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N-Heterocyclic Carbene–Palladium Complexes [(NHC)Pd(acac)Cl]: Improved Synthesis and Catalytic Activity in Large-Scale Cross-Coupling Reactions

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Abstract: From two commercially available starting materials, improved one-step, multigram-scale syntheses of [(IPr)Pd(acac)Cl] [IPr = *N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; acac = acetylacetonate] and [(IMes)Pd(acac)Cl] [IMes = *N,N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] are described. The catalytic activity of both complexes in cross-coupling reactions has been examined. The most active pre-catalyst, [(IPr)Pd(acac)Cl], has allowed for efficient large-scale (10 mmol) Buchwald–Hartwig and α-ketone arylation reactions to be carried out.

Keywords: *N*-aryl amination; cross-coupling; N-heterocyclic carbene; α-ketone arylation; large-scale; palladium

Introduction

The use of NHC ligands (NHC = N-heterocyclic carbene) is now widespread in numerous areas of organometallic catalysis.[1] Their impressive involvement in ruthenium-catalyzed alkene metathesis[2] is only one of their many possible applications in ligand-supported organometallic transformations.[3] Therefore, simple and efficient protocols to synthesize NHC-containing transition metal complexes are of wide interest.

In the last few years, we have developed several user-friendly procedures leading to diverse families of [(NHC)Pd(L)Cl] (where L = allyl, R-allyl, palladacycle).[4] These protocols allow for the synthesis of air- and moisture-stable palladium pre-catalysts possessing high activities in cross-coupling reactions.[5,6] Along these lines, we recently described the synthesis of two air- and moisture-stable NHC-bearing acetylacetonato complexes, shown in Figure 1, with the formulae [(IPr)Pd(acac)$_2$] **1** and [(IPr)Pd(acac)Cl] **2** [IPr = *N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; acac = acetylacetonate].[7] Complex **1**, bearing a η^1-*C*-bound and a κ^2-*O,O*-bound acac, was prepared from IPr and Pd(acac)$_2$, while complex **2** was prepared by reacting stoichiometrically **1** with HCl.

Complexes **1** and **2** were found to be active in the Buchwald–Hartwig reaction[8] and the α-arylation of ketone[9] involving a wide array of substrates.[10] The higher activity of **2** in these reactions when compared to **1** prompted us to design a one-pot synthesis to avoid the isolation of **1**. The remaining drawback of this early synthetic pathway was the use of the free carbene. We subsequently showed that the NHC salt (that is, NHC·HCl) could be used *in lieu* of the free NHC.[10] Nevertheless, in this synthetic procedure all reagents had to be thoroughly dried under vacuum prior to the reaction being carried out, the use of anhydrous dioxane was mandatory and the reaction had to be performed under an inert atmosphere. Herein, we report an improved synthesis of two [(NHC)Pd(acac)Cl] complexes by simply mixing and heating NHC·HCl with Pd(acac)$_2$ in technical grade dioxane and without any precautions to avoid air. Furthermore, large-scale cross-coupling reactions have been

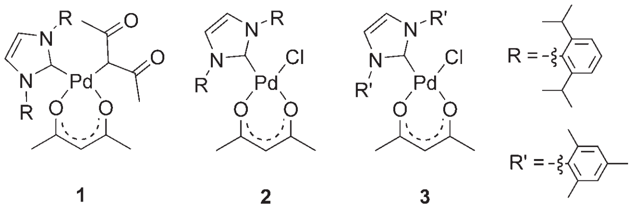


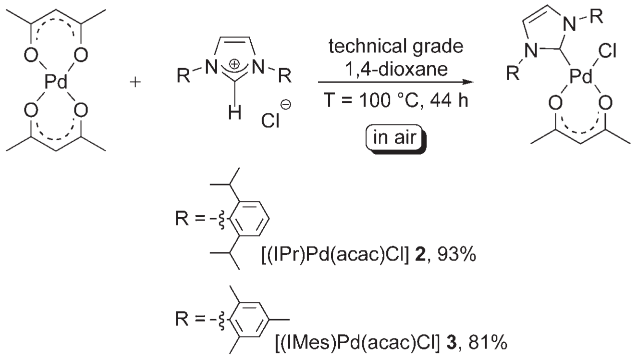
Figure 1. Structures of complexes **1**, **2** and **3**.

performed successfully using the most active precatalyst, **2**.

Results and Discussion

Our desire to design organometallic complexes with potential commercial and industrial applications prompted us to develop a synthetic pathway that would circumvent all the aforementioned drawbacks. The new synthetic pathway leading to precatalysts **2** and **3** is illustrated in Scheme 1.

