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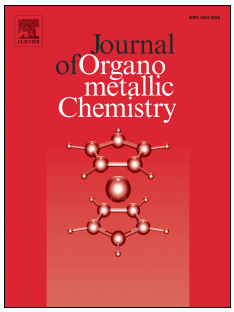

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[Pd(IPr*R)(acac)Cl]: Efficient Bulky Pd-NHC catalyst for Buchwald-Hartwig C-N cross-coupling reaction

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ABSTRACT:

A series of bulky palladium catalysts based on N-heterocyclic carbene, (Pd(NHC)(acac)Cl:

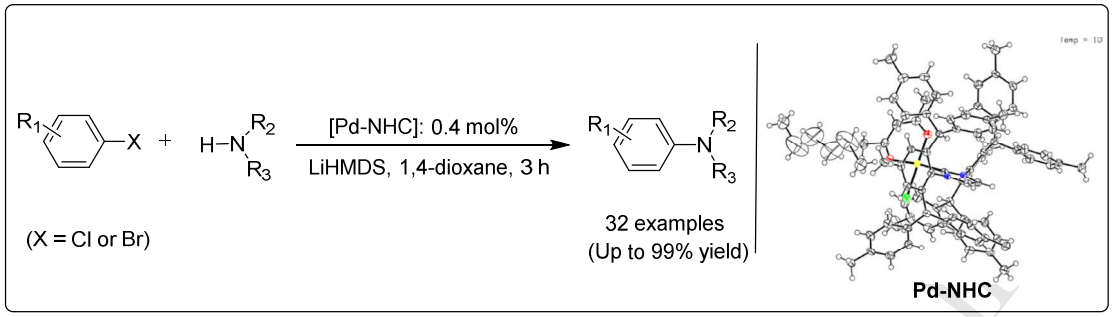
NHC = IPr*me = N,N'-bis(2,6-bis(di-p-tolylmethyl)-4-methylphenyl)-imidazol-2-ylidene, Pd(IPr*me)(acac)Cl;

NHC = IPr*ipr = N,N'-bis(2,6-bis(di-4-isopropylphenyl)-4-methylphenyl)-imidazol-2-ylidene, Pd(IPr*ipr)(acac)Cl;

and NHC = IPr*tBu = N,N'-bis(2,6-bis(di-4-(tert-butyl)phenyl)- 4-methylphenyl)-imidazol-2-ylidene, Pd(IPr*tBu)(acac)Cl;

acac = acetylacetonate), have been designed and synthesized. These three new catalysts showed much better catalytic activity in the Buchwald−Hartwig arylamination coupling reaction as compare to the earlier congener (IPr*)Pd(acac)Cl (IPr* = N,N'-bis(2,6-diphenylmethyl)-4-methylphenylimidazol-2-ylidene). The highly active Pd^{II} precatalyst [Pd(IPr*me)(acac)Cl] has been fully explored by using a wide range of substrates with different electronic and steric demands of coupling partners, for which up to 99% isolated yields were obtained. Remarkably, the

moderate isolated yield was obtained for the challenging coupling of the amine bearing very bulky groups.



1. Introduction

Palladium-catalyzed cross-coupling reactions have been extensively studied over the past 30 years[1]. In particular, palladium-catalyzed arylamination has become an important and widely employed method for the formation of C−N bonds[2]. Unlike phosphine-based ligands[3], palladium N-heterocyclic carbene (Pd-NHC) complexes feature significant air and moisture stability and strong σ-donating properties, which make them very user friendly and benefit for the oxidative addition of aryl halides during the catalytic cycle[4]. However, reports of Pd-NHC catalysts used in C-N coupling reactions are still relatively rare[5]. Recent years, the improvement in the design of catalysts, especially the design of ligands' sterical hindrance, promote the development of this field. Sterically demanding ancillary ligands can kinetically stabilize highly reactive low-valent transition metals and permit high catalytic activity[6].

