-cyclooctadiene) to the silver reaction mixture afforded corresponding Rh-Pyrpy-NHC complexes **5a–g** in good yields (Scheme 2). All of the Rh complexes were well characterized on the basis of their spectroscopic data. The ^1H NMR spectra of the complexes featured the absence of the characteristic singlet peak arising from the C-2 proton of pyrazolo[1,5-*a*]pyridinium salt at around 7.98–9.14 ppm, and the ^{13}C NMR spectra revealed a doublet peak at $\delta \approx 188$ ppm arising from the C-2 carbon bound to the Rh center. The ^1H NMR spectrum of complex **5b** showed two similar sets of doublet peak at $\approx$ 8.40 ppm, which indicated two structural isomers arising owing to the position of the methyl group (R^1) above or below the ring



Scheme 2. Synthesis of Pyrpy-NHC precursors and their metal (Rh and Pd) complexes.

system. ^{13}C NMR also support this observation showing two characteristic doublet of $C_{carbene}$ bonded to Rh.

Suitable single crystals of complexes **5a** and **5e** for X-ray analysis were obtained *via* careful layering of pentane with a CH_2Cl_2 solution. Their molecular structures are shown in Figure 2. Some selected geometrical parameters are given in Table 4. The coordination sphere is square planar for both complexes. The Rh-$C_{carbene}$ bond length is 2.024(3) Å for **5a** and 2.043(2) Å for **5e**, consistent with a Rh–C single bond. The torsional angle of the pyrazolo[1,5-*a*]pyridine ring system to the coordination plane is 99.8° for **5a** and −112.4° for **5e**, indicating significant deviation in orientation. Also, the torsional angle of the pyrazolo[1,5-*a*]pyridine ring system to the C3-substituted aryl ring is −34.9° for **5a** and 70.1° for **5e**, indicating that the orientation of the aryl group changed with the introduction of steric bulk. To measure the steric bulk provided by the ligands, the %V_{bur} of complexes **5a** and **5e** was calculated using crystallographic data with the help of the Samb*V*ca program developed by Cavallo and co-workers,[24] and %V_{bur} values of 28.7 for **5a** and 31.9 for **5e** were obtained.

Table 4. Selected bond lengths [Å] and angles [°] for complexes **5a** and **5e**.

Bond Param[a]	5a	5e
Rh_1-C_1	2.024(3)	2.043(2)
Rh_1-Cl_1	2.391(8)	2.392(6)
C_1-N_1	1.366(3)	1.372(3)
C_1-C_2	1.408(4)	1.404(3)
N_1-N_2	1.370(3)	1.374(2)
C_2-C_1-N_1	105.8(2)	105.8(2)
C_1-Rh_1-Cl_1	88.62(9)	90.83(6)
Rh_1-C_1-N_1	123.6(2)	120.1(1)
Rh_1-C_1-C_2	130.2(2)	134.1(1)
Cl_1-Rh_1-C_1-C_2	99.8(3)	–112.4(2)
C_1-C_2-C_8(C_{11})-C_9(C_{12})	–34.9(4)	70.1(3)

[a] Atom label for complex **5e** shown in bracket.

Synthesis of dicarbonyl Rh-Pyrpy-NHC complexes

To determine the electronic effects of these new Pyrpy-NHC ligands, the corresponding rhodium dicarbonyl complexes **6a–g**, were synthesized by bubbling CO through solutions of complexes **5a–g** in CH_2Cl_2 at

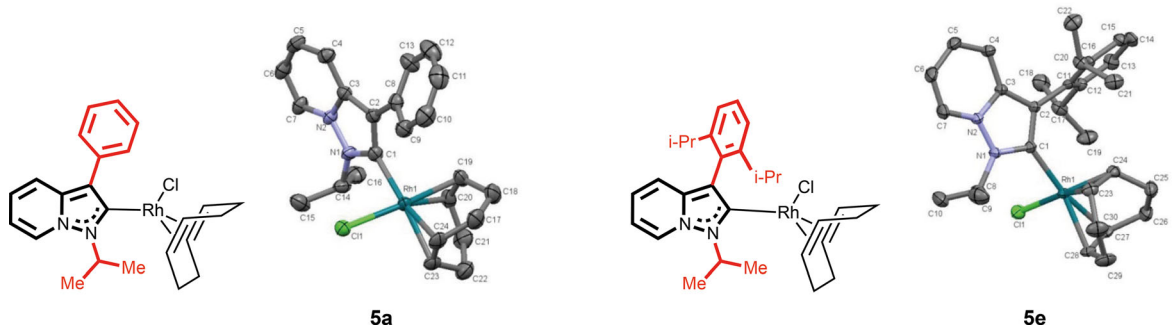


Figure 2. Molecular structures of complexes **5a** and **5e** (H atoms are not shown for clarity).[21]

Table 5. Stretching frequencies for complexes **6a–g**.

