Reaction Mechanisms

Toward an Improved Understanding of the Unusual Reactivity of Pd^0/Trialkylphosphane Catalysts in Cross-Couplings of Alkyl Electrophiles: Quantifying the Factors That Determine the Rate of Oxidative Addition**

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Palladium- and nickel-catalyzed cross-couplings are widely used tools in synthetic chemistry.[1] No doubt, such processes would be even more broadly employed if they were not largely restricted to reactions of *aryl* and *vinyl* halides and sulfonates. Recognizing the significance of this limitation, several groups have recently turned their attention to the development of methods for cross-coupling *alkyl* halides and sulfonates.[2–7] Among the palladium catalysts that have been described to date, the majority are based on sterically demanding trialkylphosphanes (PCy_3 or $P(tBu)_2Me$).[8]

The catalytic cycle for most cross-coupling reactions presumably includes a sequence of oxidative addition, transmetalation, and reductive elimination (Figure 1). With regard to the challenge of coupling alkyl electrophiles, the difficulty

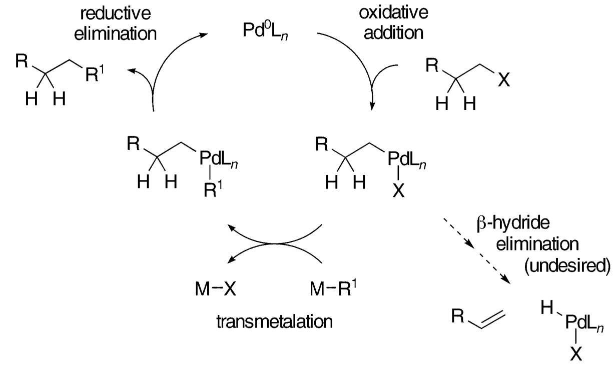

Figure 1. Generalized mechanism for a palladium-catalyzed cross-coupling reaction.

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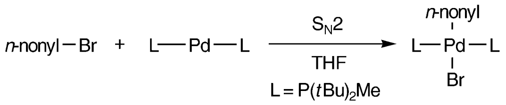
has generally been attributed to relatively slow oxidative addition and to facile β-hydride elimination (Figure 1). To complement our methods-development studies of Pd/trialkylphosphane catalysts for coupling alkyl electrophiles, we have recently initiated mechanistic work on these systems. As part of this new program, in this communication we describe a wide-ranging investigation of the initial step of the catalytic cycle, oxidative addition of an alkyl electrophile to a Pd/trialkylphosphane complex.

In an earlier study, we discovered that PdL_2 (L = PCy_3 or $P(tBu)_2Me$) can react with an alkyl electrophile (R−X) to generate an oxidative-addition adduct that, in the absence of a cross-coupling partner, can be isolated and even crystallographically characterized.[9] The relative stability of PdL_2RX toward β-hydride elimination was a pleasant surprise for us. Recognizing that there are no systematic, quantitative investigations of oxidative addition of alkyl electrophiles to palladium(o),[10] we decided to remedy this deficiency.

Through kinetics studies, we have determined that, for the oxidative addition of *n*-nonyl bromide to $Pd(P(tBu)_2Me)_2$ [Eq. (1)],[11] the activation parameters are: $\Delta G^{\ddagger} = 20.8$ kcal mol^{-1} at 20 °C; $\Delta H^{\ddagger} = 2.4$ kcal mol^{-1}; $\Delta S^{\ddagger} = -63$ eu. The large negative $\Delta S^{\ddagger}$ is consistent with the associative S_N2-type pathway suggested by our earlier stereochemical investigations.[12]



$$n\text{-nonyl}-\text{Br} + \text{L}-\text{Pd}-\text{L} \xrightarrow[\substack{\text{THF}\\ \text{L} = \text{P}(t\text{Bu})_2\text{Me}}]{S_N2} \text{L}-\underset{\text{Br}}{\overset{n\text{-nonyl}}{\text{Pd}}}-\text{L} \qquad (1)$$

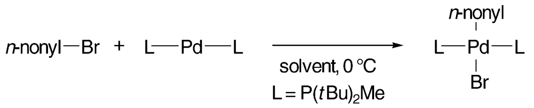
The addition of $P(tBu)_2Me$ (e.g., 2 or 4 equiv) to the reaction illustrated in Equation (1) does not affect the rate, suggesting that the alkyl bromide oxidatively adds to PdL_2, not PdL or PdL_3.[13] In contrast, in the case of cross-couplings of aryl bromides that are catalyzed by $Pd/P(tBu)_3$, the available data indicate that a palladium–monophosphane adduct undergoes oxidative addition.[14]

