Palladium catalyzed α-arylation of arylketones at low catalyst loadings

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Dedicated to our friend and colleague Professor David Cole-Hamilton on the occasion of his retirement.

Abstract: A general catalytic protocol for the α-arylation of aryl ketones has been developed. It involves the use of a pre-formed, bench stable Pd-NHC precatalyst bearing IHept as ancillary ligand, and allows the coupling of various functionalized coupling partners at very low catalyst loading. Careful choice of the solvent/base system was crucial to obtain optimum catalyst performance. The precatalyst was also successfully tested in the synthesis of an industrially relevant compound.

Palladium-catalyzed bond forming reactions are nowadays one of the most common tools synthetic chemists employ, in industry as well as in academia. [1] Enormous resources have been directed into the development of efficient methodologies to perform this class of transformations in an environmentally and economically advantageous manner. In the last two decades, the design of electron-rich, bulky ligands, has addressed many challenges in this field, allowing the coupling of highly unactivated coupling partners under mild conditions and using low catalyst loadings. [2] The α-arylation of ketones, simultaneously disclosed by Buchwald and Hartwig, [3] is potentially one of the most powerful and atom-economical C-C bond formation as it uses simple and widely available substrates and generates a minimum amount of side-products; the general reaction mechanism is depicted in Figure 1. [4]

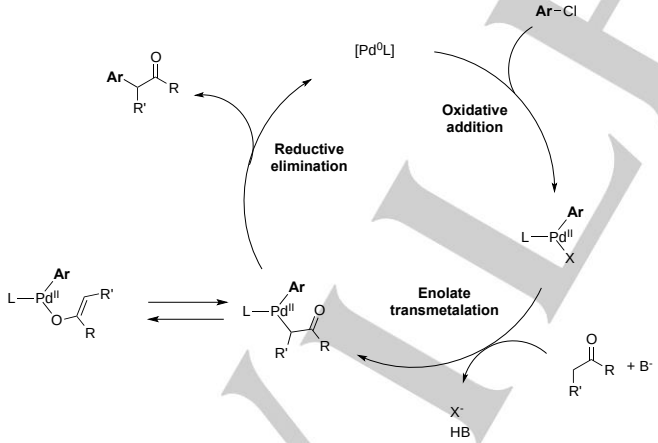

Figure 1. Mechanism of the ketone arylation reaction according to Hartwig. [4a,c]

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Starting from the late years of the last millennium, our group and many others devoted their efforts to the development of catalysts for the α-arylation of ketones and other carbonyl-containing compounds; examples of which are shown in Figure 2. [5,7] Mechanistic aspects of this reaction were studied by Hartwig and co-workers, [5a,6a] and the latest advances in the field were reported by the Stradiotto group, which developed highly efficient methods for the use of challenging substrates. [8] The recent development of useful synthetic strategies involving this reaction as the key step further underlines the importance of this class of couplings. [7b, 9]

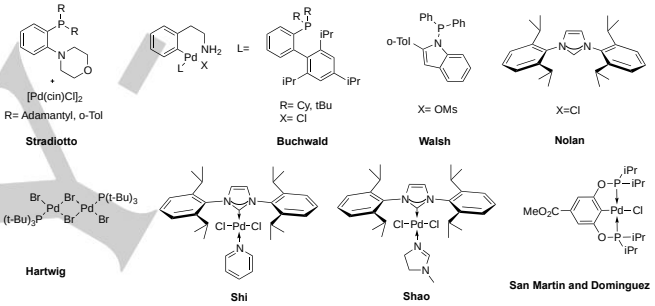


Figure 2. Examples of Pd pre-catalysts for α-arylation of carbonyl compounds.