Nolan group have done a systematic work in this filed. They developed the (IPr)Pd(acac)Cl (IPr = N,N′ -bis(2,6-diisopropylphenyl)imidazol-2-ylidene) complex and successfully applied it in Buchwald-Hartwig C-N cross-coupling reactions, achieving desired results in 2006 [5a]. Afterwards, they developed a bulkier catalyst (IPr*)Pd(acac)Cl featuring better stability and excellent catalytic activity, in which the carbene center located in center of a bowl-shaped cavity [4]. The properties of NHCs ligands have a great influence on the performance of Pd- NHC catalysts. The steric hindrance facilitated reductive elimination and stabilization of a low-valent active

intermediate [7]. Therefore, the exploration of even bulkier NHC ligands and study of their catalytic performance to further develop highly active Pd-NHC catalyst would be of great significance. We reasoned that the catalytic activity of Pd-NHC catalyst based on (IPr*)Pd(acac)Cl can be enhanced by simply introducing a bulky substituent group, such as methyl, isopropyl or tert-butyl.

To evaluate this concept, we designed and synthesized a series of Pd(NHC)(acac)Cl catalysts incorporating the bulkier methyl, isopropyl or tert-butyl substituent group in the IPr* units (Figure 1). Subsequently, they were applied in Buchwald-Hartwig C-N cross-coupling reactions and gave rise to much better catalytic activity as expected. Furthermore, the catalytic activity was tunable, and significantly enhance by increasing the steric hindrance of the ligand. Additionally, the theoretical calculations further confirmed that the energy of Pd-C bond in Pd-NHC was reduced with the increasing of the steric hindrance of the NHC ligand, thus resulted in the enhancement of the catalytic activity.

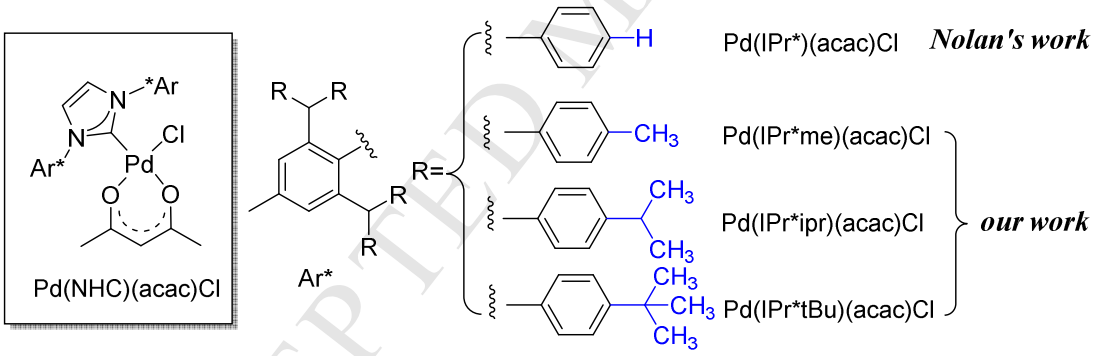
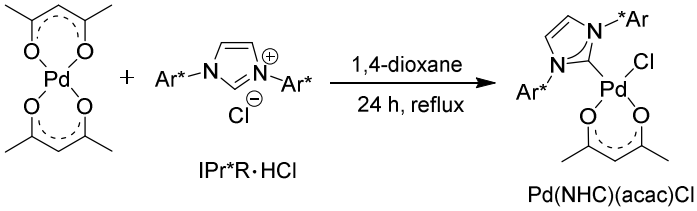


Figure 1. The chemical structure of Pd(NHC)(acac)Cl

2. Results and discussion

Multigram quantities of NHC ligands (IPr*R·HCl: IPr*·HCl, IPr*me·HCl、IPr*ipr·HCl and IPr*tBu·HCl) were successfully prepared (SI scheme 1) using the method reported in the previous literature [8]. Ultimately, the desired palladium N-heterocyclic carbene complexes (Pd-NHC) were obtained through a facile ligand exchange between $Pd(acac)_2$ and the corresponding NHC ligands.

Figure 2. Synthesis of Pd(NHC)(acac)Cl



All the Pd(NHC)(acac)Cl complexes are found to be both air and moisture stable. And the crystal of Pd(IPr*me)(acac)Cl suitable for X-ray diffraction were successfully grown by slow diffusion of hexane into a saturated benzene solution of the complex (Figure 2). The Pd(II) atom adopted a square planar geometry, coordinated to the Cl, two O from acac ligand, and the C from imidazol ring of NHC ligand.