We have examined the relationship between solvent polarity and the rate of oxidative addition. As illustrated in Table 1, we have determined that an increase in polarity[15] leads to a decrease in the activation energy, consistent with the expectation for an S_N2-type nucleophilic attack of PdL_2 on R−X.[16]

We have also investigated the impact of the leaving group X on the rate of oxidative addition of alkyl electrophiles R−X to $Pd(P(tBu)_2Me)_2$ (Table 2). We have established that an alkyl iodide rapidly oxidatively adds to $Pd(P(tBu)_2Me)_2$ even at −60 °C (entry 1), whereas the corresponding bromide requires a temperature of 0 °C to achieve a comparable rate (entry 2). Upon heating to 60 °C, an alkyl chloride (entry 3), but not a fluoride (entry 4), reacts with $Pd(P(tBu)_2Me)_2$. Finally, we have determined that an alkyl tosylate (entry 5) is intermediate between a bromide and a chloride in reactivity. The relative propensity of alkyl electrophiles to oxidatively add to $Pd(P(tBu)_2Me)_2$ (Table 2) is consistent with an S_N2 pathway for oxidative addition.[17]

Unfortunately, no catalyst, including $Pd(P(tBu)_2Me)_2$, has yet been reported to be effective for cross-couplings of unactivated secondary alkyl electrophiles. Naturally, we were interested in whether this shortcoming may be attributable to a reluctance of these compounds to undergo oxidative addition. We therefore examined the relationship between the rate of oxidative addition to $Pd(P(tBu)_2Me)_2$ and the steric demand of the electrophile.

Table 1: Correlation between solvent polarity and the activation barrier for oxidative addition.[a]

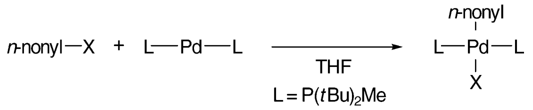


$$n\text{-nonyl}-\text{Br} + \text{L}-\text{Pd}-\text{L} \xrightarrow[\substack{\text{solvent, 0 °C}\\ \text{L} = \text{P}(t\text{Bu})_2\text{Me}}]{} \text{L}-\underset{\text{Br}}{\overset{n\text{-nonyl}}{\text{Pd}}}-\text{L}$$

Entry	Solvent	Polarity	$\Delta G^{\ddagger}$ [kcal mol^{-1}]
1	hexane	0.68	> 23.0[b]
2	toluene	1.66	20.0
3	THF	2.08	19.5
4	*tert*-amyl alcohol	2.46[c]	18.1
5	NMP[d]	2.62	18.0
6	DMF[e]	2.80	17.8

[a] All data are the average of two runs. [b] No reaction at 0–60 °C. $\Delta G^{\ddagger}$ was calculated for 60 °C. [c] Value for *tert*-butanol. [d] NMP = *N*-methylpyrrolidinone. [d] DMF = dimethylformamide.

Table 2: Effect of the leaving group on the rate of oxidative addition.[a]



$$n\text{-nonyl}-\text{X} + \text{L}-\text{Pd}-\text{L} \xrightarrow[\substack{\text{THF}\\ \text{L} = \text{P}(t\text{Bu})_2\text{Me}}]{} \text{L}-\underset{\text{X}}{\overset{n\text{-nonyl}}{\text{Pd}}}-\text{L}$$

Entry	X	$t_{1/2}$
1	I	2.2 h at −60 °C
2	Br	2.3 h at 0 °C
3	Cl	2.0 d at 60 °C
4	F	< 2 % reaction after 43 h at 60 °C
5	OTs[b]	10.4 h at 40 °C

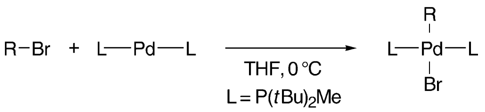
[a] All data are the average of two runs. [b] Ts = toluenesulfonyl.

