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Ligand-Controlled Regioselectivity in Palladium-Catalyzed Cross Coupling Reactions

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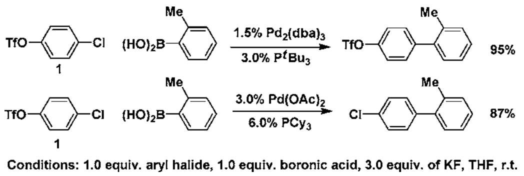
Fu et al.[1] recently described the control of regioselectivity in the Suzuki cross-coupling of chloro aryl triflate **1** with different ligands (see Scheme 1). Tricyclohexylphosphine (PCy_3) gave coupling at the C−OTf bond, while *tert*-butylphosphine (P*t*Bu_3) led to a remarkable reversal, with exclusive reaction at the C−Cl bond.[1] Subsequent theoretical and experimental studies concluded that P*t*Bu_3 most likely reacts via a monoligated Pd complex [PdP*t*Bu_3] with aryl chlorides.[2−4] It has also been proposed that PCy_3 reacts via a monophosphine Pd-species with aryl chlorides.[3] Further mechanistic studies have been reported by Brown et al. on bromo aryl triflate analogues.[5] The relatively low activation barrier of monoligated Pd in oxidative insertions has been discussed.[4] The origins of regiocontrol in the present case are not understood.[5] We have carried out computational studies that provide explanations of these phenomena.

Scheme 1



The transition states (TSs) for oxidative insertion to **1** with monoligated PdP*t*Bu_3 gave a 5.8 kcal/mol preference ($\Delta\Delta G^{\ddagger}$) for C−Cl bond insertion.[6,7] With monoligated PdPCy_3, the analogous preference for reaction at chloride ($\Delta\Delta G^{\ddagger} = 3.6$ kcal/mol) is opposite to experiment.[8] Considering the dissociation energies of PdL_2 to PdL+L as well as insertion barriers, the monoligated free energy pathway is favorable over the bisligated (see Supporting Information (SI) for free energy profiles).[9,4a] However, the relative concentration of PdL_2 vs PdL in the reaction mixture is controlled by the dissociation energy of PdL_2 and the ligand concentration.[1,3,4a] Hartwig et al. recently established the inverse dependence on phosphine concentration of the rate of oxidative insertion of $Pd(PCy_3)_n$ to aryl chlorides,[3] consistent with the formation of the less reactive bisligated active species. Our calculations on oxidative insertions of bisligated $Pd(PCy_3)_2$ to **1** gave a preference of 4.3 kcal/mol ($\Delta\Delta G^{\ddagger}$) for triflate insertion,[8] in accord with experiment.[10] This suggests that $Pd(PCy_3)_n$ reacts via a bisligated Pd species under the conditions employed (see also the discussion below on anionic palladium).

We have also calculated and analyzed the mono- and bisligated TSs derived from the reaction of $Pd(PMe_3)_n$ in the gas phase[7] and of $Pd(PH_3)_n$ in THF. These calculations predict the identical regiochemistry as was calculated with the full ligands above, showing that the ligation state of Pd is a key element for regiocontrol. The results of the calculations with PMe_3 are shown in Table 1, and those for PH_3 are given in the SI. We have (Figure 1) dissected the TS energies into the distortion energy (ΔE_{dist}, required to distort the reactants into the TS geometry) and interaction energy (ΔE_{int}, gained upon allowing the distorted fragments to interact). The sum of the two is the activation energy ($\Delta E^{\ddagger}$). Such an analysis is also known as the activation strain model.[11−13] We recently applied the model to analyze the origin of regioselectivity in Pd-catalyzed cross-coupling reactions of polyhalogenated heterocycles.[14] ΔE_{dist} is related to the bond dissociation energy (BDE). Based on BDEs,[15] the C−Cl bond is easier to distort and would be expected to be of higher reactivity than the C−OTf bond. The difference in ΔE_{int} is related to the magnitude of the coefficient of a π*-lobe at the carbon of the C−X bond to be cleaved.[14] In the substrate of interest, **1**, the LUMO coefficients at C−Cl and C−OTf are nearly the same,[16] suggesting no particular regiochemical preference, but differences appear in the distorted substrate (see below).