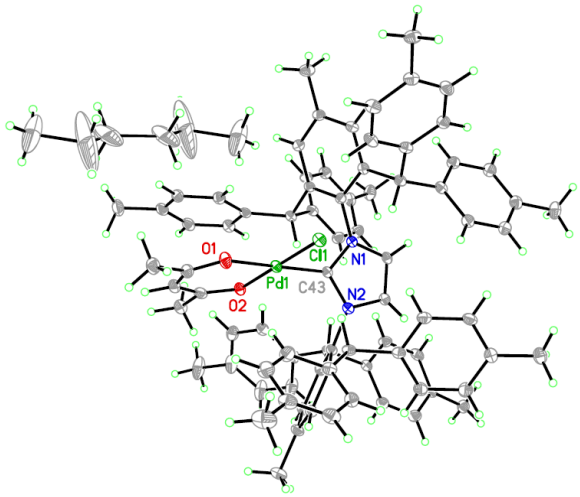
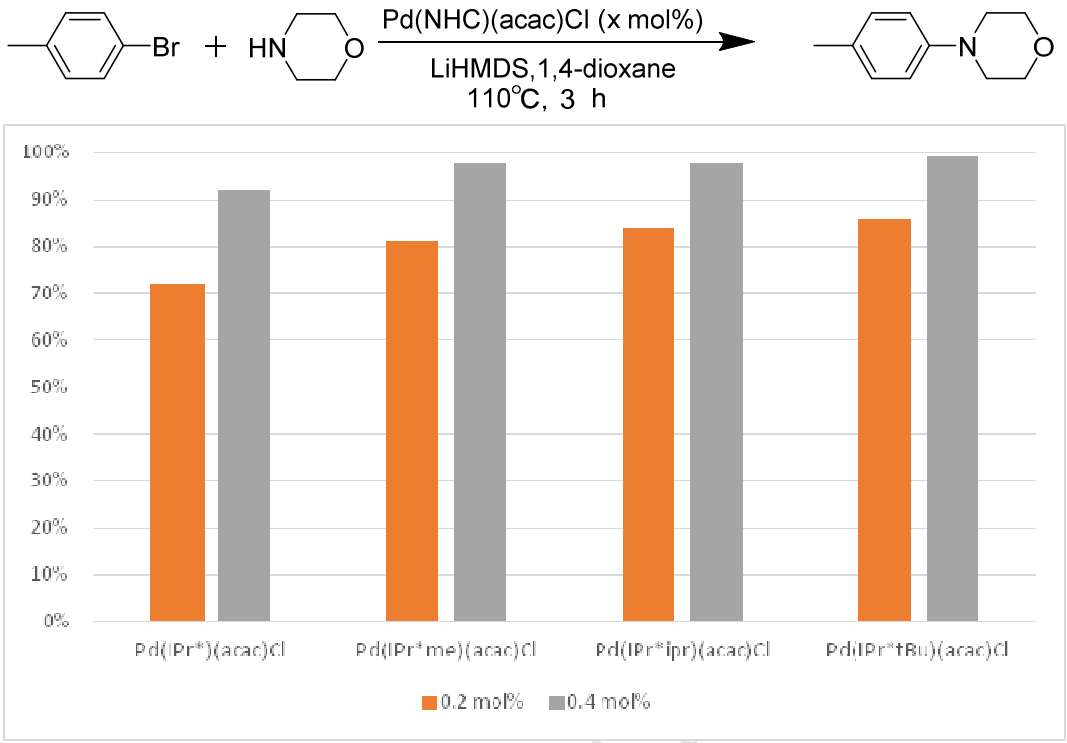


Figure 3. Molecular structure of Pd(IPr*me)(acac)Cl .

Selected bond lengths (Å) and angles (deg): Pd1−C43, 1.965(4); Pd1−O1, 2.026(7); Pd1−O2, 2.022(7); Pd1−Cl1, 2.284(3); C1−Pd1−O1, 86.5(3); O1−Pd1−O2, 93.4(3); C43− Pd1−Cl1, 87.5(3); O2−Pd1−Cl1, 179.59(2).

Figure 4. First Screening of Catalysts Performance.

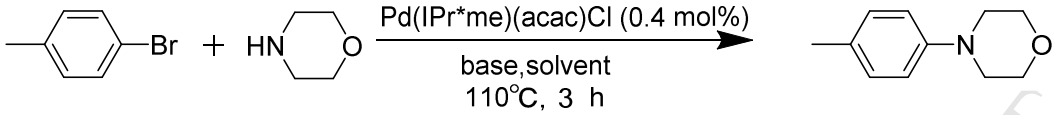


[a]Reagents and conditions: 1-bromo-4-methylbenzene (1 mmol), morpholine (1.2 mmol), Pd precatalyst (0.2-0.4 mol %), solvent (1 mL), base (1.2 mmol), 110℃, 3 h. Conversion of the coupling product based on starting aryl halide determined by NMR.

