


Abstract: The synthesis of a series of [(IPr)Pd(R-acac)Cl] precatalysts (acac = acetylacetonato; R-acac = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), where the acac ligand on palladium has been systematically modified through terminal substitution, is reported. The following substituted acac ligands are employed in this study: dibenzoylmethanato (dbm), benzoylacetonato (bac), tetramethylheptanedionato (tmhd), and hexafluoracetetylacetonato (hfac). Full spectroscopic characterization of the new complexes is provided along with X-ray studies for three of these. Investigation of their catalytic activity in cross-coupling is also presented through a comparative study in an aryl amination reaction.

Keywords: activation • amination • cross-coupling • N-heterocyclic carbenes • palladium

Introduction

Palladium-catalyzed cross-coupling reactions have impacted every area of chemistry and continue to be a major research thrust.[1] The last ten years have notably seen the development of highly efficient supporting ligands, the most successful to date probably being tertiary phosphanes and N-heterocyclic carbenes (NHCs).[2–4] An equally important aspect of catalyst performance lies in the generation of an active complex bearing the right number of ligands for optimal catalysis. It is now well accepted that for bulky electron-rich ligands, such as tertiary phosphanes and NHCs, a 1:1 ligand-to-palladium ratio is favorable.[5]

Perhaps the most efficient way to ensure this 1:1 ratio consists in using well-defined palladium precatalysts. In addition to the issue of the palladium/ligand stoichiometry, this strategy notably circumvents issues linked to efficient ligation in solution, especially at low catalyst loadings. In recent years, we have pursued such a strategy based on NHC-PdII complexes.[6] While NHC-palladium(II) precatalysts present the main advantage of being bottleable and indefinitely benchtop-stable, they, however, need to be activated (i.e. reduced) under the reaction conditions to yield a catalytically active palladium(0) species. This critical point has led us to develop several families of precatalysts possessing a common NHC-Pd[0]-Cl substructure, where the two remain-
ing coordination sites have been modified (π-allyl 1, π-(R-allyl) 2, C.N-palladacycle 3), and to study their catalytic activity.

Our most recent development makes use of the acetylacetone (acac) ligand and notably allowed us to synthesize compound 4, [(IPr)Pd(acac)Cl] (IPr = 1,3-bis(2,6-disopropylphenyl)imidazol-2-ylidene), in an extremely straightforward one-pot procedure.[9] Examination of the activity of this new catalyst composition in aryl amination and α-ketone arylation proved extremely satisfactory, 4 being able to couple aryl and heteroaryl chlorides at moderate temperatures (i.e. 60°C).[10,11] Nevertheless, a number of challenges still remained to be addressed, such as lowering the temperature and, most importantly, decreasing the catalyst loading.

To reach such goals, we thought of modifying the acac moiety bound to palladium in order to facilitate the activation of the precatalyst, a strategy that we successfully implemented by designing substituted π-allyl palladium complexes that proved more active than their unsubstituted counterparts (Scheme 1).[12]

![Scheme 1. Rationale for the design of modified [(NHC)Pd(acac)Cl] complexes.](image)

Herein, we report the synthesis of a series of [(IPr)Pd(R-acac)Cl] precatalysts where we have methodically modified, through terminal substitution, the acac ligand on palladium. We also present preliminary results of their activity in cross-coupling through a comparative study in an aryl amination reaction.

Results and Discussion


As mentioned above, simple modification of the surrounding ligands in PdII systems (e.g., from [(NHC)Pd(allyl)Cl] to [(NHC)Pd(R-allyl)Cl]; see Scheme 1) can lead to enhanced catalytic performances.[12] Hence, the success encountered with the “allyl family” encouraged us to examine the same concept with the “acac family”. In addition to a possible improvement of the catalytic activity, we thought that minor modifications in the framework of the acac ligand[13] in [(NHC)Pd(R-acac)Cl] complexes could bring crucial insights regarding the activation mode of these precatalysts.