Entry	Complex	ν_{CO} (cm^{-1})	ν_{CO}^{av} (cm^{-1})	TEP[a] (cm^{-1})
1	**6a**	2064.7, 1988.0	2026.3	2041.2
2	**6b**	2063.6, 1986.6	2025.1	2040.2
3	**6c**	2064.4, 1986.2	2025.3	2040.4
4	**6d**	2064.1, 1985.9	2025.0	2040.2
5	**6e**	2064.8, 1986.4	2025.6	2040.7
6	**6f**	2067.2, 1990.1	2028.6	2043.0
7	**6g**	2069.1, 1992.4	2030.7	2044.7

[a] TEP calculated by using the following equation: TEP = 0.8001 $\nu_{CO}^{av/Rh}$ + 420.0 cm^{-1}.

room temperature for 15 min, which caused the quick substitution of COD ligands with CO ligands (Scheme 2). The average CO stretching frequencies (ν_{CO}^{av}) of these CO ligands in the complexes ranged from 2025 to 2031 cm^{-1}, as shown in Table 5. To compare the donor strengths of these ligands with those of other carbenes, the TEP (Tolman electronic parameter) was calculated by using ν_{CO}^{av} according to the reference studies by Crabtree and co-workers[25a] and by Nolan and co-workers.[25b] Regarding the TEP of electron-withdrawing substituents, F at the *para* position has a value of 2043 cm^{-1}, while CF_3 has a value of 2045 cm^{-1}, indicating weaker electron-donating properties compared to other Pyrpy-NHCs. Moreover, we found that our Pyrpy-NHC ranked highest among other NHCs, indicating strong sigma electron-donor property (Scheme 3).[26]

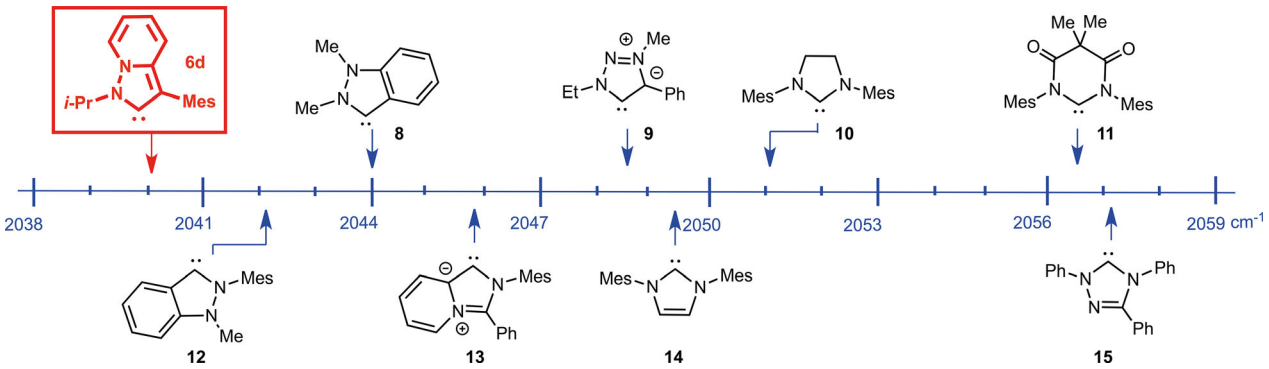
Synthesis of Pd-Pyrpy-NHC complexes

A similar silver transmetallation approach using $[Pd(allyl)Cl]_2$ was used for the synthesis of Pd-Pyrpy-NHC complexes **7b–e** (Scheme 2). Initial attempts with 1-isopropyl-3-phenylpyrazolo[1,5-*a*]pyridinium salt, **4a**, which has no substituent on the *ortho* position of the ancillary phenyl group, failed to give a stable palladium complex. This lack of stability could be attributed to easier rotation of the C3-substituted phenyl group, which pushes the *ortho* phenyl C–H bonds closer to the palladium center. Fortunately, ligand precursors **4b–e** with R^1 and/or R^2 alkyl groups, containing a chloride counter anion, gave desired products **7b–e** in good yields, while an iodide counter anion was unsuccessful. Also, the NMR spectrum of complex **7b** showed two similar sets of peak patterns indicating two structural isomers arising owing to the position of the methyl group (R^1) above or below the ring system.