To evaluate the catalytic activities, we examined the performance of these new catalysts by using the Pd(IPr*)(acac)Cl as the control in the identical condition reported by Nolan[4]. The results clearly indicated that the catalyst incorporated bulkier ligand exhibited a relatively higher catalytic activity as shown in Figure 3. All the three new catalysts exhibited higher activities than Pd(IPr*)(acac)Cl with over 10% increasing of the conversion yield. Considering the easier preparation of IPr*me·HCl, the Pd(IPr*me)(acac)Cl was selected to further expand the substrate scope of C-N cross-coupling reaction.

The optimal base/solvent systems for the Buchwald-Hartwig C-N cross-coupling reaction were of 4-Bromotoluene with N-morpholine then carefully explored under various conditions listed in Table 1. The preliminary data clearly demonstrated that the catalytic arylamination displayed the best performance in the system of LiHMDS as base and 1,4-dioxane as solvent.

Table 1. Further Screening of Base/Solvent System for Amination with [Pd(IPr*me)(acac)Cl][a]



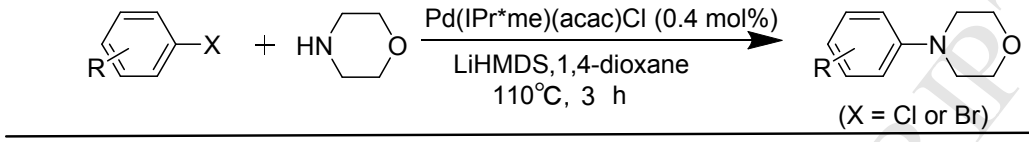
Entry	Solvent	Base	Yield (%)
1	dimethoxyethane	LiHMDS	88
2	dimethoxyethane	KO^{t}Bu	86
3	toluene	LiHMDS	90
4	toluene	KO^{t}Bu	83
5	1,4-dioxane	LiHMDS	98
6	1,4-dioxane	KO^{t}Bu	97

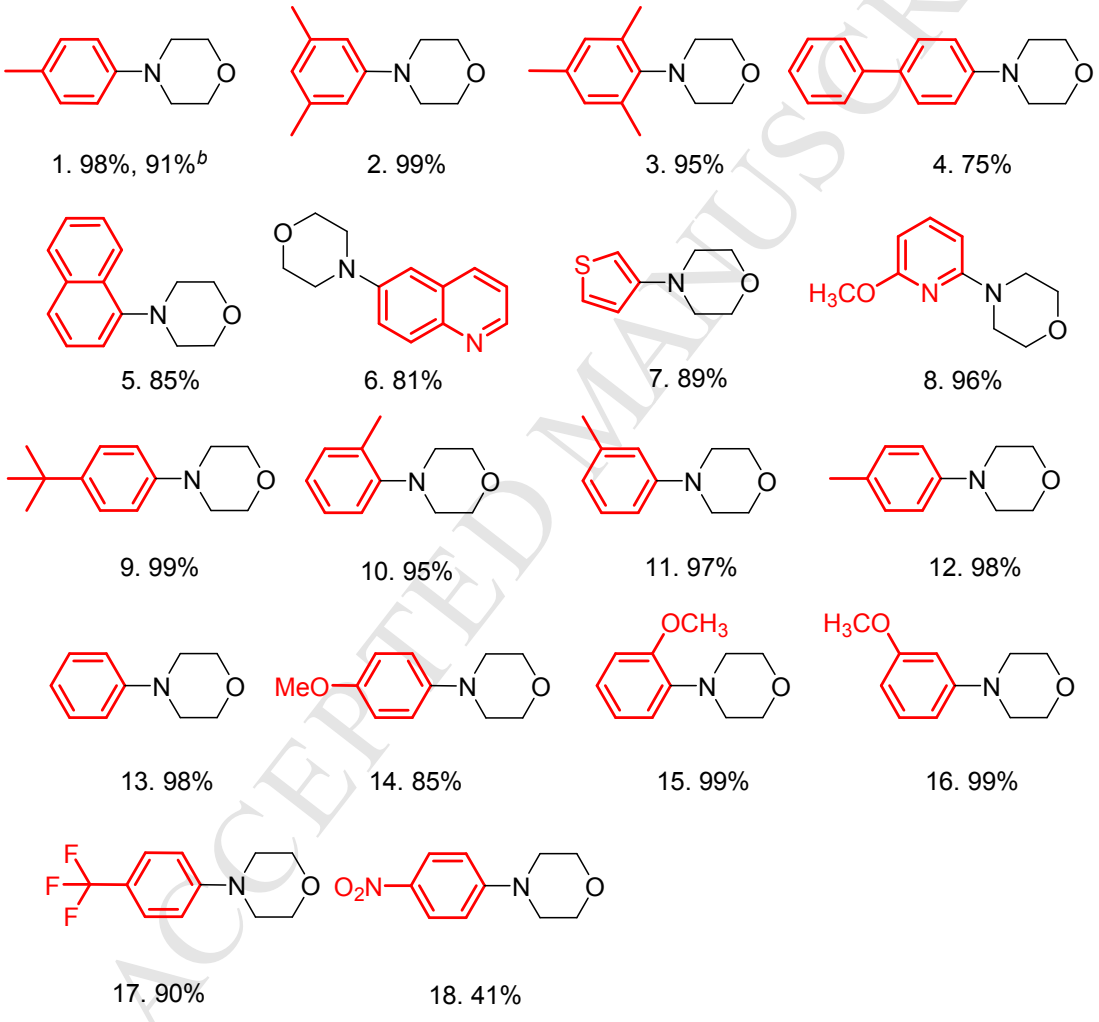
[a]Reagents and conditions: 1-bromo-4-methylbenzene (1 mmol), morpholine (1.2 mmol), Pd precatalyst 1 (0.40 mol %), solvent (1 mL), base (1.2 mmol), 110℃, 3 h. Conversion to coupling product based on starting aryl halide determined by NMR.