Direct reaction of a slight excess of the imidazolium salt IPr·HCl with $Pd(acac)_2$ in refluxing 1,4-dioxane for 44 h led to the formation of **2** in high yield (90%). This procedure has been improved since our last report and no longer requires a large excess of NHC·HCl salt (from 1.4 equivs. to 1.1 equivs.).[11]



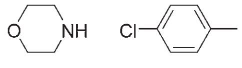
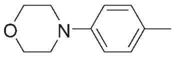
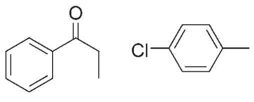
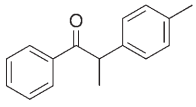
Scheme 1. Improved synthesis of [(NHC)Pd(acac)Cl].

Furthermore, it was discovered that anhydrous conditions are no longer mandatory to obtain the desired complexes. The reaction can be carried out in air with technical grade 1,4-dioxane with no loss of yield. We carried out a synthesis, starting with 7.16 g of $Pd(acac)_2$ to obtain 14.1 g of [(IPr)Pd(acac)Cl] precatalyst (i.e., 93% yield).

The same protocol, albeit in shorter reaction time, can be applied to the synthesis of [(IMes)Pd(acac)Cl] **3** [IMes = *N*,*N′*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] again in very good yield (81%) starting from the corresponding NHC salt, IMes·HCl. Complex **3** has been characterized by ^{1}H and ^{13}C NMR spectroscopy and its purity further established by elemental analysis and high resolution mass spectrometry (HR-MS). Overall, this improved procedure simply requires the aerobic addition of technical grade 1,4-dioxane to a round-bottom flask previously loaded with a 1:1.1 mixture of $Pd(acac)_2$ and NHC·HCl, followed by heating. Every manipulation is done in air and none of the chemicals needs to be dried prior to use.

Next, we examined the activity of these complexes in the Buchwald–Hartwig and the α-ketone arylation reactions. The IPr-bearing complex was found more effective in both palladium-catalyzed couplings (Table 1), presenting superior turnover numbers (TON) and turnover frequencies (TOF). Hence, in reaction A, a difference in TONs was observed for **2** and **3** (98 and 34, respectively), which was even larger in TOFs (196 h^{-1} and 5.7 h^{-1}). The same trend was noticed in reaction B (TONs of 97 and 21, TOFs of 97 h^{-1} and 3.5 h^{-1}). However, if the reaction tempera-

Table 1. Activity of **2** and **3** in cross-coupling reactions.

Substrates	Product	[Pd]	*T* [°C]	Time [h]	Conversion [%][b]
Reaction A 		**2**	50	0.5	98
		3	50	0.5	0
		3	50	6	34
		2	100	0.5	100[c]
		3	100	0.5	97[c]
Reaction B 		**2**	60	1	97
		3	60	1	4
		3	60	6	21
		2	100	0.5	98
		3	100	0.5	87

[a] *Reaction conditions:* Reaction A: morpholine (1.1 mmol), 4-chlorotoluene (1 mmol), **2** or **3** (1 mol%), KO-*t*-Bu (1.1 mmol), DME (1 mL). Reaction B: propiophenone (1.1 mmol), 4-chlorotoluene (1 mmol), **2** or **3** (1 mol%), NaO-*t*-Bu (1.5 mmol), toluene (1 mL).

[b] GC conversions are the average of 2 runs.

[c] Reaction performed in 1,4-dioxane.

ture was increased, pre-catalysts **2** and **3** were found to have comparable performance.

We previously showed that **2** performs efficiently in *N*-arylamination and α-ketone arylation reactions with a variety of substrates, including unactivated aryl chlorides, hindered amines or heteroaromatic ketones.[10] To extend further the scope of our catalytic system and make it an appealing tool for synthetic chemists at an academic or industrial level, we carried out four cross-coupling reactions on a 10-mmol scale.

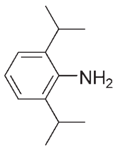
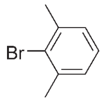
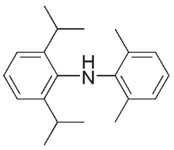
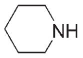
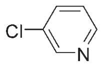
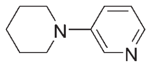
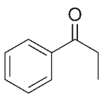
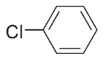
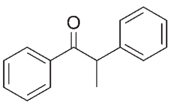
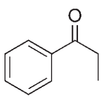
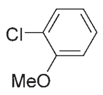
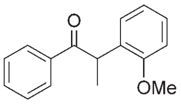
Overall, the present catalytic system was found to be highly efficient in large-scale couplings, yielding at least 88 % of pure isolated arylated product. We deliberately chose challenging substrates to highlight the generality and the efficiency of the process (see Table 2). For example, two extremely hindered partners could be coupled in high yield, producing more than 2.5 g of a tetra-*ortho*-substituted diarylamine (Table 2, entry 1). Strongly unactivated heteroaromatic chlorides[12] reacted also in high yield (entry 2). As an added advantage, the coupling products of both *N*-arylamination reactions were found to be of very good purity (>95 %) by ^{1}H and ^{13}C NMR spectroscopies after a simple extraction with *tert*-butyl methyl ether followed by a filtration through a plug of Celite, therefore avoiding further purification by flash chromatography on silica gel.