Catalytic studies of palladium complexes

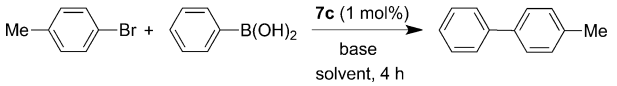
The catalytic activities of the Pd-Pyrpy-NHC complexes in the Suzuki–Miyaura coupling reaction were tested under ambient atmosphere using 4-bromotoluene and phenylboronic acid as model substrates. Using complex **7c**, we optimized the reaction conditions by determining the GC conversion and yield using dodecane as an internal standard, and the results are summarized in Table 6. The reaction was performed using 4-bromotoluene (1.0 equiv) and phenylboronic acid (1.5 equiv) in the presence of 2.0 equiv of base and 1.0 mol% of **7c** at 80 °C. Toluene was the optimum solvent among the tested solvents (1,4-dioxane, *N*,*N*-dimethylformamide (DMF), dimethylacetamide (DMA), CH_3CN, and tetrahydrofuran (THF)) using K_2CO_3 (entries 1–5). The other bases (Cs_2CO_3, Na_2CO_3, KO*t*Bu, K_3PO_4, and KF) were also tested in toluene, but K_2CO_3 turned out to be the best (entries 6–11). When we doubled the amount of phenylboronic acid, yield increased to 99% (entry 12). Decreasing the amount of catalyst to 0.5 mol% resulted in nearly the same yield (entry 13).

To compare the reactivities of Pd-Pyrpy-NHC complexes **7b–e**, we investigated reaction conversion under the optimized condition (Table 7 and Figure 3). We found that complex **7c** revealed the best catalytic activity among others.[27] For the comparison with classical *n*NHC, we tested (SIMes)Pd(allyl)Cl and



Scheme 3. Comparison of TEPs of different NHC ligands.

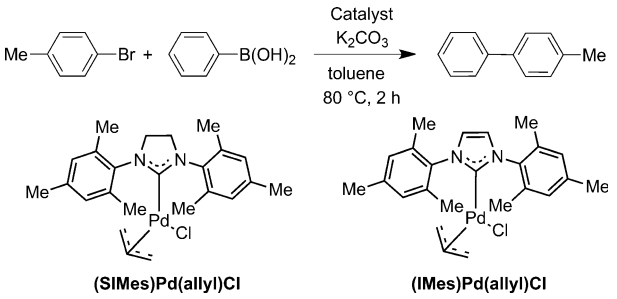
Table 6. Optimization of Suzuki–Miyaura reaction using **7c**.[a]



Entry	Solvent	Base	Yield (%)[b]
1	dioxane	K_2CO_3	<5
2	DMF	K_2CO_3	NR
3	DMA	K_2CO_3	NR
4	CH_3CN	K_2CO_3	<5
5	THF	K_2CO_3	<5
6	toluene	K_2CO_3	84
7	toluene	Cs_2CO_3	18
8	toluene	Na_2CO_3	<5
9	toluene	KO*t*Bu	28
10	toluene	K_3PO_4	79
11	toluene	KF	26
12[c]	toluene	K_2CO_3	99
13[c,d]	toluene	K_2CO_3	98

[a] Reaction conditions: 4-bromotoluene (1.0 equiv), phenylboronic acid (1.5 equiv), base (2.0 equiv), Pd catalyst **7c** (1 mol%), solvent (0.2 M), 80 °C.
[b] GC yield using dodecane as an internal standard.
[c] Phenylboronic acid (2.0 equiv).
[d] 0.5 mol% of **7c** was used

Table 7. Comparison of Pd-Pyrpy-NHC catalysts.[a]



Entry	Catalyst	Conversion/yield (%)
1	**7b**	83/80
2	**7c**	97/96
3	**7d**	77/77
4	**7e**	78/76
5	(SIMes)Pd(allyl)Cl	38/35
6	(IMes)Pd(allyl)Cl	21/11

[a] Reaction conditions: 4-bromotoluene (1.0 equiv), phenylboronic acid (2.0 equiv), K_2CO_3 (2.0 equiv), Pd catalyst (0.5 mol%), toluene (0.2 M), 80 °C.
[b] GC conversion/yield using dodecane as an internal standard.

(IMes)Pd(allyl)Cl[28] in the same condition and found 21% and 38% conversion in 2 h, respectively. The conversion was stalled after 20 min presumably due to the catalyst degradation.