The optimized condition, 0.4 mol % of catalyst loading at 110 °C in 1,4-dioxane with LiHMDS for 3h, was established, which was the same as the condition reported by Nolan[4]. Under the optimized base/solvent system, we screened the coupling of different aryl halides with N-morpholine. As listed in Table 2, excellent catalytic activities were successfully achieved with good isolated yields up to 99%. The yield of the hindered aryl bromide (entries 3, 5 and 10) in the coupling reaction was also satisfactory. The inactive aryl chloride also could provide a good yield of 91% (entry 1). The aryl bromides bearing weakly steric groups (entries 9, 11 and 13) and heterocyclic aryl bromides (entries 6,7 and 8) also proved to be suitable partners. Aryl bromides bearing electron-donating groups (entries 14, 15 and 16) showed high activity in the reaction. Aryl bromides bearing electron-withdrawing substituents, including trifluoromethyl group, were well-tolerated, affording the coupled products in a good yield (entry 17), but aryl

bromides bearing nitro substituent coupled with aniline proceeded with only moderate yields (entry 18). According to the relevant literature，we speculated that the catalyst may form a (nitroso)Pd(II) species and lose its activity [9].

Table 2. Arylamination Screening of Various Aryl halides with N-morpholine[a]





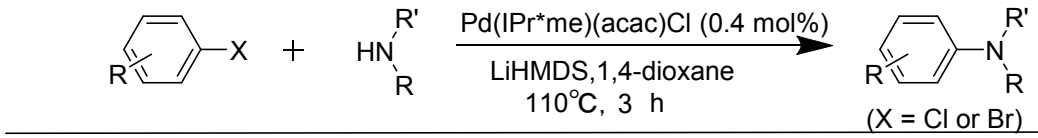
[a]Reagents and conditions: aryl bromide (1 mmol), morpholine (1.2 mmol), Pd precatalyst 1 (0.40 mol %), solvent (1 mL), base (1.2 mmol), 110 ℃, 3 h. Isolated yield after chromatography on silica gel.

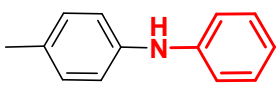
[b]Ar-Cl as material

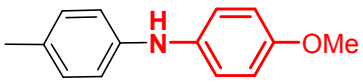
The selected optimized conditions were also generally applied to a wide number of amine substrates. The good to excellent isolated yields were obtained (Table 3). The p-toluidine and aniline were successfully coupled with 4-Bromotoluene under these conditions (entries 1 and 5), affording the coupled products in excellent yields. N-methylaniline also proved to be suitable partners, successfully coupled with aryl chloride (entry 7), aryl bromide (entries 4 and 10) and heterocyclic (entry 8), affording the coupled products in excellent yields. Aniline with electron- donating groups has a higher activity in reaction than that with electron-withdrawing substituents (entry 2 vs entry 3). In addition, piperidine and 4-Bromotoluene (entry 6) were successfully coupled and excellent isolated yields were obtained.