Table 1. Distortion/Interaction Analysis of TSs Involving PMe_3 as Ligand[a]

insertion position	Pd Species	$\Delta E^{\ddagger}$	ΔE_{dist} (Pd)	ΔE_{dist} (substrate)	ΔE_{int}	$\Delta G^{\ddagger}$
C−Cl	$PdPMe_3$	14.4	3.2	32.1	−20.9	13.7
C−OTf	$PdPMe_3$	19.9	4.3	52.6	−37.0	20.1
C−Cl	$Pd(PMe_3)_2$	*21.5*	16.9	20.9	−16.3	*35.1*
C−OTf	$Pd(PMe_3)_2$	*16.9*	21.8	55.9	−60.8	*31.8*

[a] Barriers (in kcal/mol) are given with respect to $PdPMe_3$/π-complex or *$Pd(PMe_3)_2$*, respectively. See SI for full energy profiles.

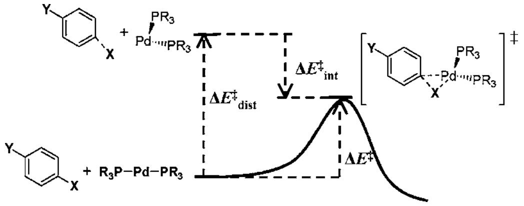


Figure 1. Distortion/interaction model for oxidative insertion.

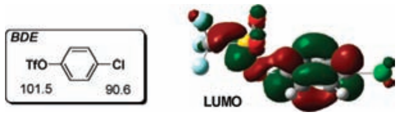


Figure 2. BDE and LUMO of **1**.

The results of the distortion/interaction analysis are summarized in Table 1.[17] With monoligated Pd, a π-complex forms prior to oxidative insertion (see SI). This is the reference point for the analysis of monoligated TSs.[18] Bisligated TSs are analyzed with respect to the isolated reactants. For the insertions at triflate, with both mono- and bisligated Pd, the substrate distortion energies (ΔE_{dist}) are significantly higher than those of C−Cl, correlating with BDEs. The short and strong C−O bond is significantly stretched (by 0.54 Å) and bent (out-of-plane by 45°) prior to cleavage, which causes the LUMO to be lowered.[19] The C−Cl bond in contrast, being a weaker bond, requires much less out-of-plane bending (31°) and stretching (0.24−0.45 Å) to be cleaved (Figure 3). This causes the C−Cl LUMO to be higher than that of triflate in the distorted

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geometries. Palladium primarily reacts as a nucleophile in oxidative insertions.[5] Analyzing the orbital energies of the Pd species in their TS geometries reveals that bisligated Pd is more nucleophilic, exhibiting a high-lying HOMO.[20,21] Thus, the most nucleophilic species, PdL_2, reacts at the C−OTf bond, which is, in its distorted TS geometry, the site of lowest LUMO energy, and therefore greatest interaction. The regioselectivity is thus interaction controlled.

With monoligated Pd, reaction at the C−Cl bond is favored (Table 1). The TS for oxidative addition to C−Cl is now relatively late (Figure 3); there is only small Pd−L distortion, and the C−Cl bond is easier to distort than the C−O bond of the triflate. Stretching the C−Cl bond lowers the substrate LUMO, increasing the interaction with Pd. In addition, the greater interaction of the C−Cl bonding orbital with the vacant Pd orbital further stabilizes this TS. Insertion to C−O is more ionic in character, and the bridging O interaction with Pd in the C−O insertion TS is less important. The principal reason for the preferential attack on the C−Cl bond by monoligated Pd is the low C−Cl distortion energy.