The couplings of phenylboronic acid with a number of aryl halides using complex **7c** were then investigated under the optimized conditions, and the results are summarized in Table 8. Activated, unactivated, and deactivated aryl bromides coupled smoothly with phenylboronic acid to give good to excellent yields (77–

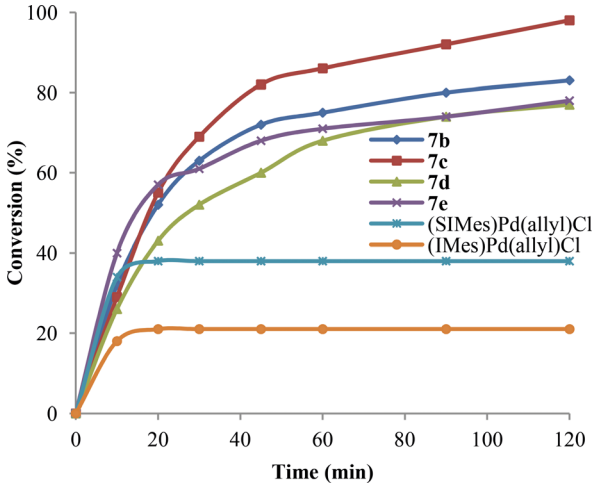
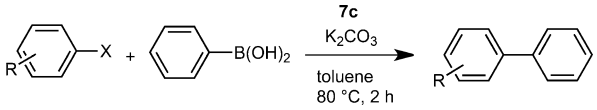


Figure 3. Reaction profiles catalyzed by **7b–e**, (SIMes)Pd(allyl)Cl, and (IMes)Pd(allyl)Cl.

Table 8. Substrate scope.[a]



Entry	X	R	Yield (%)[b]
1	Br	H	98
2	Br	2-Me	79
3	Br	3-Me	96
4	Br	4-Me	94
5	Br	2-CF_3	87
6	Br	2,3-Me,Me	82
7	Br	3,4-Me,Me	79
8	Br	2,6-Me,Me	51
9	Br	2,4,6-Me,Me,Me	62
10	Br	4-*t*Bu	77
11	Br	4-COMe	98
12	Br	4-CN	96
13	Br	4-NO_2	98
14	Br	4-NH_2	92
15	Br	4-OMe	98
16	CH_2Br	H	75
17	Br	2-pyridine	93
18[c]	Cl	4-COMe	24
19[d]	Cl	4-COMe	66

[a] Reaction conditions: aryl halide (1.0 equiv), phenylboronic acid (2.0 equiv), K_2CO_3 (2.0 equiv), catalyst **7c** (0.5 mol%), toluene (0.2 M), 80 °C.
[b] Isolated yield.
[c] K_3PO_4 (2.0 equiv), 120 °C.
[d] K_3PO_4 (2.0 equiv), phenylboronic acid (3.0 equiv), catalyst **7e** (1 mol%), 120 °C.

99%), and a wide range of functional groups was tolerated. However, reduced yields were observed with sterically hindered aryl bromides (entries 8 and 9). Coupling between sp^3-carbons and sp^2-carbons was achieved by using benzyl bromide and phenylboronic acid in 75% yield (entry 16). 2-Bromopyridine also gave the coupling product in excellent yield (entry 17). Aryl chloride derivatives failed to couple with phenylboronic acid under the optimized conditions. However, the desired product was obtained in 24% yield along with the product of homocoupling of phenylboronic acid when the base was changed to K_3PO_4 and temperature was increased to 120°C (entry 18). A longer reaction time did not affect the yield, which may be attributed to catalyst decomposition. The use of catalyst **7e**, which could have better stability owing to the sterically bulky wing tip, with 3.0 equiv of phenylboronic acid under an inert atmosphere increased the yield to 66%, minimizing the formation of the homocoupled product (entry 19).

Conclusions

We have developed an efficient method for direct synthesis of 3-substituted pyrazolo[1,5-*a*]pyridine derivatives *via* decarboxylative arylation using a Pd/Cu bimetallic system. This method can also be applied to the synthesis of multi-substituted pyrazolo[1,5-*a*]pyridine derivatives. We have also designed and synthesized a series of Pyrpy-NHC ligand precursors derived from the pyrazolo[1,5-*a*]pyridine backbone. Air-stable Pd and Rh complexes of these ligands were synthesized *via* mild transmetallation of Ag-Pyrpy-NHC to the corresponding metal complexes and characterized using X-ray and NMR analysis. The Pd-Pyrpy-NHC complexes showed promising catalytic activity in the Suzuki–Miyaura reaction.

Experimental Section

General information

All reagents were prepared using chemicals obtained from commercial sources and used without purification unless otherwise noted. Decarboxylative arylation reactions were performed in 7 mL vials in an aluminum heating block. All reactions were monitored using GC and ^{1}H NMR and by analytical thin layer chromatography (TLC) using Merck pre-coated silica gel glass plates (0.25 mm) with F254 indicator. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (Cambridge Isotope Laboratories, Inc.) with a 300 MHz Fourier transform spectrometer. Chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. Infrared (IR) spectra are reported in frequency of the absorption (cm^{-1}). High-resolution mass spectra (HRMS) were acquired on a high-resolution Q-TOF mass spectrometer (ionization mode: ESI). Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh).