As illustrated in Table 3, the bulk of the electrophile has a large impact on the reaction rate. Branching in the γ-position leads to a roughly fivefold decrease in reactivity relative to an unbranched substrate (entry 2 vs. entry 1), and branching in the β-position attenuates the reactivity by a factor of ~20 (entry 3 vs. entry 1). Consistent with the failure of $Pd(P(tBu)_2Me)_2$ to catalyze cross-couplings of secondary alkyl electrophiles, no oxidative addition occurs if the branch is in the α-position (entry 4).

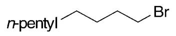
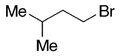
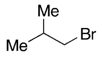
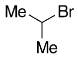
For couplings of primary alkyl electrophiles catalyzed by Pd/PR_3, in earlier work we observed a remarkable dependence of the efficiency of the reaction on the structure of the phosphane.[3d,e] We have now determined that cross-coupling efficiency correlates with the propensity of PdL_2 to undergo oxidative addition (Table 4). Thus, adducts of $P(tBu)_2Me$ or PCy_3 readily add *n*-nonyl bromide (Table 4, entries 1 and 2), in keeping with their effectiveness in a range of coupling processes. In contrast, complexes of $P(tBu)_2Et$ or $P(tBu)_3$ are relatively unreactive toward oxidative addition (entries 3 and 4), as well as ineffective at cross-coupling alkyl electrophiles.

The divergent reactivity of PdL_2 complexes of $P(tBu)_2Me$ (cone angle: 161°) and $P(tBu)_2Et$ (cone angle: 165°),[18] which

Table 3: Correlation between the steric demand of the electrophile and the activation barrier for oxidative addition.[a]

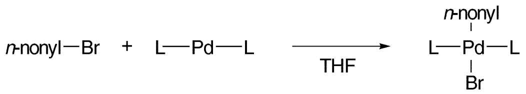


$$\text{R–Br} + \text{L–Pd–L} \xrightarrow[\text{L = P}(t\text{Bu})_2\text{Me}]{\text{THF, 0 °C}} \text{L–}\overset{\text{R}}{\underset{\text{Br}}{\text{Pd}}}\text{–L}$$

Entry	R–Br	k_{rel}	$\Delta G^{\ddagger}$ [kcal mol^{-1}]
1		1.0	19.5
2		0.19	20.3
3		0.054	21.0
4		<0.0001	>24.0[b]

[a] All data are the average of two runs. [b] Extrapolated from a reaction run at 60 °C.

Table 4: Effect of the phosphane on the activation barrier for oxidative addition.[a]



$$n\text{-nonyl–Br} + \text{L–Pd–L} \xrightarrow{\text{THF}} \text{L–}\overset{n\text{-nonyl}}{\underset{\text{Br}}{\text{Pd}}}\text{–L}$$

Entry	L	$\Delta G^{\ddagger}$ [kcal mol^{-1}][b]
1	$P(tBu)_2Me$	19.5 (0 °C)
2	PCy_3	20.0 (0 °C)
3	$P(tBu)_2Et$	25.4 (60 °C)
4	$P(tBu)_3$	>28.4 (60 °C)

[a] All data are the average of two runs. [b] The temperature at which $\Delta G^{\ddagger}$ was measured is noted in parentheses.

at first glance appear to be nearly isosteric, is particularly striking (Table 4, entries 1 and 3; $k_{rel} > 10^3$). However, computation of the energy of the various conformers of palladium–phosphane adducts leads to a reasonable explanation for this initially surprising difference. Through B3LYP/LanL2DZ DFT calculations, we have determined that conformer **1**, in which Me and Pd are eclipsed, is ~3.5 kcal mol^{-1} lower in energy than conformer **2**, in which Me and Pd are *anti*, due to the presence of additional *syn*-pentane-like interactions in **2** (Figure 2a).[19] Figure 2b shows that, in the illustrated conformation of $Pd(P(tBu)_2Et)_2$ (**3**), approach of an electrophile to Pd would be impeded significantly by the Me groups. In contrast, higher energy conformation **4** presents a steric environment around Pd that resembles that of $Pd(P(tBu)_2Me)_2$.[20] We believe that this analysis provides an adequate rationalization for the difference in reactivity between $Pd(P(tBu)_2Et)_2$ and $Pd(P(tBu)_2Me)_2$.