For the α-ketone arylation reactions we performed, the same trend in NHC ligand control on catalyst activity was observed as above. Aryl chlorides, inexpensive and widely available when compared to bromides or iodides, reacted smoothly with propiophenone on a 10-mmol scale (entries 3 and 4). Even the strongly unactivated and sterically hindered 2-chloroanisole could be coupled in near 90 % yield.[13]

Conclusions

In summary, a synthetically appealing (one-pot/in air/multigram-scale) procedure, from two commercially available materials [i.e., Pd(acac)$_2$ and NHC·HCl], leading to two NHC-Pd complexes has been described. These indefinitely air-stable complexes are useful pre-catalysts for a number of C−C and C−N bond forming reactions. Studies aimed at capitalizing on this simple protocol and synthesizing related [(NHC)Pd(acac)Cl] complexes are currently ongoing in our laboratories.

Table 2. Large-scale cross-coupling reactions.

Entry	Substrates		Product	Time [h]	Yield [%][b]	Amount of product [g]
1				8	92	2.58
2				4	96	1.43
3				3	93	1.95
4				6	88	2.12

[a] *Reaction conditions:* for entries 1 and 2: amine (10 mmol), aryl halide (10 mmol), **2** (1 mol %), KO-*t*-Bu (11 mmol), DME (10 mL), $T=50$ °C. For entries 3 and 4: ketone (10 mmol), aryl chloride (10 mmol), **2** (1 mol %), NaO-*t*-Bu (15 mmol), toluene (10 mL), $T=60$ °C.

[b] Isolated yields, average of 2 runs.

Experimental Section

General Information

All aryl halides, amines and ketones were used as received. All solvents (anhydrous and technical grade) and the bases (potassium *tert*-butoxide and sodium *tert*-butoxide) were used as received and stored under argon in a glove-box. Flash chromatography was performed on silica gel 60 (230–400 mesh). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a 300 or a 400 MHz spectrometer at ambient temperature in $CDCl_3$, C_6D_6 or DMSO-d_6. Assignments of some ^{1}H and ^{13}C NMR signals relied on COSY and/or HMBC experiments.

Synthesis of [(NHC)Pd(acac)Cl] Complexes

[(IPr)Pd(acac)Cl] (2) [in square brackets, figures for the *large-scale synthesis*]: In a round-bottom flask equipped with a magnetic stir bar and a condenser, $Pd(acac)_2$ (0.716 g, 2.35 mmol) [7.16 g, 23.50 mmol], IPr·HCl (1.10 g, 2.59 mmol) [11.00 g, 25.85 mmol] and technical grade 1,4-dioxane (15 mL) [150 mL] were loaded and the reaction mixture was refluxed for 44 h. 1,4-Dioxane was then evaporated under vacuum and diethyl ether was added. The mixture was filtered over a plug of Celite to afford a clear yellow solution. Ether was removed and the orange/yellow powder obtained was washed with pentane and dried, affording the desired complex as a pale yellow powder; yield: 1.36 g (90%) [14.1 g (93%)]. NMR data were found in good agreement with previously reported characterization data.[7a,10]