Capitalizing on the synthetic routes we previously developed,[9–11] [(IPr)Pd(R-acac)Cl] derivatives 5–8 were synthesized, employing either free IPr or IPr·HCl and the corresponding [Pd(R-acac)Cl] salt,[14] results are summarized in Scheme 2. Of note, even though both routes can be used, better yields were generally obtained with the free IPr procedure. At this point, it should be noted that these procedures seem to be fairly general and should allow for the synthesis of other derivatives of the type [(NHC)Pd(R-acac)X].[15]

All complexes were characterized by 1H and 13C NMR spectroscopy and elemental analysis. The NMR spectra presented characteristic signals for the IPr ligand as well as for the β-diketonato moiety similar to the ones observed with the unsubstituted acac complex 4. Not surprisingly, when compared to 4 (δ = 5.12 ppm), the resonance for the enolic proton was increasingly shifted downfield upon substitution of the acac ligand with one and two phenyl groups (5: δ = 5.98 ppm, 6: δ = 6.70 ppm, 7: δ = 6.95 ppm). Interestingly, at room temperature, the resonances for the methine and methyl protons of the isopropyl groups in IPr show different splitting patterns as a function of the R-acac ligand bound to the palladium center. Hence, the hexafluoroacac complex 8, similarly to the unsubstituted acac 4, present a single septuplet accounting for all four methine protons of the four isopropyl groups and two sharp doublets for the methyl groups. This clearly indicates free rotation around the Pd–C bond as well as the N–C bond. In the other three R-acac complexes 5–7, the methine resonance is split into two broad signals and the methyl protons appear as three broad peaks. This observation can be attributed to hindered rotation around the C–Pd bond. Remarkably, a similar observation was made by Navarro and co-workers in the case of [(SIPr)Pd(acac)Cl], a complex where additional steric hindrance is provided by the saturated NHC ligand.[11] Thus, it seems that even slight modification of the initial structure of 4, either through the NHC or the acac ligand, leads to a more constrained environment around the palladium center.

Complexes 5–7 were then subjected to single-crystal diffraction study to unambiguously establish the atom connectivity in these molecules (Figure 1).[16] Similarly to 4, all complexes presented a very slightly distorted square-planar geometry around the palladium center; selected bond
lengths and angles are presented in Table 1. No specific trends across the acac series could be observed in terms of bond lengths and angles. Nevertheless, it should be noted that in all complexes, as previously observed in 4, the imidazole plane of the NHC is placed almost perpendicularly to the plane formed by palladium and the \( \beta \)-diketonato moiety, presumably to release steric pressure. Without much doubt, minimized steric hindrance is also the main reason for the arrangement of the bac ligand in 5—the only unsymmetrical acac in this study—around the palladium center, with the bulkier phenyl side sitting trans to the NHC, thus allowing the less hindered methyl side to be cis to the encumbering IPr ligand.

### Comparative Study in Aryl Amination

We investigated the different catalytic activities of 5–8 in the Buchwald–Hartwig reaction and compared them with the “standard” \([\text{IPr}]\text{Pd(acac)}\text{Cl}\) (4). We deliberately chose challenging coupling partners, 4-chlorotoluene and dibutylamine, so that differences in activity would be emphasized. The results obtained with 4–8 are gathered in Figure 2.

![Scheme 2. Synthesis of \([\text{IPr}]\text{Pd(acac)}\text{Cl}\) complexes 5–8.](image)

![Figure 1. Ball-and-stick representations of \([\text{IPr}]\text{Pd(acac)}\text{Cl}\) complexes 5–7.](image)

