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η^2-dba Complexes of Pd(0): The Substituent Effect in Suzuki–Miyaura Coupling

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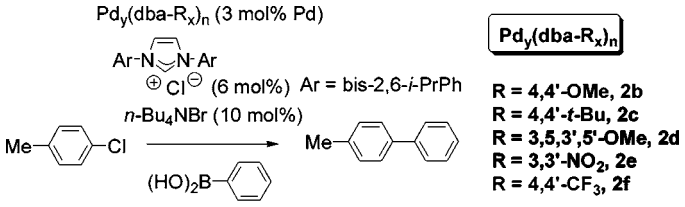
ABSTRACT



The electronic properties of substituents on the aryl groups of dba modulate the catalyst activity

The influence of aryl substituents in dibenzylidene acetone (dba) ligands, for Pd(0) complexes, has been evaluated for Suzuki–Miyaura cross-coupling reactions. Electron-withdrawing substituents such as NO_2 or CF_3 deactivate the catalyst species whereas strongly donating substituents such as OMe increase catalytic activity over that of unsubstituted dba ligands.

Palladium-catalyzed cross-coupling reactions constitute some of the most important and applied transformations in natural product synthesis, pharmaceutical targets, and conjugated materials.[1] Carbon−carbon and carbon−heteroatom bond-forming processes, catalyzed by palladium, such as Heck, Hartwig−Buchwald, Negishi, Sonogashira, Suzuki−Miyaura, and Stille reactions, are being used increasingly throughout the synthetic community. There has been a recent flurry of activity in the design of highly reactive Pd-catalysts for these processes,[2] particularly for Suzuki−Miyaura coupling.[3]

Palladium(0) or palladium(II) precursors, in the presence of donor ligands, facilitate efficient cross-coupling of deactivated and sterically hindered aryl chlorides with various organometallic reagents.Without question, the most routinely employed phosphine-free Pd(0) precursor is the air-stable complex Pd_2dba_3 (dba = *trans*,*trans*-dibenzylidene acetone).[4] The importance attached to this complex has been highlighted in the seminal mechanistic studies conducted by Amatore and Jutand.[5] No matter what the nature of the phosphine ligands used, the most reactive Pd(0) species in the oxidative addition with iodobenzene is the lowest ligated complex "PdL_n". Ligation by dba, via η^2-alkene coordination, diminishes the concentration of this species, affecting the overall reactivity.[5a] Therefore, in consideration of the classic catalytic cycle, dba ligand dissociation is required prior to oxidative addition.

The strength of Pd-η^2-dba coordination could be affected by the π-electron-accepting ability[6] of the dba ligand.

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Electron-rich σ-donor ligands could increase back-bonding from the d^{10} palladium center to dba, thus strengthening this interaction and thereby reducing the overall concentration of the active PdL_n species, whether bis- or monoligated. The incorporation of an electron-withdrawing substituent onto the dba ligand should further enhance this back-bonding. Conversely, the incorporation of electron-releasing substituents as part of the dba ligand will destabilize back-bonding and thus increase the concentration of the active catalyst species (Figure 1).

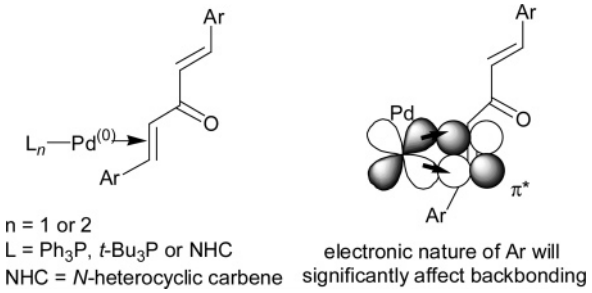
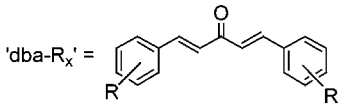


Figure 1. Back-bonding in "Pd(dba)L_n" complexes (n = 1 or 2).

To test this hypothesis, we have synthesized several substituted dba Pd(0) complexes, using a procedure described for Pd_2dba_3 **2a** from $PdCl_2$ (Scheme 1),[7] with a view to

Scheme 1. Synthesis of Pd Complexes



R = H (dba) **1a**, 4,4'-OMe **1b**, 4,4'-*t*-Bu **1c**, 3,5,3',5'-OMe **1d**, 3,3'-NO_2 **1e**, 4,4'-CF_3 **1f**.