Despite these important advances, only one example of such methodology employing low catalyst loading (<0.1%) is reported using bromides, [5d] and one single example of arylation reaction is reported using chlorides at low catalyst loading. [5g] Surprisingly, none of the "new generation" Pd-NHC-based pre-catalysts reported so far [10] have been tested in this interesting reaction. We disclose herein the first example of ketone arylation employing 200-500 ppm catalyst loading for most cases examined, by using the recently developed Pd(ITent) class of pre-catalysts (Figure 3).[11]

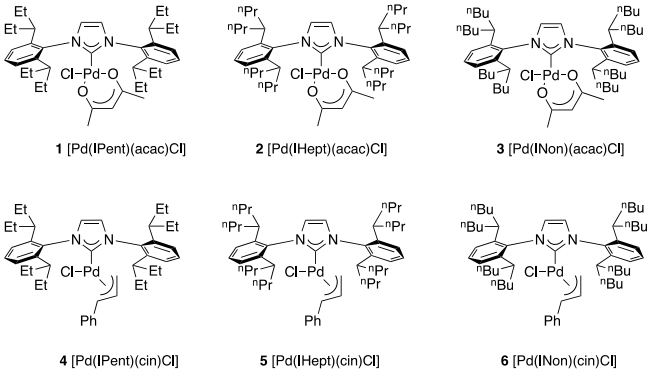


Figure 3. The Pd(ITent) pre-catalyst family.

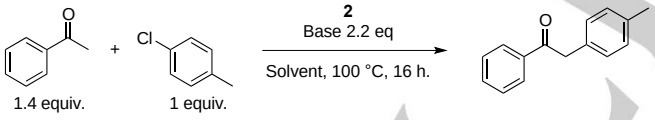
Our study began with the testing of various pre-catalysts in the reaction between acetophenone and 4-chlorotoluene: IPr*-based

precatalysts (IPr* =1,3-bis(2,6-bis(diphenylmethyl)-4-(methylphenyl)imidazo-2-ylidene) showed poor catalytic activity at low catalyst loading, while IPent gave high conversions. Comparing the entire ITent family, only [Pd(IHept)(acac)Cl] **2** was catalytically active at 100 ppm (see Supporting Information). Notably, as already reported, this pre-catalyst also proved to be the most active in the Buchwald-Hartwig reaction. [11]

The optimization of the base/solvent system was crucial: *tert*-butoxides provided the desired product, while other types of bases resulted in low or no conversion (see Supporting Information). We observed that the counterion of these bases played a crucial role in the reaction: when sodium *tert*-butoxide was used instead of the potassium analogue, the conversion was much higher (compare entries 1 and 5), while employing lithium *tert*-butoxide the conversion decreased (entry 3). In the latter two cases, the acetophenone signal was not detected, even though it was used in excess.