General procedure for synthesis of 3-substituted pyrazolo[1,5-*a*]pyridines 2a–s

Pyrazolo[1,5-*a*]pyridine-3-carboxylic acid (0.24 mmol), arylbromide derivatives (0.36 mmol), $Pd(PPh_3)_4$ (0.012 mmol), copper(I) chloride (0.024 mmol), 1,10-phenanthroline (0.024 mmol), cesium carbonate (0.36 mmol) and DMF (2.4 mL) were added to screw-capped vial. The reaction mixture was heated to 160°C in an aluminum heating block for 7–12 h. After cooling to room temperature, the reaction mixture was filtered through Celite and washed with CH_2Cl_2. The solvent was concentrated and the residue was purified by silica gel flash chromatography to afford the desired products **2a–s.**

General method for the synthesis of ligand precursors 4a–g

A septum-capped vial (7 mL) was charged with 3-substituted pyrazolo[1,5-*a*]pyridine derivatives (1.0 mmol) and 2-iodopropane (16.0 mmol). The reaction mixture was then stirred at 120°C for 24–48 h. Subsequently, Et_2O (2 mL) was added. The resulting precipitate was filtered off and recrystallized from CH_2Cl_2/Et_2O. A solution of the above iodonium salt in MeOH was passed through a column of Dowex 1×8 chloride anion exchange beads. MeOH was removed under reduced pressure and the resulting precipitate was recrystallized from CH_2Cl_2/Et_2O to give analytically pure products **4a–g**.

General method for the synthesis of rhodium complexes 5a–g

To a solution of pyrazolo[1,5-*a*]pyridinium chloride salt (0.1 mmol) in dry CH_2Cl_2, Ag_2O (0.05 mmol) was added, and the mixture was stirred at room temperature in the dark for 3–16 h. The reaction mixture was filtered through Celite to give a clear solution. $[Rh(COD)Cl]_2$ (0.05 mmol) was added to the solution, and the mixture was stirred for 4 h. The suspension was filtered through Celite and the solvent was removed under reduced pressure. Analytically pure compounds **5a–g** were obtained after elution through a short path column of alumina using CH_2Cl_2.

General method for the synthesis of dicarbonyl rhodium complexes 6a–g

Through a solution of complexes **5a–g** in CH_2Cl_2, CO was bubbled for 15 min at room temperature. The solvent was removed under reduced pressure and washed with hexanes to give rhodium dicarbonyl complexes **6a–g**.

General method for the synthesis of palladium complexes 7b–e

To a solution of pyrazolo[1,5-*a*]pyridinium chloride (0.1 mmol) in dry CH_2Cl_2, Ag_2O (0.05 mmol) was added and the mixture was stirred at room temperature in the dark for 3–16 h. The reaction mixture was filtered through Celite to give a clear solution. $[Pd(allyl)Cl]_2$ (0.05 mmol) was added

to the solution, and the mixture was stirred for 4 h. The suspension was filtered through Celite, and the solvent was removed under reduced pressure. Analytically pure compounds **7b–e** were obtained after elution through a short path column of alumina using CH_2Cl_2.

General procedure for the Suzuki–Miyaura reaction

To a 7 mL vial equipped with a magnetic stir bar, catalyst **7c** (0.5 mol%, 0.001 mmol), K_2CO_3 (0.4 mmol), $ArB(OH)_2$ (0.4 mmol), toluene (1.0 mL), and aryl halide (0.2 mmol) were added under ambient atmosphere. The reaction mixture stirred at 80 °C, and the progress of the reaction was monitored by GC. Upon complete consumption of aryl halide, the mixture was allowed to cool to room temperature, quenched with water, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue obtained was purified by column chromatography with Et_2O/EtOAc as the eluent.

Acknowledgements

This work was supported by a 2-Year Research Grant of Pusan National University.

References

[1] a) W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342–1363; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309; b) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824–2870; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813; c) J. D. Egbert, C. S. J. Cazin, S. P. Nolan, *Catal. Sci. Technol.* **2013**, *3*, 912–926; d) K. Riener, S. Haslinger, A. Raba, M. P. Högerl, M. Cokoja, W. A. Herrmann, F. E. Kühn, *Chem. Rev.* **2014**, *114*, 5215–5272; e) S. Dıez-Gonzalez, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612–3676; f) L.-A. Schaper, S. J. Hock, W. A. Herrmann, F. E. Kühn, *Angew. Chem.* **2013**, *125*, 284–304; *Angew. Chem. Int. Ed.* **2013**, *52*, 270–289; g) J. C. Garrison, W. J. Youngs, *Chem. Rev.* **2005**, *105*, 3978–4008.

