

Communications

In-Silico Prediction of Pd-Catalyzed Cross-Coupling Processes: Dibenzylidene Acetone (dba) Ligand Control

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Summary: DFT calculations allow us to predict the electronic properties of dba-*n,n'*-Z ligands and thereby control the reactivity of their corresponding Pd⁰ complexes in Suzuki–Miyaura, α -arylation, and Heck cross-couplings.

The complex Pd₂(dba)₃ (dba = *E,E*-dibenzylidene acetone)¹ is commonly used as a primary Pd⁰ precursor source in synthesis and catalysis. Variants of this complex include solvates and different Pd:dba stoichiometries. Donor ligands (L) such as phosphines and N-heterocyclic carbenes are routinely added to Pd₂(dba)₃ and related complexes, to generate complexes of the type L_{*n*}Pd⁰(η^2 -dba) (*n* = 1 or 2), usually *in situ*.² The dissociation of dba from the electron-rich Pd⁰ species is believed to control the concentration of catalytically active L_{*n*}Pd⁰ species in cross-coupling processes.³ Ligand by dba (a π -acidic ligand) ultimately stabilizes the Pd⁰ center via η^2 -alkene coordination,⁴ where synergic effects ($d\pi$ – π^* back-bonding) dominate the interaction, metering out active catalyst species from the catalytic cycle(s). Crucially, there is an antagonistic effect between the high intrinsic reactivity of the L_{*n*}Pd⁰ complex (with organohalides) and its concentration in equilibrium with L_{*n*}Pd⁰(dba),⁵

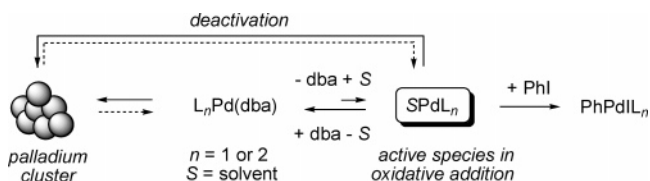


Figure 1. Postulated interplay between palladium and dba ligands during cross-coupling processes.

a situation exacerbated by the use of more electron-rich donor ligands (Figure 1); that is, such ligands increase the electron density on Pd⁰, resulting in greater back-bonding to the π^* -antibonding orbitals of the alkene. Other π -acidic alkenes, e.g., fumaronitrile,⁶ *p*-fluorostyrene,⁷ and several other alkenes,⁸ are known to promote cross-coupling reactions,⁹ a property that is arguably underutilized.¹⁰

(5) Oxidative addition of organohalides to L_{*n*}Pd⁰(dba) complexes is negligible where L is a monodentate ligand, e.g. PPh₃. For complexes where L is a bidentate ligand, oxidative addition reactions occur, but at a much slower rate than seen for LPd⁰ complexes that are not ligated by dba (see ref 3c). There is only one phosphine ligand known where dba does not play an inhibiting role in oxidative addition, namely, 1-phenyldibenzophosphole; see: Amatore, C.; Jutand, A.; Thuilliez, A. *J. Organomet. Chem.* **2002**, *643*, 416.

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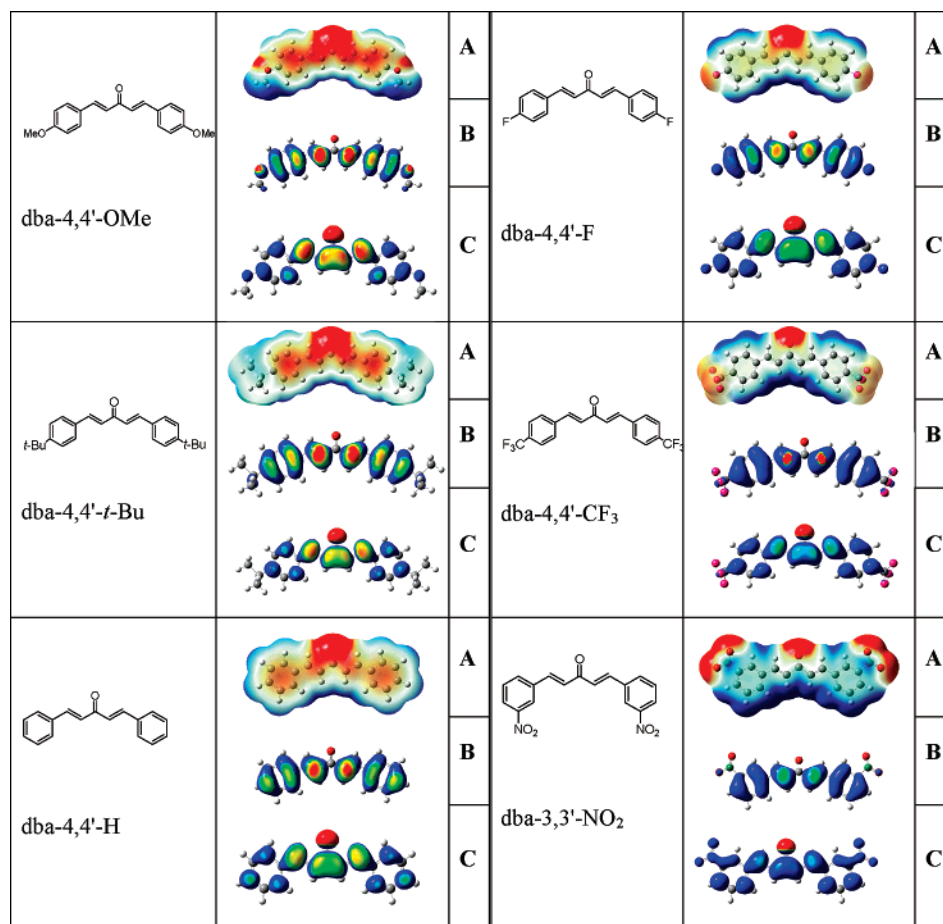