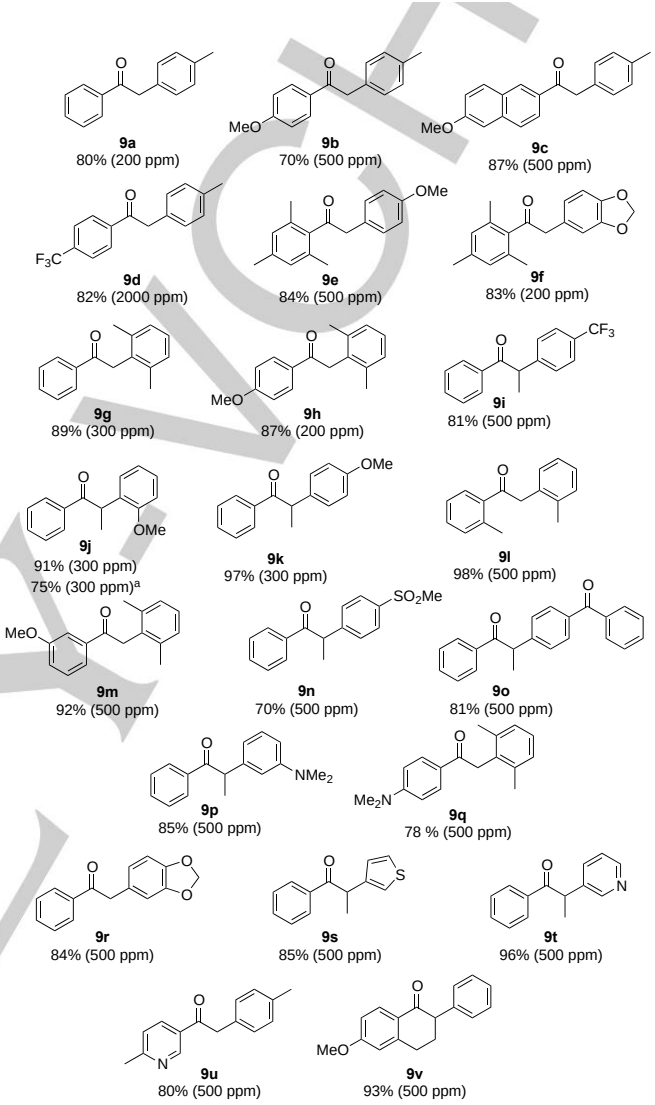
Control experiments, using potassium- and sodium *tert*-butoxide in the absence of pre-catalyst, showed that in the former case the starting materials were recovered, but in the latter the ketone was completely consumed. Although not conclusive, these results suggest that, while potassium tert-butoxide does not allow efficient formation of the enolate nucleophile, lithium tert-butoxide results in a significantly faster side reaction (presumably aldol condensation). [4a] Sodium *tert*-butoxide appears to provide a good balance between the cross coupling and the side-reactions. It has to be noted, however, that different precatalysts require different optimized conditions, suggesting that the Pd source influences also this aspect of the catalytic process. [12] The influence of the solvent was also studied, and toluene led to the highest conversion when using sodium *tert*-butoxide (compare entry 5 with entries 7 and 9). An increase of the catalyst loading to 200 ppm (Table 2, entry 5) allowed us to obtain the coupling product **9a** in 80% isolated yield.

Table 1. Optimization of the solvent/base system.



Entry	Solvent	Base	Conversion[a]
1	Toluene	KO^{t}Bu	22
2	Toluene	KO^{t}Am	0
3	Toluene	LiO^{t}Bu	20[b]
4	Toluene	NaO^{t}Bu	91[b]
5[c]	Toluene	NaO^{t}Bu	99 [b] (80%) [d]
6	Dioxane	KO^{t}Bu	51
7	Dioxane	NaO^{t}Bu	76[b]
8	DME	KO^{t}Bu	16
9	DME	NaO^{t}Bu	0[b]

Reaction conditions: acetophenone (0.7 mmol, 1.4 equiv.), 4-chlorotoluene (0.5 mmol, 1 equiv.), base (1.1 mmol, 2.2 equiv.), **2** 100 ppm in solvent (1mL), 100°C, 16h. [a] Conversion of 4-chlorotoluene as measured by GC. [b] No starting ketone remaining. [c] 200 ppm of **2** were used. [d] Isolated yield, average of 2 runs, after column chromatography.



Scheme 1. Reaction scope. Reaction conditions: ketone (0.7 mmol, 1.4 equiv.), aryl chloride (0.5 mmol, 1 equiv.), NaO^{t}Bu (1.1 mmol, 2.2 equiv.), **2** (0.02 mol% - 0.2 mol%), toluene (1 mL), 100 °C, 16 h. Isolated yields are average of two runs. a) reaction performed in air.

With this optimized system in hand, we explored the scope of the reaction (Scheme 1). Most of the substrates studied required a small increase in catalyst loading, to 300 ppm or 500 ppm.

We found that electron-rich ketones were suitable substrates for the transformation (**9b**, **9c**), while the use of an electron-poor acetophenone analogue (**9d**) required higher catalyst loading to afford good yield of the desired product. *Ortho*- (**9e-h**)and *meta*-substitution (**9m**, **9p**) were well tolerated on both partners. (**9f**, **9h**). Propiophenone proved to be especially suitable for this reaction, giving the desired products in good to excellent yields (**9i**-**k**), presumably because the steric hindrance on the