In conclusion, we have described the first systematic investigation of the oxidative addition of alkyl electrophiles to Pd^0, specifically, adducts of trialkylphosphanes. The reactivity of these complexes is of high current interest due to their unusual effectiveness as cross-coupling catalysts for alkyl electrophiles. We have determined that the species that undergoes oxidative addition is PdL_2 and that the activation parameters for this S_N2 process are: $\Delta G^{\ddagger} = 20.8$ kcal mol^{-1} at 20 °C; $\Delta H^{\ddagger} = 2.4$ kcal mol^{-1}; $\Delta S^{\ddagger} = -63$ eu. In addition, we have quantified the impact of the following parameters on the rate of oxidative addition of R–X to PdL_2: the solvent, the leaving group (X = I, Br, Cl, F, OTs), and the steric demand of the electrophile (R) and the ligand (L). Furthermore, based on DFT calculations, we have provided a rationale for the remarkable difference in reactivity between $Pd(P(tBu)_2Me)_2$ and $Pd(P(tBu)_2Et)_2$. Additional mechanistic studies of these intriguing cross-coupling catalysts are underway.

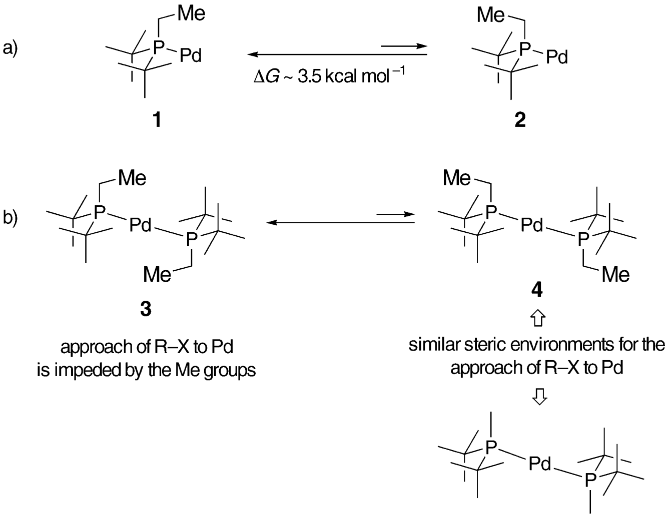


Figure 2. A rationale for the divergent reactivity of $Pd(P(tBu)_2Me)_2$ and $Pd(P(tBu)_2Et)_2$.

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[1] For reviews of metal-catalyzed cross-coupling reactions, see: a) *Metal-Catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, New York, **1998**; b) "Cross-Coupling Reactions: A Practical Guide": *Top. Curr. Chem.* **2002**, *219* (Ed.: N. Miyaura); c) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), Wiley Interscience, New York, **2002**.

[2] For an overview of the difficulty of achieving coupling reactions of $C(sp^3)$–X electrophiles, see: D. J. Cárdenas, *Angew. Chem.* **1999**, *111*, 3201–3203; *Angew. Chem. Int. Ed.* **1999**, *38*, 3018–3020; D. J. Cárdenas, *Angew. Chem.* **2003**, *115*, 398–401; *Angew. Chem. Int. Ed.* **2003**, *42*, 384–387. See also: T.-Y. Luh, M.-k. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187–3204.

[3] Suzuki reaction: a) T. Ishiyama, S. Abe, N. Miyaura, A. Suzuki, *Chem. Lett.* **1992**, 691–694; b) M. R. Netherton, C. Dai, K. Neuschütz, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100; c) J. H. Kirchhoff, C. Dai, G. C. Fu, *Angew. Chem.* **2002**, *114*, 2025–2027; *Angew. Chem. Int. Ed.* **2002**, *41*, 1945–1947; d) M. R. Netherton, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4066–4068; *Angew. Chem. Int. Ed.* **2002**, *41*, 3910–3912; e) J. H. Kirchhoff, M. R. Netherton, I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.

[4] Negishi reaction: a) A. Devasagayaraj, T. Stüdemann, P. Knochel, *Angew. Chem.* **1995**, *107*, 2952–2954; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2723–2725; b) R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *Angew. Chem.* **1998**, *110*, 2512–2515;

Angew. Chem. Int. Ed. **1998**, *37*, 2387 – 2390; c) R. Giovannini, P. Knochel, *J. Am. Chem. Soc.* **1998**, *120*, 11186 – 11187; d) R. Giovannini, T. Stüdemann, A. Devasagayaraj, G. Dussin, P. Knochel, *J. Org. Chem.* **1999**, *64*, 3544 – 3553; e) M. Piber, A. E. Jensen, M. Rottländer, P. Knochel, *Org. Lett.* **1999**, *1*, 1323 – 1326; f) A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79 – 85; g) J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 12527 – 12530.

