Cross-Coupling

DOI: 10.1002/anie.201101746

Solvent Effect on Palladium-Catalyzed Cross-Coupling Reactions and Implications on the Active Catalytic Species**

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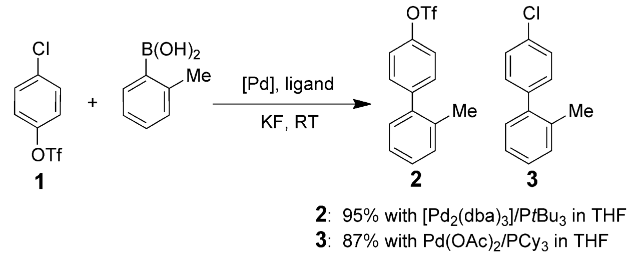
One of the milestones in pushing the limits of the oxidative addition step in palladium-catalyzed cross-coupling reactions was the discovery that bulky phosphine ligands trigger unprecedented high reactivity in palladium catalysis. A variety of monodentate ligand systems were developed, for example $PAdtBu_2$ (Ad = 1-adamantyl),[1] $((Ph_5C_5)(C_5H_4)Fe)PtBu_2$ ferrocenyl = $(C_5H_5)(C_5H_4)Fe$ (Q-phos),[2] PAd_2nBu,[3] and Buchwald's biaryl phosphine ligands.[4] The groups of Nishiyama[5] and Fu[6] demonstrated the power of the bulky tri-*tert*-butylphosphine ligand, $PtBu_3$. Fu and co-workers showed that a combination of $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) and $PtBu_3$ allows cross-coupling of aryl chlorides at room temperature.[6,7] Experimental and theoretical mechanistic studies indicated that a monoligated palladium species would be the active catalyst in reactions of Pd and $PtBu_3$.[8–12]

Fu and co-workers further demonstrated a remarkable ligand effect in Pd-catalyzed coupling of chloroaryl triflate **1** (Scheme 1).[7,13] Whereas PCy_3 gave coupling at the C–OTf bond, $PtBu_3$ led to a reversal, with exclusive reaction at the C–Cl bond.[7] DFT calculations were applied to explore the origins of this chemoselectivity.[14]

It was found that monoligated palladium (which is favored with $PtBu_3$ under these conditions) favors C–Cl insertion and bisligated palladium (which is the active species with PCy_3) favors C–OTf insertion.[14] Notably, calculations with different ligands, for example, PMe_3, showed that only the ligation state of Pd is crucial for the selectivity, and a rationalization of that behavior was also deduced.[14] Regioselectivity is controlled by the distortion energy (and thus by the bond dissociation energy of the C–X bond) for monoligated Pd, which therefore reacts with the weakest bond, that is, C–Cl. With bisligated Pd, in contrast, selectivity is controlled by the greatest interaction in the transition state (TS; reaction at C–OTf).[14] These investigations have thus revealed a reactivity system to differentiate mono- from bisligated catalytic species.



Scheme 1. Ligand-dependant chemoselectivity.[7]

Herein, we provide indirect evidence for a change of the catalytically active species in polar solvents. The results suggest that the active species under conditions employing coordinating additives in polar solvents is inconsistent with monoligated $[Pd(PtBu_3)]$ and suggests an anionic palladium complex as the reactive species.

Fu and co-workers demonstrated the regioselectivity of the reaction shown in Scheme 1 in THF.[7] We were interested in studying the solvent effect on the selectivity. We performed experiments on chloroaryl triflate **1** under the conditions determined by Fu and co-workers[7] using $[Pd_2(dba)_3]/PtBu_3$ in a range of solvents. Table 1 reports the results of the experiments.[17] We found that in analogy to Fu's original study in THF, exclusive C–Cl insertion takes place in the nonpolar solvent toluene (see entry 1, Table 1). In polar solvents such as DMF and MeCN, in contrast, the selectivity is reversed, and there is remarkably high selectivity for C–OTf insertion (entries 2, 3, Table 1).[15,16]

Intrigued by this discovery, we set out to study the origin of the selectivity reversal in polar solvents. Previous computational studies concluded that $[Pd(PtBu_3)]$ would react selec-

Table 1: Variation of solvent and base in the reaction shown in Scheme 1.[17][a]