[2] a) H. Jacobsen, A. Correa, A. Poater, C. Costabile, L. Cavallo, *Coord. Chem. Rev.* **2009**, *253*, 687–703; b) S. Diez-Gonzalez, S. P. Nolan, *Coord. Chem. Rev.* **2007**, *251*, 874–883; c) L. Cavallo, A. Correa, C. Costabile, H. Jacobsen, *J. Organomet. Chem.* **2005**, *690*, 5407–5413.

[3] C. M. Crudden, D. P. Allen, *Coord. Chem. Rev.* **2004**, *248*, 2247–2273.

[4] a) R. H. Crabtree, *Coord. Chem. Rev.* **2013**, *257*, 755–766; b) A. Krüger, M. Albrecht, *Aust. J. Chem.* **2011**, *64*, 1113–1117.

[5] a) S. Gründemann, A. Kovacevic, M. Albrecht, J. W. Faller, R. H. Crabtree, *Chem. Commun.* **2001**, 2274–2275; b) S. Gründemann, A. Kovacevic, M. Albrecht, J. W. Faller, R. H. Crabtree, *J. Am. Chem. Soc.* **2002**, *124*, 10473–10481; c) L. N. Appelhans, D. Zuccaccia, A. Kovacevic, A. R. Chianese, J. R. Miecznikowski, A. Macchioni, E. Clot, O. Eisenstein, R. H. Crabtree, *J. Am. Chem. Soc.* **2005**, *127*, 16299–16311.

[6] O. Schuster, L. Yang, H. G. Raubenheimer, M. Albrecht, *Chem. Rev.* **2009**, *109*, 3445–3478.

[7] a) A. R. Chianese, A. Kovacevic, B. M. Zeglis, J. W. Faller, R. H. Crabtree, *Organometallics* **2004**, *23*, 2461–2468; b) R. Tonner, G. Heydenrych, G. Frenking, *Chem. Asian J.* **2007**, *2*, 1555–1567; c) X. Xu, B. Xu, Y. Li, S. H. Hong, *Organometallics* **2010**, *29*, 6343–6349; d) T. Nakamura, T. Terashima, K. Ogata, S.-I. Fukuzawa, *Org. Lett.* **2011**, *13*, 620–623; e) X. Gong, H. Zhang, X. Li, *Tetrahedron Lett.* **2011**, *52*, 5596–5600; f) S. Saha, T. Ghatak, B. Saha, H. Doucet, J. K. Bera, *Organometallics* **2012**, *31*, 5500–5505; g) M. Heckenroth, E. Kluser, A. Neels, M. Albrecht, *Angew. Chem.* **2007**, *119*, 6409–6412; *Angew. Chem. Int. Ed.* **2007**, *46*, 6293–6296.

[8] a) M. Albrecht, *Chem. Commun.* **2008**, 3601–3610; b) S.-J. Chen, Y.-D. Lin, Y.-H. Chiang, H. M. Lee, *Eur. J. Inorg. Chem.* **2014**, 1492–1501; c) M. Heckenroth, A. Neels, M. G. Garnier, P. Aebi, A. W. Ehlers, M. Albrecht, *Chem. Eur. J.* **2009**, *15*, 9375–9386.

[9] a) E. Aldeco-Perez, A. J. Rosenthal, B. Donnadieu, P. Parameswaran, G. Frenking, G. Bertrand, *Science* **2009**, *326*, 556–559; b) P. Mathew, A. Neels, M. Albrecht, *J. Am. Chem. Soc.* **2008**, *130*, 13534–13535; c) M. Alcarazo, S. J. Roseblade, A. R. Cowley, R. Fernández, J. M. Brown, J. M. Lassaletta, *J. Am. Chem. Soc.* **2005**, *127*, 3290–3291; d) G. Song, Y. Zhang, X. Li, *Organometallics* **2008**, *27*, 1936–1943.

[10] a) H. V. Huynh, Y. Han, R. Jothibasu, J. A. Yang, *Organometallics* **2009**, *28*, 5395–5404; b) R. Jothibasu, H. V. Huynh, *Chem. Commun.* **2010**, *46*, 2986–2988; c) H. Sivaram, R. Jothibasu, H. V. Huynh, *Organometallics* **2012**, *31*, 1195–1203; d) J. C. Bernhammer, N. X. Chong, R. Jothibasu, B. Zhou, H. V. Huynh, *Organometallics* **2014**, *33*, 3607–3617; e) Y. Zhou, Q. Liu, W. Lv, Q. Pang, R. Ben, Y. Qian, J. Zhao, *Organometallics* **2013**, *32*, 3753–3759.