The Buchwald−Hartwig arylamination is a very powerful synthetic tool for the preparation of a wide range of biologically active molecules[10]. However, there was few satisfied results obtained in the C-N cross-coupling reaction based on the substrates with very bulky group[6]. Therefore, we proposed examining the reactivity of several aryl groups bearing hindered substituents, excellent yields were obtained (entries 9, 11, 12 and 13). Surprisingly, a moderate isolated yield could be obtained for the challenging coupling of both sterically and electronically disfavored amine with 4-Bromotoluene (entry 14). Meanwhile, the Buchwald−Hartwig arylamination is also been applicated in small-molecule organic light emitting diodes (OLEDs) component synthesis[11]. And this system is more efficient, obtained an good yield product of 92% (entry 15).

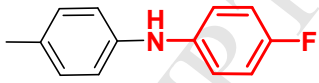
Table 3. Arylamination Screening of Various Aamines with Aryl halides[a]



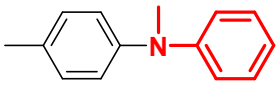

1. 99%



2. 99%



3. 70%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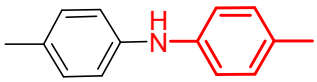
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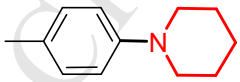
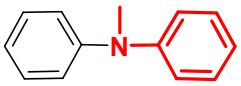
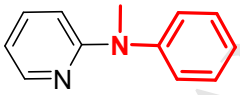
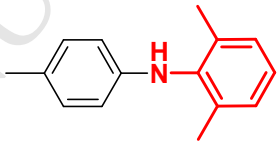
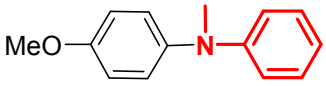

6. 97%

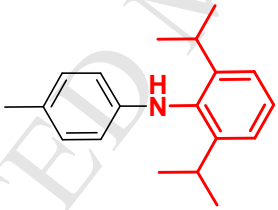

7[b]. 99%

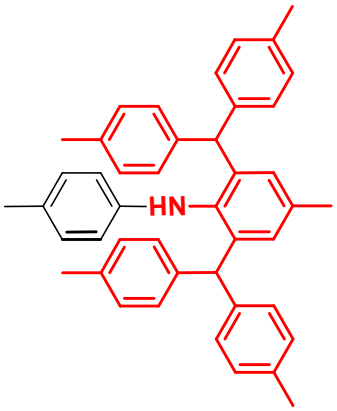

8. 99%


9. 99%

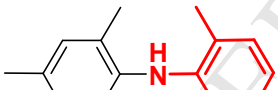


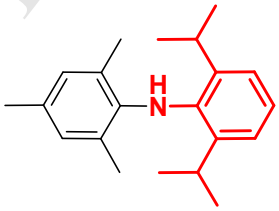
10. 97%

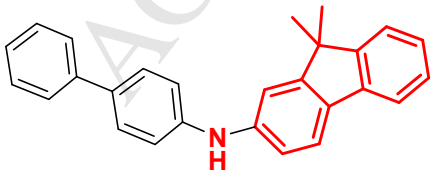

11. 98%



14. 52%, 68%[c]


12. 98%


13. 98%


15. 92%

[a] Reagents and conditions: aryl halides (1 mmol), amines (1.2 mmol), Pd precatalyst 1 (0.40 mol %),

solvent (1 mL), base (1.2 mmol), 110℃, 3 h. Isolated yield after chromatography on silica gel.

[b]Ar-Cl as material.

[c] 12 h.

Besides the experiment, we also used theoretical calculations to verify our assumptions about the subject. All the theoretical calculations were carried out using Gaussian 09 [12]. The density functional theory (DFT) [13] at the gradient-corrected correlation functional PBE1PBE [14] was used to optimize molecular geometries without symmetry constraint. During the optimization processes, the convergent values of maximum force, root-mean-square (RMS) force, maximum displacement, and RMS displacement are set by default. The 6-31G(d，p) [15] basis set was used for C, H, N, O, and Cl, while the Stuttgart–Dresden (SDD) [16] basis set and the effective core potentials (ECP) were employed for Pd. The optimized geometries were confirmed with all real frequencies.