![Table 1. Selected bond lengths (Å) and angles (°) for complexes 5–7.](image)
First, we observed that after 8 h at 50°C, [(IPr)Pd(hfac)Cl] (8) did not yield any product. When harsher conditions were tested (T = 80°C, overnight), we did not notice any difference in reactivity. Interestingly, the appearance of Pd black was never observed, the solution remaining pale yellow over time. These results tend to show that the active Pd⁰ species was not formed and therefore that electron-withdrawing groups on the acetylacetonato ligand inhibit the activation of the catalyst. On the contrary, [(IPr)Pd(bac)Cl] (5) and [(IPr)Pd-dbmc] (6) were quickly activated. After 3 h, the reaction was almost completed but proceeded more slowly afterwards to eventually reach 80–90% conversion after 8 h. It is interesting to notice that the activity of 5—with the bac ligand bearing one methyl group and one phenyl group—was found to reside between that of 6—dbm ligand with two phenyl groups—and the unsubstituted acac complex 4. Thus, changing the nature of the substituents has immediate consequences on the activity of the catalyst. This result is promising and could permit to combine several characteristics we observed into a rationally designed precatalyst. Finally, [(IPr)Pd(tmhd)Cl] (7) was very rapidly activated. In 30 min, the reaction reached 75% conversion. Nevertheless, we did not observe further conversion after the first 30 min. Thus, bulkiness and electron-donating effects appear to be important factors influencing the activation rate.

Relevance to the Activation Mechanism

The information gathered with the acac-modified complexes 5–8 brings support to our initial mechanistic proposal (Scheme 3) for the activation (PdII→Pd⁰) of [(IPr)Pd(acac)Cl] complexes. The steric impact of the acac substitution seems to play an important role in the activation rate. Regarding the steric hindrance of the ligand, a trend is observed: acac < hfac < bac < dbm < tmhd. With the exclusion of the hexafluoroacac complex 8, which is inactive, the rate of activation follows a trend where the bulkier the R-acac moiety is associated with a faster activation. This appears to support the intermediacy of T-shaped intermediate B (Scheme 3), obtained after O,O- to C-bound rearrangement of the acac ligand. Indeed, the added steric pressure of the acac substituents around the palladium center should favor the reductive elimination of diketone C (Scheme 3), leading to the formation of [(IPr)Pd⁰]. Additionally, the inertness of [(IPr)Pd(hfac)Cl] (8), which exhibits a similar steric environment as 4, raises the question of the electronic effects in the present system. Trifluoromethyl groups are clearly electron-withdrawing and therefore render the internal position of the β-diketono moiety less prone to C coordination. This might prevent the formation of B with hfac and the subsequent reductive elimination step leading to the active palladium(0) species.

Conclusions

Relying on efficient synthetic procedures previously developed, we have synthesized a series of [(IPr)Pd(acac)Cl] precatalysts 5–8 where we have systematically modified, through terminal substitution, the acac ligand on palladium. These complexes were fully characterized spectroscopically.
and X-ray structures of 5-7 were obtained. Comparative analysis of their activity in cross-coupling was conducted using an aryl amination reaction and revealed important discrepancies as a function of the steric bulk of the acac substituents. Hence, it was found that increased steric hindrance led to a faster activation rate, while the strongly electron-withdrawing CF3 group proved deleterious to catalytic activity.

Interestingly, we found the activity of 5 (buc ligand) to reside between that of 6 (dmb ligand) and the unsubstituted acac complex 4. This result is promising and could permit to combine several characteristics observed into a rationally designed fine-tuned precatalyst.

**Experimental Section**

**General information:** 4-Chlorotoluene, dibutylamine, and the different [(R-acac)-(tmhd)PdCl] complexes were used as received (Aldrich, Acros). Anhydrous solvents (1.2-MDE and 1.4-dioxane) and potassium tert-butoxide (Acros) were stored under argon in an MBraun glovebox. IPr·HCl and tert-(Acros) were stored under argon in an MBraun glovebox. IPr·HCl and dry dioxane (50 mL), and sealed with a rubber cap. The mixture was stirred at room temperature for two hours outside the glovebox. Then, the solvent was allowed to stir at room temperature for another 2 h. The solvent was washed with diethyl ether (2/C14810 mL). The filtrate was collected and the obtained powder was kept under vacuum overnight to yield the desired product.

**A C H T U N G T R E N N U N G**

**Synthesis of [(IPr)Pd(acac)Cl] using IPr:**

**General procedure:** In a glovebox, a Schlenk flask equipped with a magnetic stir bar and a condenser, [Pd(acac)2] (2.35 mmol), IPr·HCl (11.0 g, 2.59 mmol), and technical grade 1.4-dioxane (14 mL) were loaded and the reaction mixture was refluxed for 44 h. The solvent was then evaporated in vacuo and diethyl ether was added until no more solid dissolved (20 mL). The mixture was filtered and the solid was washed with diethyl ether (2 x 10 mL). The filtrate was collected and the solvent was evaporated in vacuo, and the obtained powder was kept under vacuum overnight to yield the desired product.