	Solvent	Base	*t* [h]	Yield [%] 2	3	1
1[b,c]	toluene	KF	48	70[b]	–	20[b]
2[c]	MeCN	KF	48	3	74	–
3[c]	DMF	KF	48	3	22	37
4[d]	THF	DIPA	24	14	7	41
5[d]	MeCN	DIPA	48	2	27	35
6[e]	MeCN	lutidine	48	<1	25	56

[a] With 1.5% $[Pd_2(dba)_3]$ and $PtBu_3$ as ligand.[b] Heating (at 70°C for 48 h) gives 83% **2** and 6% recovery of **1**. [c] Conditions: 3.0 equiv KF, 1.01 equiv $RB(OH)_2$, 1.0 equiv **1**, RT. [d] Conditions as in [c], but with 3.0 equiv diisopropylamine rather than KF. [e] Conditions as in [c], but with 3.0 equiv lutidine rather than KF.

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[**] We thank ETH Zürich for financial support and the Laboratory of Organic Chemistry for instrumental support, in particular the groups of Profs. Bode, Chen, and Diederich for access to their GC-MS and HPLC facilities. We thank Franziska Lissel for early work on the project. Calculations were performed on the ETH High-Performance Cluster Brutus.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201101746.

tively with C—Cl.[14] However, these conclusions were based on studies and calculations in THF and in the gas phase. A polar solvent might stabilize the C—OTf insertion TS more strongly than the C—Cl insertion TS and could thus cause a selectivity change. To test this hypothesis, we applied computational studies.[18] We optimized the transition states for C—Cl and C—OTf insertion by [Pd(PtBu$_3$)] in MeCN using a CPCM solvation model and several methods. Table 2 reports the results. All calculations gave a preference for C—Cl insertion, although to a varying extent. Thus, the experimentally observed preference for C—OTf insertion is not due to electrostatic stabilization by the more polar solvent.[19]

Table 2: Calculation of $\Delta\Delta G^{\neq}$ for the insertion of C—OTf and C—Cl by [Pd(PtBu$_3$)] with different methods.[a]

Method	$\Delta\Delta G^{\neq} = \Delta G^{\neq}_{\text{C-OTf}} - \Delta G^{\neq}_{\text{C-Cl}}$
B3LYP/6-31+G(d)[b]	4.1
B3PW91/6-31+G(d,p)[c]	5.8
BLYP/6-31+G(d,p)[c]	1.6
M06L/6-31+G(d,p)[c]	0.8
M052X/6-31+G(d,p)[c]	1.1

[a] Optimized in MeCN, energies in kcal mol^{-1}. [b] ECP for Pd is LANL2DZ. [c] ECP for Pd is SDD.

Polar solvents usually have a greater basicity and nucleophilicity than nonpolar solvents. Thus, there might be coordination of the polar donor solvent to the palladium species in the transition state.[20] Our calculations show that solvent-coordinated transition states indeed favor triflate insertion (by $\Delta\Delta G^{\neq} = 4.9$ kcal mol^{-1} with [Pd(PtBu$_3$)(MeCN)]), which would be in accord with the results of the experiments. However, we calculated the reaction free-energy paths under solvent coordination and compared those to the insertion pathways for catalyst without solvent coordination, that is, [Pd(PtBu$_3$)Sol] versus [Pd(PtBu$_3$)] as active species. Figure 1 shows the results. The free-energy reaction profile shows that solvent coordination in the TS is disfavored with energy barriers much higher (ca. 44 kcal mol^{-1} for C—OTf insertion) than those for the monoligated, uncoordinated pathways (27.9 kcal mol^{-1} for C—Cl insertion and 33.7 kcal mol^{-1} for C—OTf insertion).[21] This finding suggests that the experimentally observed selectivity reversal is due neither to solvent coordination nor to electrostatic stabilization by the polar solvents. Thus, monoligated [Pd(PtBu$_3$)] as active species is inconsistent with the reactivity observed in polar solvents and suggests that a different catalytic species is active.