nucleophilic carbon of this substrate prevents double arylation. We also tested the reaction with more complex substrates, and were delighted to find the protocol compatible with a wide range of functionalities: methylsulfone- and ketone-containing aryl chlorides could be employed, despite their relative sensitivity towards basic conditions (**9n**, **9o**); tertiary amines could be introduced on either reactants (**9p**, **9q**); a benzodioxole derivative reacted efficiently (**9f**, **9r**), and nitrogen- or sulfur-containing heterocycles were also well- tolerated (**9s**-**u**). The industrially relevant derivative **9t**, a known intermediate in the synthesis of Selective Estrogen Regulator Modulators (SERMs) Nafoxidine and Lasofoxifene, was also obtained in high yield using our protocol, with lower catalyst loading than in the reported methods. [13] In order to highlight the robustness of our method, the product **9j** was synthesized without any involvement of glovebox or Schlenk techniques, and obtained in 75% yield using dry, degassed toluene.

In conclusion, a general protocol for the α-arylation of ketones at low catalyst loading has been developed. The careful selection of reaction conditions allowed coupling of a wide range of functionalized partners, including substrates bearing sensitive functional groups and a low catalyst loading of 500 ppm, for most cases, or lower. This protocol was also successfully applied to the synthesis of a known intermediate involved in the preparation of pharmaceutically relevant SERMs.

Experimental Section

General procedure for the arylation of ketones. Inside a glovebox, a vial containing a stir bar was charged with NaO^{t}Bu (105 mg, 1.1 mmol, 2.2 equiv.), Solid ketones (0.7 mmol, 1.4 equiv.) and/or aryl chlorides (0.50 mmol, 1.0 equiv.) were added at this point and dissolved in toluene, and the vial was sealed. A stock solution of [Pd(IHept)(acac)Cl] **2** in toluene was prepared and dispensed with a syringe (e.g.: 4.3 mg in 2 mL. 0.1 mL of this solution correspond to 500 ppm catalyst loading. Total reaction volume was 1 mL). Outside of the glovebox, ketone and/or the aryl chloride were added if liquids, followed by the stock solution. Finally, the vial was stirred at 100 °C overnight. The solution was then cooled to room temperature, some drops of water were added and the crude was filtered through silica eluting with ethyl acetate. Column chromatography of the crude (typically hexane/ethyl acetate 9/1) gave the desired product.

Synthesis of 9j in air. In a screw cap vial equipped with a stirring bar, NaO^{t}Bu (105 mg, 1.1 mmol, 2.2 eq.) was weighted and dissolved in 0.9 mL of dry toluene. A stock solution of **2** was prepared in a second vial (2.6 mg in 2 mL of dry toluene). Propiophenone (90 L, 91 mg, 0.68 mmol, 1.36 eq.), 2-Cl-anisole (71 mg, 0.5 mmol, 1 eq.) and 0.1 mL of the stock solution (corresponding to 300 ppm) were added to the vial containing the base. The vial was then sealed and magnetically stirred at 100°C overnight. The workup reported above afforded 181 mg (75%) of the desired product.

Acknowledgements

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Keywords: Palladium • NHC • Well-defined pre-catalysts • Monodentate ligands • Ketones arylation

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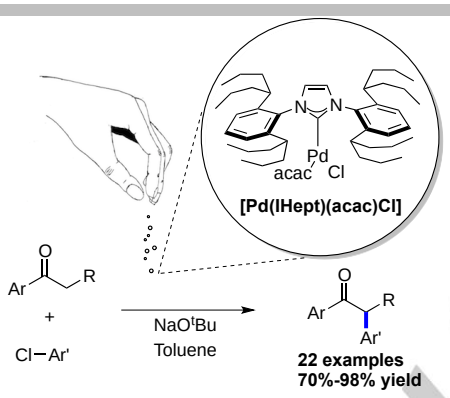
COMMUNICATION

Less than a pinch: Arylation of ketones at very low catalyst loadings has been achieved by using a member of the Pd-ITent-based pre-catalysts family. The system has a wide substrate scope, including functionalized partners, and gives the desired product in good to excellent yields. The synthesis of a key pharmaceutical intermediate was also achieved using this protocol.



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