[11] a) J. D. Kendall, A. J. Marshall, A. C. Giddens, K. Y. Tsang, M. Boyd, R. Frederick, C. L. Lill, W.-J. Lee, S. Kolekar, M. Chao, A. Malik, S. Yu, C. Chaussade, C. M. Buchanan, G. W. Rewcastle, B. C. Baguley, J. U. Flanagan, W. A. Denny, P. R. Shepherd, *Med. Chem. Commun.* **2014**, *5*, 41–46; b) B. A. Johns, K. S. Gudmundsson, S. H. Allen, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2858–2862; c) J. Tang, B. Wang, T. Wu, J. Wan, Z. Tu, M. Njire, B. Wan, S. G. Franzblauc, T. Zhang, X. Lu, K. Ding, *ACS Med. Chem. Lett.* **2015**, *6*, 814–818.

[12] K. H. Park, Blue luminescent compounds, WO 2013163019 A1, **2013**.

[13] a) J. J. Mousseau, A. Fortier, A. B. Charette, *Org. Lett.* **2010**, *12*, 516–519; b) J. J. Mousseau, J. A. Bull, C. L. Ladd, A. Fortier, D. S. Roman, A. B. Charette, *J. Org. Chem.* **2011**, *76*, 8243–8261; c) Y. Hoashi, T. Takai, E. Kotani, T. Koike, *Tetrahedron Lett.* **2013**, *54*, 2199–2202; d) D. C. Mohan, C. Ravi, S. N. Rao, S. Adimurthy, *Org. Biomol. Chem.* **2015**, *13*, 3556–3560; e) J. D. Kendall, *Current Organic Chemistry* **2011**, *15*, 2481–2518.

[14] a) P. A. Bethel, A. D. Campbell, F. W. Goldberg, P. D. Kemmitt, G. M. Lamont, A. Suleman, *Tetrahedron* **2012**, *68*, 5434–5444; b) S. Löber, T. Aboul-Fadl, H. Hübner, P. Gmeiner, *Bioorg. Med. Chem. Lett.* **2002**,

12, 633–636; c) H.-C. Wu, J.-H. Chu, C.-W. Li, L.-C. Hwang, M.-J. Wu, *Organometallics* **2016**, *35*, 288–300; we reported one example of decarboxylative coupling using phenyl bromide: d) K. H. Oh, S. M. Kim, M. J. Lee, J. K. Park, *Adv. Synth. Catal.* **2015**, *357*, 3927–3935.

[15] a) Y. Xiong, B. Ullman, J.-S. K. Choi, M. Cherrier, S. Strah-Pleynet, M. Decaire, K. Feichtinger, J. M. Frazer, W. H. Yoon, K. Whelan, E. K. Sanabria, A. J. Grottick, H. Al-Shamma, G. Semple, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1870–1873; b) S. Löber, H. Hübner, P. Gmeiner, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97–102.

[16] M. Nilsson, *Acta Chem. Scand.* **1966**, *20*, 423–426.

[17] For review papers, see: a) N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030–5048; b) S. Rui, L. Lei, *Sci. China Chem.* **2011**, *54*, 1670–1687; c) L. J. Goossen, N. Rodríguez, K. Goossen, *Angew. Chem.* **2008**, *120*, 3144–3164; *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120; d) K. Park, S. Lee, *RSC Adv.* **2013**, *3*, 14165–14182; for recent Pd/Ag-catalyzed arylation, see: e) J.-B. E. Y. Rouchet, C. Schneider, C. Fruit, C. Hoarau, *J. Org. Chem.* **2015**, *80*, 5919–5927; for recent Ag-catalyzed arylation, see: f) J. Kan, S. Huang, J. Lin, M. Zhang, W. Su, *Angew. Chem.* **2015**, *127*, 2227–2231; *Angew. Chem. Int. Ed.* **2015**, *54*, 2199–2203; for recent Ni-catalyzed arylation, see: g) J. M. Crawford, K. E. Shelton, E. K. Reeves, B. K. Sadarananda, D. Kalyani, *Org. Chem. Front.* **2015**, *2*, 726–729. For recent Cu-catalyzed arylation, see; h) L. Chen, L. Ju, K. A. Bustin, J. M. Hoover, *Chem. Commun.* **2015**, *51*, 15059–15062.

[18] P. Forgione, M.-C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey, F. Bilodeau, *J. Am. Chem. Soc.* **2006**, *128*, 11350–11351.