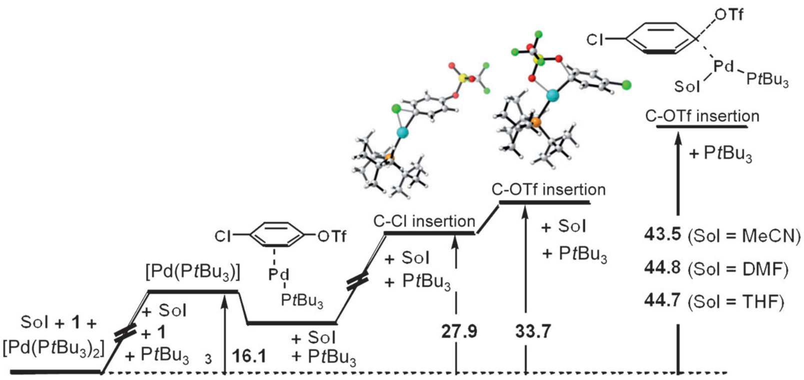
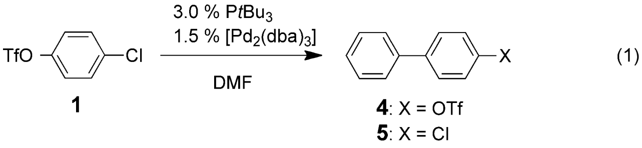


Figure 1. Free-energy profile for oxidative insertion to **1**.[21] Energies in kcal mol^{-1}. Calculated with B3LYP/6-31+G(d), LANL2DZ (Pd).

What is the active species in polar solvents? Several previous studies have suggested that anions can coordinate to the Pd^0 catalyst prior to oxidative insertion.[22,23] Roy and Hartwig performed kinetic investigations on the oxidative insertion of [Pd{P(o-tolyl)$_3$}$_2$] to ArOTf.[24] They found that added anions would accelerate oxidative insertion into the C—OTf bond and suggested that initial exchange of one ligand would take place to form [Pd{P(o-tolyl)$_3$}X]$^-$ (with X = Br, Cl), which would then undergo oxidative insertion.[24,25] To investigate whether the presence of anionic Pd species is consistent with the reactivity observed in polar solvents, we undertook DFT calculations[26] of the corresponding anionic transition states involving [Pd(PtBu$_3$)F]$^-$. These calculations revealed indeed clear preference for triflate insertion ($\Delta\Delta G^{\neq} = 2.3$ kcal mol^{-1} in MeCN and 5.4 kcal mol^{-1} in toluene). Thus, if [Pd(PtBu$_3$)F]$^-$ were to be formed,[27] it would preferentially give rise to triflate insertion. To test for the importance of KF, we did experiments in the absence of KF and instead used the sterically demanding organic bases diisopropylamine (DIPA, entry 4, 5, Table 1) or lutidine (entry 6, Table 1). Despite the absence of fluoride, the selectivity preferences (for C—OTf in MeCN and C—Cl in THF) remained the same.[28] In these cases (i.e. entries 4–6, Table 1), the reactivity in polar solvents would be consistent with the coordination of deprotonated boronic acid to Pd and oxidative insertion by [Pd(PtBu$_3$)(ArBO$_2$H)]$^-$.[29] Our calculations of the TSs of oxidative insertion by [Pd(PtBu$_3$)(ArBO$_2$H)]$^-$ predict a clear preference for triflate insertion ($\Delta\Delta G^{\neq} = 3.9$ kcal mol^{-1} in MeCN).[30] Figure 2 illustrates the corresponding anionic TSs. Thus, the applied computational and experimental studies suggest that in the presence of coordinating species, such as salt or boronic acid, [Pd(PtBu$_3$)X]$^-$ (with X = F or ArBO$_2$H) is active in polar solvents and [Pd(PtBu$_3$)] in nonpolar solvents. Changes in the polarity of the reaction medium thus have a dramatic effect on the activity of one species in competition with another, resulting in a complete selectivity reversal.

If these mechanistic conclusions were correct, predominant C—Cl insertion should be observed in polar solvents in the absence of coordinating additives such as KF or ArB(OH)$_2$. To test this hypothesis, we decided to perform Stille cross-coupling reactions on substrate **1** [Eq. (1)], as those can be done additive-free, and the stannane coupling partner is non-coordinating.[31,32] Table 3 gives the results of the Stille test reactions. We now indeed see high selectivity for C—Cl insertion in DMF if no coordinating anions or coupling partner are present (see Table 3, entries 1 and 2).[33,34] Addition of KF or CsF (Table 3, entries 3 and 4) once again results in predom-