Figure 2. Total electron density mapped against electrostatic potentials (A). Color scale ± 0.02 electrons; red areas are electron-rich. The HOMOs (B) and LUMOs (C) are also shown for each ligand.

We recently developed a concept whereby the electronic properties of dba-derived ligands, e.g., dba- n,n' - Z (where $n,n' = 3$ or 4 and $Z = \text{OMe}, t\text{-Bu}, \text{H}, \text{F}, \text{CF}_3, \text{NO}_2$), can be subtly tuned through minor structural changes to the aryl moieties. The π -electron-accepting ability of the dba ligand appears to modulate the strength of Pd^0 - η^2 -dba coordination.¹¹ In collaboration with Jutand, we showed that the dba- n,n' - Z ligand principally influences the oxidative addition reaction with aryl iodides.¹² This effect is most dominant when the oxidative addition step is rate-limiting, as is the case for aryl chloride coupling. It is thus clear that globally electron-deficient alkenes can play a significant role in cross-coupling processes.

In this communication we develop a theoretical tool for predicting the importance of Pd^0 -dba interactions in cross-coupling chemistry through DFT calculations. These have allowed us to probe the relationship between the electronic structure of a family of well-characterized dba- n,n' - Z ligands and the associated catalytic reactivity of their Pd^0 complexes.

Calculations on free dba- n,n' - Z ligands were all undertaken with the GAUSSIAN 03 software suite¹³ using the B3LYP functional and 6-311G(d,p) basis set. Geometry and frequency

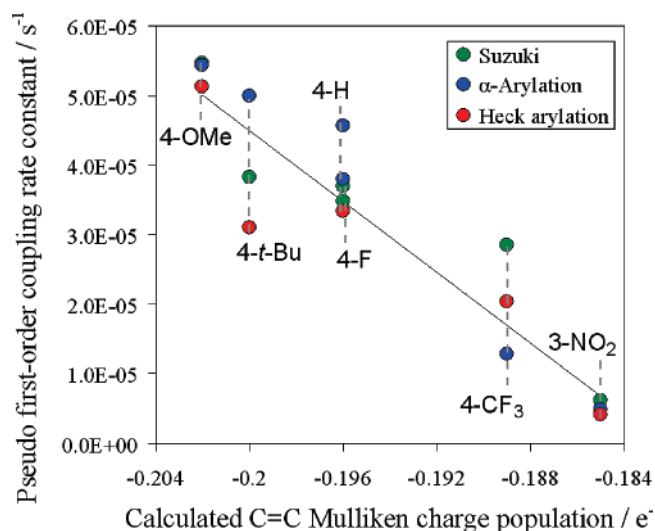


Figure 3. Relationship of C=C total electron charge in dba- n,n' - Z ligands with cross-coupling reaction rates (with line of best fit).

optimizations were followed by single-point energy calculations on the optimized structures to explore the influence of ring substitution on molecular electron density and orbital energies.

The total electron densities for the different dba- n,n' - Z ligands are shown in Figure 2. These electron density maps provide an immediate qualitative visualization of charge variations within the alkene function, which are in agreement with our intuitive chemical predictions. If one simply considers the HOMO set for the six ligands, it is clear that with electron-releasing

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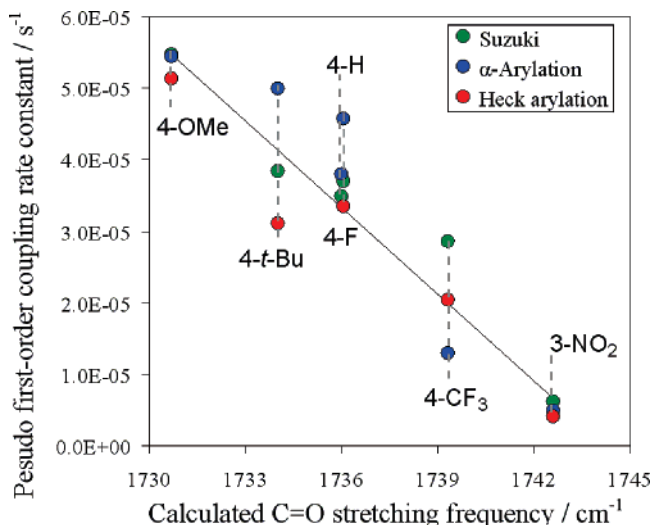