Why is it that monoligated Pd gives lower activation barriers ($\Delta G^{\ddagger}$) for oxidative insertion? This is because monoligated Pd does not distort to reach the TS geometry as opposed to bisligated Pd, which has to bend and hence has significant distortion energies (compare Table 1). In the monoligated TSs, only substrate distortion contributes significantly to the total distortion energy, which is directly related to the BDE.[14] C−Cl is the weaker bond and has lower ΔE_{dist}. Thus, the regioselectivty is controlled by distortion energy differences.

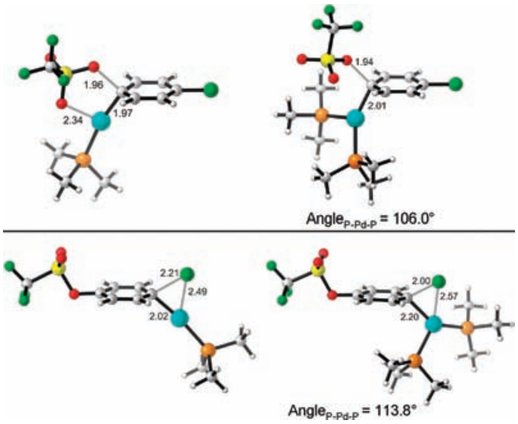

Figure 3. TSs for oxidative insertion into C−OTf (top) and C−Cl (bottom) with $PdPMe_3$ (left) and $Pd(PMe_3)_2$ (right).

We established analogous results also for other substrates[22] and also considered alternative mechanisms involving anionic Pd.[23] We investigated several anionic TSs with $[Pd(PMe_3)_nX]^-$, with $n = 0$, 1, 2 (X = OAc, F, Cl, $B(OH)_2F$); see SI. All Pd species with $n > 0$ favor insertion at the triflate site (by $\Delta\Delta G^{\ddagger} = 5.2-7.2$ kcal/mol),[24] where monoligated Pd (i.e., $PdCl^-$, $n = 0$)[25] favors chloride insertion. This is in line with the above findings that the ligation state of Pd is crucial for regiocontrol.

In conclusion, for substrates with substituents that have substantial differences in their BDEs, the regioselectivity is distortion-controlled (= BDE of C−X) for monoligated Pd but interaction-controlled for bisligated Pd. Monoligated Pd is more reactive predominantly due to lack of distortion of the Pd species, but steric crowding of the ligand is crucial for initial ligand dissociation to form $PdPR_3$.[4a]

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Supporting Information Available: Full ref 6; reaction paths with PH_3, PMe_3, PCy_3 and P*t*Bu_3 as ligands; energies; Cartesian coordinates; orbital energies are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Calculated with the ONIOM method; see SI for details.
(9) Where $\Delta\Delta G^{\ddagger}$ between mono- and bisligated pathways is 1.4−2.3 kcal/mol for PMe_3 and PH_3, it is larger for PCy_3 (4.4 kcal/mol). For bimolecular processes (i.e., PdL_2 pathway), a discrepancy between gas-phase calculated free energies and experimental solution reactivity exists, causing $\Delta\Delta G$ to be overestimated. Previous theoretical studies have applied corrections to $\Delta G^{\ddagger}$ (−2.6 kcal/mol) to account for this, based on the 'theory of free volume'; see: (a) Liu, Q.; Lan, Y.; Liu, J.; Li, G.; Wu, Y.-D.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 10201. (b) Benson, S. W. *The Foundations of Chemical Kinetics*; R.E. Krieger: Malabar, FL, 1982.
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(17) See also SI for distortion/interaction analysis of TSs involving full ligands.
(18) Analysis of the π-complex shows small distortion of the substrate (2.3 kcal/mol) and the Pd species (1 kcal/mol).
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(25) We thank the Reviewer for the suggestion to also investigate $PdCl^-$.

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