The calculated bond lengths of Pd-Cl and Pd-C of Pd(IPr*me)(acac)Cl by the PBE1PBE functional are 2.30 and 1.97 Å, which are close to the corresponding bond lengths (2.28 and 1.96 Å) in its X-ray structure. The calculated bond energies of the Pd-C bonds for Pd(IPr*)(acac)Cl, Pd(IPr*me)(acac)Cl, Pd(IPr*ipr)(acac)Cl, and Pd(IPr*tBu)(acac)Cl by the PBE1PBE functional are 1.96, 1.88, 1.69, 1.47 eV, respectively, indicating that the increasing steric bulk of the NHCs leads to a decrease of the Pd-C bond energy. The better activity of Pd(IPr*me)(acac)Cl would be related to its lower Pd-C bond energy.

3. Summary

Three new well-designed bulky catalysts Pd(NHC)(acac)Cl (Pd(IPr*me)(acac)Cl, Pd(IPr*ipr)(acac)Cl, and Pd(IPr*tBu)(acac)Cl) were successfully synthesized and applied in the Pd catalyzed C-N cross-coupling reaction. They show better activities than its earlier generation [Pd(IPr*)(acac)Cl] congener, which is attributed to the improving of the sterical hindrance in NHC ligand. [Pd(IPr*me)(acac)Cl] showed excellent performance in C-N bond formation between the aryl-chlorides/bromides

and amines, including sterically hindered and deactivated substrate. Our strategy of simple ligand modification successfully leads to the remarkable promotion of catalyst activity further verify the theory proposed by Nolan and provide the guideline for further exploitation and application of palladium N-heterocyclic carbene catalysts. Further investigations are ongoing in our laboratory to extend its use to other reactions.

4. Experimental section

4.1. Materials and instruments

All aryl halides and amines were used as purchased without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker at 300 and 75 MHz, respectively, in $CDCl_3$ with tetramethylsilane as internal reference standard or DMSO-d^6. High resolution mass spectra (HRMS) were recorded in positive ion mode by Electrospray Ionization (ESI) using time of flight mass spectrometer. Column chromatography was performed using 300-400 mesh silica gel and technical grade solvents.

4.2 General Procedure for the Synthesis of [Pd(NHC)(acac)Cl]

In a Schlenk flask equipped with a magnetic stirring bar, IPr*R·HCl (1.4 eq) and $Pd(acac)_2$ (1 eq) were dissolved in dry 1,4-dioxane (15 mL) under an atmosphere of nitrogen. The reaction mixture was then refluxed at 110℃ for 12 h. After removal of the dioxane solvent, the residue was re-dissolved in CH_2Cl_2, filtered on a pad of silica covered with Celite. The crude product was obtained after evaporating the CH_2Cl_2 solvent. After chromatography on silica gel, the pure complex was obtained as a yellow powder.

4.3. Buchwald−Hartwig Cross-Coupling of Aryl Halides with Primary or Secondary Amines: General Procedure.

A glass vial was charged with [Pd(IPr*me)(acac)Cl] (1) , neat amine (1.1 mmol), and the aryl halide (1 mmol) in dry 1,4-dioxane (1 mL) under an atmosphere of argon，and sealed with a screw cap fitted with a septum. LiHMDS (1.1 mmol) was subsequently injected at room temperature under argon, the reaction mixture was then

refluxed at 110 ℃ for 3 h, After this time, dioxane was evaporated, the crude product was dissolved in CH_2Cl_2. The solution was filtered on a pad of silica covered with Celite, and the pad was eluted with CH_2Cl_2. After chromatography on silica gel, the pure complex was obtained.

Acknowledgments

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Highlights

1) We have design and synthesis a series of bulky palladium catalysts based on N-heterocyclic carbine for C-N cross-coupling reaction.
2) .They all show better activities than its earlier generation [Pd(IPr*)(acac)Cl] congener, which is attributed to the improving of the sterical hindrance in NHC ligand.
3) This strategy of simple ligand modification successfully leads to the remarkable promotion of catalyst activity further verify the theory proposed by Nolan and provide the guideline for further exploitation and application of palladium N-heterocyclic carbine catalysts.