[5] Kumada reaction: a) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2002**, *124*, 4222 – 4223; b) A. C. Frisch, N. Shaikh, A. Zapf, M. Beller, *Angew. Chem.* **2002**, *114*, 4218 – 4221; *Angew. Chem. Int. Ed.* **2002**, *41*, 4056 – 4059; c) J. Terao, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2003**, *125*, 5646 – 5647.

[6] Stille reaction: a) K. Menzel, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 3718 – 3719; b) H. Tang, K. Menzel, G. C. Fu, *Angew. Chem.* **2003**, *115*, 5233 – 5236; *Angew. Chem. Int. Ed.* **2003**, *42*, 5079 – 5082.

[7] Hiyama reaction: J.-Y. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 5616 – 5617.

[8] For exceptions, see refs. [3a] and [6b].

[9] a) Ref. [3e]; b) I. D. Hills, M. R. Netherton, unpublished results.

[10] For an excellent review of oxidative addition, including the chemistry of Pd^0, see: J. K. Stille in *The Chemistry of the Metal–Carbon Bond* (Ed.: S. Patai), Wiley, New York, **1985**, chap. 9. See also: M. Huser, M.-T. Youinou, J. A. Osborn, *Angew. Chem.* **1989**, *101*, 1427 – 1430; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1386 – 1388.

[11] We chose to focus on complexes of $P(t\mathrm{Bu})_2\mathrm{Me}$ because it generally furnishes the most active catalyst.

[12] a) Ref. [3d]; b) I. D. Hills, M. R. Netherton, unpublished results.

[13] When $\mathrm{Pd}(P(t\mathrm{Bu})_2\mathrm{Me})_2$ is dissolved in THF, the only phosphorus-containing species that is present according to ^{31}P NMR spectroscopy is the PdL_2 adduct (e.g., no PdL_1), and there is no change in the spectrum in the presence of excess $P(t\mathrm{Bu})_2\mathrm{Me}$ (e.g., no PdL_3).

[14] a) A. F. Littke, G. C. Fu, *Angew. Chem.* **1998**, *110*, 3586 – 3587; *Angew. Chem. Int. Ed.* **1998**, *37*, 3387 – 3388; A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020 – 4028; b) J. P. Stambuli, R. Kuwano, J. F. Hartwig, *Angew. Chem.* **2002**, *114*, 4940 – 4942; *Angew. Chem. Int. Ed.* **2002**, *41*, 4746 – 4748, and references therein; M. Prashad, X. Y. Mak, Y. Liu, O. Repic, *J. Org. Chem.* **2003**, *68*, 1163 – 1164. See also: E. Galardon, S. Ramdeehul, J. M. Brown, A. Cowley, K. K. Hii, A. Jutand, *Angew. Chem.* **2002**, *114*, 1838 – 1841; *Angew. Chem. Int. Ed.* **2002**, *41*, 1760 – 1763.

[15] The values for solvent polarity are according to the S′ scale. For an overview, see: J. Zou, Q. Yu, Z. Shang, *J. Chem. Soc. Perkin Trans. 2* **2001**, 1439 – 1443.

[16] In our methods-development studies, we have consistently found nonpolar solvents such as hexane and toluene to be unsuitable for cross-coupling reactions of alkyl electrophiles.

[17] Consistent with the possibility that oxidative addition is the turnover-limiting step of the catalytic cycle, the same order of reactivity ($\mathrm{Br} > \mathrm{OTs} > \mathrm{Cl}$) is observed for Suzuki reactions catalyzed by $\mathrm{Pd/PR}_3$.[3b–d]

[18] These values were calculated by the method of Tolman: C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313 – 348.

[19] Notes: a) The only other energy minimum that was located is the conformation in which Me and Pd are *gauche*. This lies ~0.6 $\mathrm{kcal\,mol^{-1}}$ higher in energy than the eclipsed conformation. b) These calculations are, of course, imperfect, since they do not account for effects such as solvation.

[20] The PdL_2 structures in Figure 2b are not the direct result of calculations—they are derived from computed structures **1** and **2**.