$PdCl_2$ → 1. NaCl (2 equiv), MeOH, rt; 2. **1a-f** (3 equiv), 60 °C, 0.15 h; then add NaOAc (6 equiv), 1 h, cool to 25 °C, 2 h

[$Pd_2(dba)_3$], **2a**
[Pd_2(dba-4,4'-OMe)$_3$], **2b**
[Pd_2(dba-4,4'-*t*-Bu)$_3$], **2c**
[Pd(dba-3,5,3',5'-OMe)$_2$], **2d**
[Pd_2(dba-3,3'-NO_2)$_2$·H_2O], **2e**
[Pd(dba-4,4'-CF_3)$_2$·H_2O], **2f**

controlling the extent of dba dissociation and thus rate of reaction.

Novel Pd_y(dba-R_x)$_n$ complexes (y = 1 or 2, n = 2 or 3) containing 4,4′-bismethoxy (**2b**), 4,4′-bis-*tert*-butyl (**2c**), 3,5,3′,5′-tetramethoxy (**2d**), 3,3′-bisnitro (**2e**) and 4,4′-bis-(trifluoromethyl) (**2f**) substituents[8] were synthesized in isolated yields >65% (see the Supporting Information for characterization). The pure Pd(0) precursor complexes were evaluated against a highly active system recently reported by Caddick and co-workers[9] for Suzuki−Miyaura coupling. We chose the reaction of 4-chlorotoluene **3** with phenylboronic acid **4** catalyzed by Pd_2dba_3 **2a** (3 mol %)/NHC **6** (3 mol %) to give **5** (Figure 2). The reaction was used as a

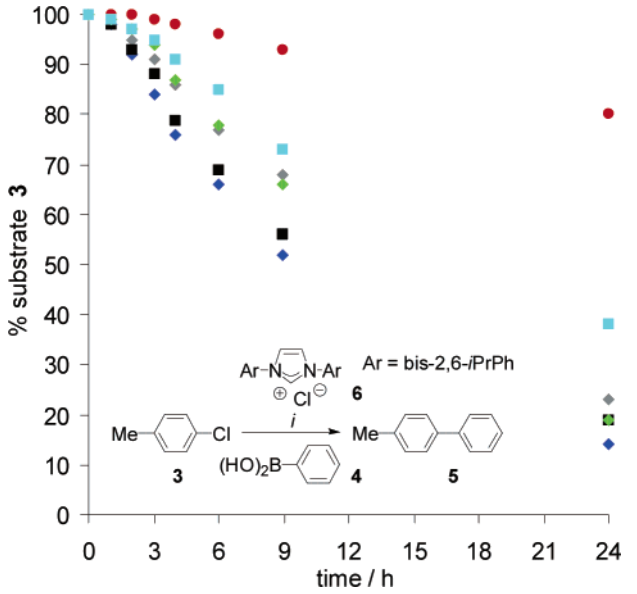


Figure 2. Conversion of **3** in the reaction with **4** catalyzed by Pd_y(dba-R_x)$_n$ **2a**−**f**/NHC **6** to give **5** (concentration of **3** = 0.137 M). Legend: gray, dba, **2a**; black, dba(4,4′-OMe), **2b**; green, dba-(4,4′-*t*-Bu), **2c**; dark blue, dba(3,5,3′,5′-OMe), **2d**; red, dba(4,4′-NO_2), **2e**; light blue, dba(4,4′-CF_3), **2f**. Reagents and conditions: (i) **6** (3 mol %), Pd complexes **2a**−**f** (based on Pd, 3 mol %), n-Bu_4-NBr (10 mol %), KOMe (3 equiv in MeOH), toluene, 40 °C.

benchmark for all of the Pd(0) precursor complexes **2b**−**f**—each reaction was followed by GC analysis, facilitating the generation of kinetic profiles.

Using **2a** as the precursor catalyst, the reaction reaches 77% conversion to product **5** after 24 h. For methoxy derivative **2b**, after the same period of time, 81% conversion to **5** was reached. An identical conversion was seen for the *tert*-butyl derivative **2c**. The largest difference was seen between the most electron-rich complex **2d**, which showed an 86% conversion, and the electron-deficient nitro derivative **2e**, which showed only 20% conversion to **5**. The trifluoromethyl derivative **2f** showed a level of conversion intermediate (62%) between that of **2a** and **2e**. These differences were maintained throughout the course of the reaction.

We have further investigated the Pd(0) complexes against a ligand-free[10] system for the cross-coupling of the activated bromo-2-pyrone[11] **7** with 4-fluorophenylboronic acid **8** to

(5) (a) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168. (b) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176. (c) Amatore, C.; Jutand, A.; Meyer, G. *Inorg. Chim. Acta* **1998**, *273*, 76.

(6) The π-donor properties of the dba ligand are not expected to play a decisive role when strongly σ-donating ligands are employed. They could become important using more π-accepting phosphine ligands.

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(8) Complexes **2e** and **2f** were isolated as hydrate complexes.

(9) Arentsen, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 3511.