Figure 4. Relationship of C=O stretching frequency in dba-*n,n'*-Z ligands with cross-coupling reaction rates (with line of best fit).

substituents (OMe or *t*-Bu) more electron density resides in the C=C bond. The introduction of electron-withdrawing substituents (F, CF₃, or NO₂) into the rings results in a significant loss of electron density from the C=C bond. As a series, the C=C electron density decreases in the order OMe > *t*-Bu > H > F > CF₃ > NO₂.

A more quantitative evaluation of the impact of the C=C charge density on the corresponding catalytic performance of cross-coupling reactions employing Pd⁰_x(dba-*n,n'*-Z)_y complexes (*x* = 1 or 2; *y* = 2 or 3) is shown in Figure 3. Here, the pseudo-first-order rate constants (for consumption of the aryl halide) for Suzuki–Miyaura cross-coupling of chlorotoluene with phenylboronic acid, α-arylation of *tert*-butyl acetate with bromobenzene, and Heck arylation of *n*-butyl acrylate with bromobenzene were determined from initial reaction rates (pre-established experimental data).^{11b}

A strong linear correlation is immediately apparent across the dba series, despite all the differences between choice of substrate and reaction conditions (solvent/base system, temperature, and dba concentration)! Remarkably, this allows us to quantitatively predict the effect of pushing charge into the C=C bonds of dba and the resulting substantial rate enhancements for archetypal cross-couplings. The relationship between the C=C charge and the reaction rate is expressed in eq 1 below.

$$k' = (-0.00255q) - 0.000465 \quad (1)$$

where *q* = total Mulliken charge localized across the C=C bond.

Figure 4 reveals a similar relationship between the calculated carbonyl stretching frequency (bond strength) for each substituted dba and its associated rate constant, offering a rapid experimental tool for verifying the electronic properties of future, new dba-*n,n'*-Z ligand variants, as expressed in eq 2.

$$k' = (-0.000004039\nu_{\text{C=O}}) + 0.007045 \quad (2)$$

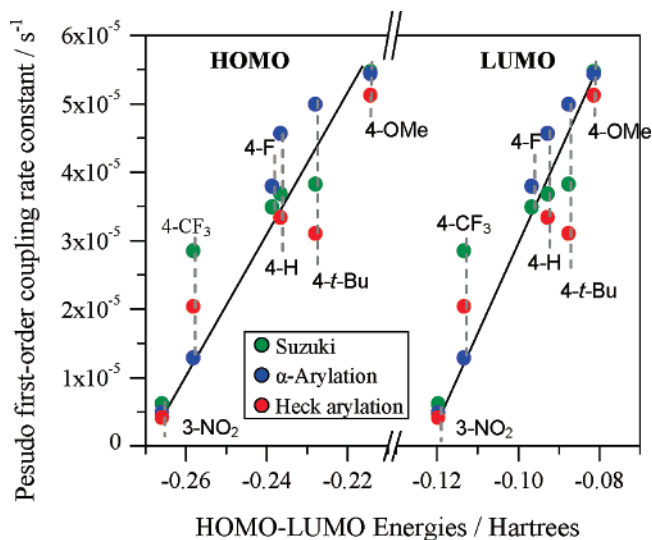


Figure 5. Relationship between corresponding Pd-catalyzed cross-coupling reaction rate constants (with line of best fit).

We purposely calculated the frequencies for the free dba ligands in the gas phase, in the absence of solvation effects.¹⁴ As seen in Figure 4, electron-releasing substituents delocalize charge onto the enone moiety, with the C=O stretch falling commensurately. Such a change will result in greater C=O→Pd⁰ participation,¹⁵ a more labile coordination mode than η²-coordination of C=C to Pd⁰.

A more detailed examination of the origin of electronic changes provided by the molecular orbitals helps to identify an increase in both HOMO and LUMO energies with increasing donation into the π-system of the enone moiety (Figure 5).

In summary, our results confirm that dba dissociation from L_nPd⁰(η²-dba) is the rate-limiting step under our reaction conditions and illuminate the predictive power of simple *in-silico* methods for tailoring high performance in π-acidic alkenyl ligands¹⁶ for Pd⁰-catalyzed cross-couplings.

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Supporting Information Available: The complete citation for Gaussian 03, coordinates, and Mulliken charges. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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