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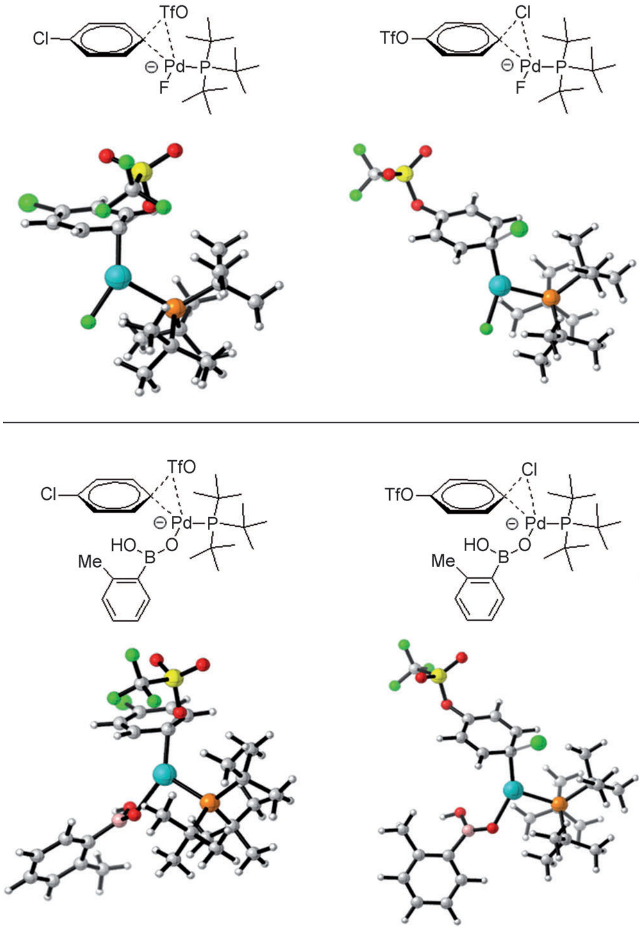

Figure 2. Tranistion states for C–OTf (left) and C–Cl (right) insertion using $[Pd(PtBu_3)X]^-$ with X = F (top), ArB(OH)O (bottom), optimized in MeCN. $\Delta\Delta G^{\neq} = 2.3$ kcal mol^{-1} (for X = F) and 3.9 kcal mol^{-1} (for X = $ArBO_2H$) in favor of C–OTf insertion, calculated with CPCM (MeCN) B3LYP/6-31+G(d), LANL2DZ (Pd).

Table 3: Stille cross-couplings with **1** [Eq. (1)].

	Additive[a]	T	t	Coupling partner	Ratio of compounds[b] 1	4	5
1	KPF_6	RT	38 h	Bu_3SnPh	45	47	8
2[c]	KPF_6	100 °C	7 d	Bu_3SnPh	3	88	9
3	KF	RT	38 h	Bu_3SnPh	18	30	51
4	CsF	RT	38 h	Me_3SnPh	–	21	79

[a] 3.0 equiv. [b] Ratio determined by calibrated GC-MS analysis. [c] 1.5 % $[Pd(PtBu_3)_2]$/0.75 % $[Pd_2(dba)_3]$.[34]

inant triflate insertion.[35] These findings are strong evidence of the validity of our computational and experimental mechanistic conclusions.

In conclusion, using computational studies combined with experiments, we provide strong support of a change of the catalytically active species in polar solvents in the presence of coordinating cross-coupling partner or additives, leading to a reversal of regioselectivity. The results suggest that the active species under such conditions in polar solvents is inconsistent with monoligated $[Pd(PtBu_3)]$ and reinforce the proposals of Amatore, Jutand et al. of anionic palladium as active catalytic species,[22] in line with recent conclusions by Hartwig.[24] Changes in solvent polarities can thus have a dramatic effect on the activity of one catalytic species in competition with another, resulting in a complete selectivity reversal.

Received: March 10, 2011
Revised: April 30, 2011

Keywords: palladium · regioselectivity · solvent effects · Suzuki coupling

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[16] A 50:50 mixture of MeCN/toluene results in mixture of C–Cl and C–OTf insertion. The ratio of compounds **2**/**3**/**1** is 25:64:11 (applying conditions [b] in Table 1). See the Supporting Information for further information.

[17] Table 1 reports the yields after isolation and purification. The crude mixture prior to purification was analyzed by GC-MS in each case, confirming that the yields of isolated product are a true reflection of selectivity. Reaction times of up to 48 h were chosen to ensure high conversion.

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