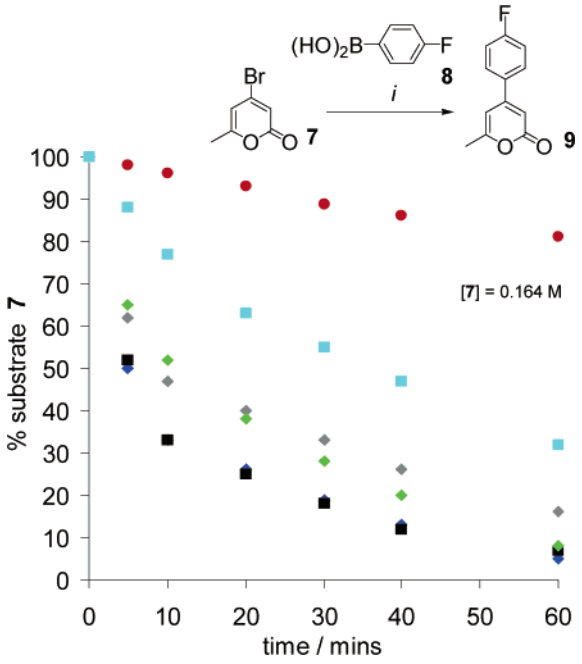


Figure 3. Conversion of **7** in the reaction with **8** catalyzed by $Pd_y(dba\text{-}R_x)_n$ complexes **2a**−**f** to give **9** (concentration of **7** = 0.164 M). Legend as for graph 1. Reagents and conditions: (i) Pd complexes **2a**−**f** (based on Pd 1 mol %), THF, 1 M Na_2CO_3 (1.5:1, v/v), 25 °C.

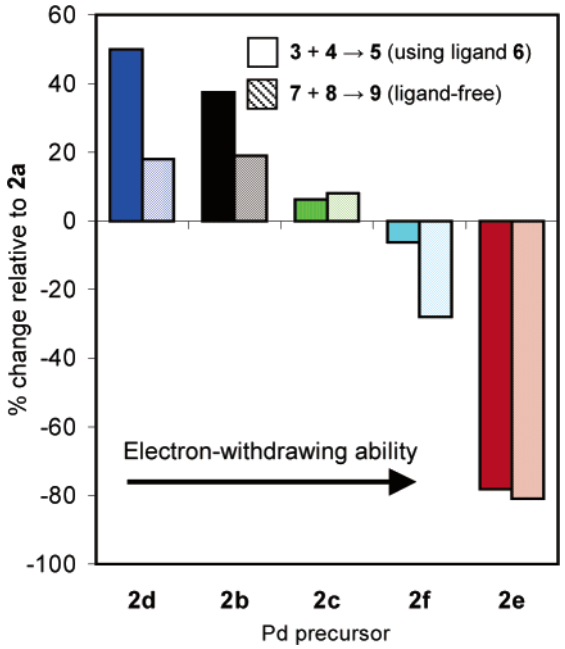


Figure 4. Substituent effect calculated as the relative conversion to cross-coupled products mediated by ligands **2b**−**f** versus **2a**. For the reaction **3** + **4** → **5**, the percent change was calculated after 9 h reaction time; for the reaction **7** + **8** → **9**, the percent change was calculated after 40 min.

give **9** (Figure 3). This graph illustrates that electron donating dba ligands give rise to higher conversions to **9**; compare 84% for **2a**, versus 95% for **2d**, while electron-deficient dba ligands give rise to lower conversions; compare 19% for **2e** and 68% for **2f**. This illustrates that the choice of the substituent on the dba ligand also influences the so-called ligand free system.

More detailed analysis of the preceding reaction profiles reveals the substituent effect was independent of the presence of additional NHC donor ligands in the Pd complex but was strongly dependent on the nature of the substituent on dba (Figure 4). The electron-withdrawing nitro substituent in **2e** resulted in the poorest performance relative to Pd_2dba_3 **2a**, whereas the most electron-rich complex, **2d**, was the most reactive. This effect is dramatic and allows the catalytic activity to be tuned over an order of magnitude while keeping the dba ligand framework intact. Traditionally, changes of this magnitude would only be expected upon alteration of the donor ligand.