[(IMes)Pd(acac)Cl] (3): In a round-bottom flask equipped with a magnetic stir bar and a condenser, $Pd(acac)_2$ (0.893 g, 2.93 mmol), IMes·HCl (1.000 g, 2.93 mmol) and technical grade 1,4-dioxane (15 mL) were loaded and the reaction mixture was refluxed for 24 h. 1,4-Dioxane was then evaporated under vacuum and cold diethyl ether was added leading to the formation of a yellow precipitate. The mixture was filtered over a plug of silica (immobilizing the precipitate) and washed with cold diethyl ether until the solvent came through colorless. The filtrate was discarded and the plug of silica was washed with dichloromethane affording a bright yellow solution. After evaporation of the DCM, the desired complex was obtained as a yellow powder; yield: 1.342 g (81%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.06$ (s, 2H, N-C*H*), 7.01 (s broad, 2H, H^{Ar}), 6.97 (s broad, 2H, H^{Ar}), 5.10 (s, 1H, C(O)-C*H*), 2.34 (s, 6H, CH_3), 2.30 (s broad, 6H, CH_3), 2.14 (s broad, 6H, CH_3), 1.75 [s, 3H, C(O)-CH_3], 1.74 [s, 3H, C(O)-CH_3]; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 187.5$ (C, *C*=O), 183.6 (C, *C*=O), 154.1 (C, N-*C*-N), 139.6 (C, N-C^{Ar}), 137.4 (C, C^{Ar}), 136.1 (C, C^{Ar}), 135.3 (C, C^{Ar}), 130.1 (CH, C^{Ar}), 129.2 (CH, C^{Ar}), 124.2 (CH, N-*C*H), 100.1 (CH, C(O)-*C*H), 27.5 (CH_3, C(O)-*C*H_3), 26.0 (CH_3, C(O)-*C*H_3), 21.6 (CH_3), 19.2 (CH_3), 18.2 (CH_3); HR-MS: $m/z = 550.1686$, calcd. for $C_{28}H_{34}N_3O_2Pd$ [M+MeCN−Cl$^-$]: 550.1707; anal. calcd. (%) for $C_{28}H_{31}N_2O_2PdCl$ (MW 545.41): C 57.26, H 5.73, N 5.14; found: C 57.21, H 5.87, N 5.11.

Large-Scale Cross-Coupling Reactions

General Procedure for Buchwald–Hartwig Reactions: In a glove-box, [(IPr)Pd(acac)Cl] **2** (0.1 mmol, 63 mg, 0.01 equiv.), potassium *tert*-butoxide (11 mmol, 1.24 g, 1.1 equivs.) and anhydrous 1,2-dimethoxyethane (DME) (10 mL) were added in turn to a vial equipped with a magnetic stir bar, and sealed with a screw cap fitted with a septum. Outside the glove-box, the amine (10 mmol, 1 equiv.) and the aryl halide (10 mmol, 1 equiv.) were injected in turn through the septum. The reaction mixture was then stirred at 50 °C and monitored by GC. When the reaction was found complete, water was then added to the reaction mixture, the organic layer was extracted with *tert*-butyl methyl ether (MTBE), dried over magnesium sulfate and the solvent was evaporated under vacuum. The crude product was dissolved in pentane and filtered through a plug of Celite, yielding the desired product. The reported yields and quantities are the average of two runs.

***N*-(2,6-Diisopropylphenyl)-*N*-(2,6-dimethylphenyl)amine** (Table 2, entry 1): Following the above general procedure with *N*-(2,6-diisopropylphenyl)amine (10 mmol, 1.88 mL) and 2-bromo-*m*-xylene (10 mmol, 1.33 mL), the reaction afforded the title compound; yield: 2.58 g (92%). NMR data were found in good agreement with previously reported characterization data.[10,14]

***N*-(3-Pyridyl)piperidine** (Table 2, entry 2): Following the above general procedure with piperidine (10 mmol, 0.99 mL) and 3-chloropyridine (10 mmol, 0.95 mL), the reaction afforded the title compound; yield:1.43 g (96%). NMR data were found in good agreement with previously reported characterization data.[10,15]

General Procedure for the α-Ketone Arylation Reactions

In a glove-box, [(IPr)Pd(acac)Cl] **2** (0.1 mmol, 63 mg, 0.01 equiv.), sodium *tert*-butoxide (15 mmol, 1.44 g, 1.5 equivs.) and anhydrous toluene (10 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw-cap fitted with a septum. Outside the glove-box, the ketone (10 mmol, 1 equiv) and the aryl halide (10 mmol, 1 equiv) were injected in turn through the septum. The reaction mixture was then stirred at 60 °C and monitored by GC. When the reaction was found to be complete, water was added to the reaction mixture, the organic layer was extracted with *tert*-butyl methyl ether (MTBE), dried over magnesium sulfate and the solvent was evaporated under vacuum. The product was purified by flash chromatography on silica gel.

1,2-Diphenylpropan-1-one (Table 2, entry 3): Following the above general procedure with propiophenone (10 mmol, 1.33 mL) and chlorobenzene (10 mmol, 1.02 mL), the reaction afforded, after flash chromatography on silica gel (pentane/MTBE, 80/20), the title compound; yield:1.95 g (93%). NMR data were found in good agreement with previously reported characterization data.[10,16]

2-(2-Methoxyphenyl)-1-phenylpropan-1-one (Table 2, entry 4): Following the above general procedure with propiophenone (10 mmol, 1.33 mL) and 2-chloroanisole (10 mmol, 1.27 mL), the reaction afforded, after flash chromatography on silica gel (pentane/MTBE, 85/15), the title compound; yield: 2.12 g (88%). NMR data were found in good agreement with previously reported characterization data.[10,17]

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