**Synthesis of [(IPr)Pd(acac)Cl] using IPr-HCl:**

**General procedure:** In a round-bottom flask equipped with a magnetic stir bar and a condenser, [Pd(acac)2] (1.5 mmol), IPr-HCl (1.1 g, 1.0 equiv), and dry dioxane (50 mL), and sealed with a rubber cap. The mixture was stirred at room temperature for two hours outside the glovebox. Then, 1.25 mL of HCl 4 M in dioxane was added to the solution, and the mixture was allowed to stir at room temperature for another 2 h. The solvent was then evaporated in vacuo and diethyl ether was added until no more solid dissolved (20 mL). The mixture was filtered and the solid was washed with diethyl ether (2 x 10 mL). The filtrate was collected and the solvent was evaporated in vacuo, and the obtained powder was kept under vacuum overnight to yield the desired product.

**A C H T U N G T R E N N U N N G**

**Synthesis of [(IPr)Pd(acac)Cl] (5): The general “free IPr” procedure, using 0.72 g of [Pd(bac)]2, yielded 1.0 g (87%) of the title complex.** 1H NMR (400 MHz, CDCl3, 25° C, TMS): δ = 7.91-7.87 (m, 2H, H2), 7.49 (t, J = 7.8 Hz, 2H, H4), 7.42-7.37 (m, 7H, H7), 7.20 (2H, N-CH), 5.98 (s, 1H, C(O)-CH3), 3.99 (s broad, 2H, CH2(CH3)2), 2.77 (s broad, 2H, CH2(CH3)2), 2.01 (s, 3H, C(O)-CH3), 1.50 (s broad, 6H, CH3(CH2)2), 1.22 (d, J = 6.9 Hz, 12H, CH2(CH3)2), 0.93 ppm (s broad, 2H, CH2(CH3)2); 13C NMR (100 MHz, CDCl3, 25° C, TMS): δ = 186.1 (C, O=C), 128.5 (C, C≡O), 156.2 (C, N-C≡O), 147.0 (C, N-C≡O), 139.8 (C, C≡O), 138.6 (C, C≡O), 136.2 (C, C≡O), 131.4 (C, C≡O), 130.9 (CH, C≡O), 130.6 (CH, C≡O), 128.0 (CH, C≡O), 127.9 (CH, C≡O), 127.5 (C, C≡O), 127.2 (CH, C≡O), 125.6 (CH, C≡O), 124.6 (CH, N-CH), 124.3 (CH, N-CH), 95.6 (CH, C(O)-CH(O)), 28.7 (CH, CH2(CH3)2), 28.3 (CH, C(O)-CH3)
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[14] dbm = dibenzoylmethanato; bac = benzoylacetonato; tmhd = tetra-methylheptanedionato; hfac = hexafluoroacetylacetonato.


[16] Despite repeated attempts we were unable to obtain suitable crystals for X-ray analysis of 8.

[17] This is in sharp contrast with the observation by Cavel and co-workers that [(IPr)Pd(fac)Me] (IPr = 1,3-dimethylimidazol-2-ylidenec, fac = trifluoroacetylacetonato) and [(IPr)Pd(fac)Me] are active precatalysts for the Heck reaction; see reference [15e].

Such a short catalyst life could be the consequence of high concentration of bare monoligated palladium(0) species, which will aggregate and precipitate. We are currently investigating, among others, this hypothesis.


[20] Preliminary studies using IA MALDI/TOF MS techniques (IA MALDI-TOF MS—inert atmosphere matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) have allowed for the observation of C (m/z 171.9) and bare 12-electron [(IPr)PdF] (m/z 494.2); N. Marion, M. D. Eielman, D. E. Fogg, S. P. Nolan, unpublished results.


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