The magnitude of the substituent effect was also to a large degree independent of the choice of substrate, as shown in Figure 5. This compares the enhancements obtained for a diverse range of coupling reactions after 4 h (for complete

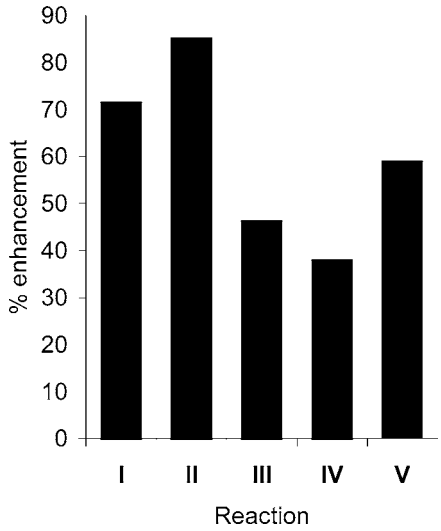
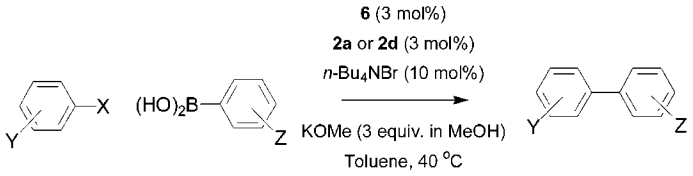


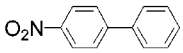
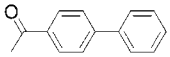
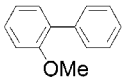
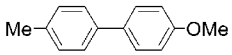
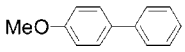
Figure 5. Percent enhancement seen for **2d** versus **2a** after 4 h (see Table 1 for complete details of reactions and percent conversions to cross-coupled products).

(10) The phrase "ligand-free" is used when no additional ligand, such as a phosphine, is added to the reaction; see: de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285.

(11) We have employed this substrate for several cross-coupling processes; see: (a) Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3509. (b) Marrison, L. R.; Dickinson, J. M.; Ahmed, R.; Fairlamb, I. J. S. *Tetrahedron Lett.* **2002**, *43*, 8853. (c) Marrison, L. R.; Dickinson, J. M.; Ahmed, R.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2667. (d) Fairlamb, I. J. S.; Lu, F.-J.; Schmidt, J.-P. *Synthesis* **2003**, 2564. (e) Fairlamb, I. J. S.; Bäuerlein, P. S.; Marrison, L. R.; Dickinson, J. M. *Chem. Commun.* **2003**, 632. (f) Niemela, E. H.; Lee, A. F.; Fairlamb, I. J. S. *Tetrahedron Lett.* **2004**, *45*, 3593. (g) Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F.-J.; Schmidt, J.-P. *Bioorg. Med. Chem.* **2004**, *12*, 4285.

Table 1. Comparison of **2a** and **2d**, in the Presence of NHC Ligand **6**, for the Suzuki−Miyaura Cross-Coupling or Arylboronic Acids with Various Aryl Halides



reaction	aryl halide	aryl boronic acid	coupled product	% conversion to product using **2a** / NHC **6**[a]	% conversion to product using **2d** / NHC **6**[a]
I	Y = 4-NO_2 X = Cl	Z = H		**21**, 80[b]	**36**, 89[b]
II	Y = 4-COMe X = Cl	Z = H		**20**, 61[c]	**37**, 79[c]
III	Y = 2-OMe X = Br	Z = H		**39**, 73[d]	**57**, 79[d]
IV	Y = 4-Me X = Cl	Z = 4-OMe		**37**, 83[e]	**51**, 89[e]
V	Y = 4-OMe X = Br	Z = H		**34**, 63[f]	**54**, 83[f]

[a] Numbers in bold are the percent conversion to products after 4 h. [b] Final percent conversion recorded after 20 h. [c] Final percent conversion recorded after 9 h. [d] Final percent conversion recorded after 8 h. [e] Final percent conversion recorded after 10 h. [f] Final percent conversion recorded after 8 h. Conditions used are identical to that shown in Figure 2. Overall concentration of substrate = 0.137 M.

details of percent conversions, see Table 1, conditions are identical to that shown in Figure 3) mediated by our most reactive complex **2d** relative to our benchmark system **2a**. The substrates chosen are representive of activated aryl chlorides (reactions I and II) and deactivated aryl bromides (reactions III and V).

Where a deactivated aryl chloride was utilized, an activated arylboronic acid was employed (reaction IV).

These results indicate that dba dissociation from the active palladium species is the rate-limiting step prior to oxidative addition of the aryl halide, supporting the studies by Amatore and Jutand.[4,5] Furthermore, since complex **2d**, identified as the most reactive in the preceding reactions, is also efficient in enhancing reactions I−V, the substituent effect appears to be generic.

In summary, we have shown that the electronic properties of substituents on the aryl groups of dba modulate the Suzuki−Miyaura cross-coupling of organohalides with arylboronic acids. Electron-donating substituents increase the rate of reaction, relative to unsubstituted dba, while electron-withdrawing substituents decrease the reaction rate. This effect appears to be related to the relative strength of the Pd-η^2-dba interaction.

This study has highlighted the importance of tuning the 'non-innocent' dba ligand, in addition to the donor ligand properties. In due course, full details of our kinetic, structural, and theoretical studies will be reported.

Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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