[19] K. Fagnou, M. Lautens, *Angew. Chem.* **2002**, *114*, 26–49; *Angew. Chem. Int. Ed.* **2002**, *41*, 26–47.

[20] L. J. Goossen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662–664.

[21] CCDC 1477499 (**5a**) and CCDC 1477496 (**5e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[22] The distinguishable difference in NMR for both chloride and iodide salt is that the doublet of the C-7 proton of the iodide salt is somewhat downfield shifted compared to that of chloride salt. For an alternative synthetic method for the salt preparation, see: D. J. Kim, K. H. Oh, J. K. Park, *Green Chem.* **2014**, *16*, 4098–4101.

[23] J. C. Garrison, W. J. Youngs, *Chem. Rev.* **2005**, *105*, 3978–4008.

[24] A. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano, L. Cavallo, *Eur. J. Inorg. Chem.* **2009**, 1759–1766.

[25] a) A. R. Chianese, X. Li, M. C. Janzen, J. W. Faller, R. H. Crabtree, *Organometallics* **2003**, *22*, 1663–1667; b) R. A. Kelly, H. Clavier, S. Giudice, N. M. Scott, E. D. Stevens, J. Bordner, I. Samardjiev, C. D. Hoff, L. Cavallo, S. P. Nolan, *Organometallics* **2008**, *27*, 202–210; c) T. Dröge, F. Glorius, *Angew. Chem.* **2010**, *122*, 7094–7107; *Angew. Chem. Int. Ed.* **2010**, *49*, 6940–6952.

[26] The TEPs of NHCs were calculated according to the following equation. TEP = $0.8001\nu_{CO}^{av/Rh}$ + 420.0 cm^{-1} and TEP = $0.8475\nu_{CO}^{av/Ir}$ + 336.2 cm^{-1}; a) R. Jothibasu, H. V. Huynh, *Chem. Commun.* **2010**, *46*, 2986–2988; for (NHC)Rh(CO)$_2$Cl complex **8**, ν_{CO}^{sym} = 2069, ν_{CO}^{asym} = 1991; b) P. Mathew, A. Neels, M. Albrecht, *J. Am. Chem. Soc.* **2008**, *130*, 13534–13535; for (NHC)Rh(CO)$_2$Cl complex **9**, ν_{CO}^{sym} = 2075, ν_{CO}^{asym} = 1996; c) K. Denk, P. Sirsch, W. A. Herrmann, *J. Organomet. Chem.* **2002**, *649*, 219–224; for (NHC)Rh(CO)$_2$Cl complex **10**, ν_{CO}^{sym} = 2081, ν_{CO}^{asym} = 1996; d) V. César, N. Lugan, G. Lavigne, *Eur. J. Inorg. Chem.* **2010**, 361–365; for (NHC)Rh(CO)$_2$Cl complex **11** (in cm^{-1}), ν_{CO}^{sym} = 2086, ν_{CO}^{asym} = 2005; e) Y. Zhou, Q. Liu, W. Lv, Q. Pang, R. Ben, Y. Qian, J. Zhao, *Organometallics* **2013**, *32*, 3753–3759; for (NHC)Rh(CO)$_2$Cl complex **12**, ν_{CO}^{sym} = 2068, ν_{CO}^{asym} = 1987; f) M. Alcarazo, S. J. Roseblade, A. R. Cowley, R. Fernández, J. M. Brown, J. M. Lassaletta, *J. Am. Chem. Soc.* **2005**, *127*, 3290–3291; for (NHC)Rh(CO)$_2$Cl complex **13**, ν_{CO}^{sym} = 2072, ν_{CO}^{asym} = 1992; g) C. A. Urbina-Blanco, X. Bantreil, H. Clavier, A. M. Z. Slawin, S. P. Nolan, *Beilstein J. Org. Chem.* **2010**, *6*, 1120–1126; for (NHC)Rh(CO)$_2$Cl complex **14**, ν_{CO}^{sym} = 2077, ν_{CO}^{asym} = 1996; h) R. A. Kelly, H. Clavier, S. Giudice, N. M. Scott, E. D. Stevens, J. Bordner, I. Samardjiev, C. D. Hoff, L. Cavallo, S. P. Nolan, *Organometallics* **2008**, *27*, 202–210; for (NHC)Ir(CO)$_2$Cl complex **15**, ν_{CO}^{sym} = 2072, ν_{CO}^{asym} = 1989.

[27] Base upon the similar TEP values of **7c** and **7d**, sigma donation should not be the only factor for reactivity.

[28] L. Canovese, F. Visentin, C. Levi, A. Dolmella, *Dalton Trans.* **2011**, *40*, 966–981.