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Palladium(II)-Catalyzed Direct Alkoxylation of Arenes: Evidence for Solvent-Assisted Concerted Metalation Deprotonation

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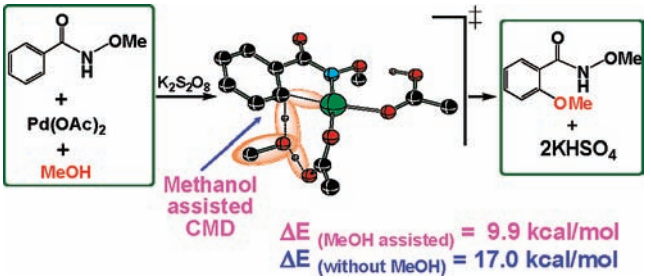
ABSTRACT



Density functional theory investigations on the mechanism of palladium acetate catalyzed direct alkoxylation of *N*-methoxybenzamide in methanol reveal that the key steps involve solvent-assisted N−H as well as C−H bond activations. The transition state for the critical palladium−carbon bond formation through a concerted metalation deprotonation (CMD) process leading to a palladacycle intermediate has been found to be more stable in the methanol-assisted pathway as compared to an unassisted route.

Transition-metal-catalyzed functionalizations of organic compounds using C−H bond activations is a ubiquitous synthetic protocol.[1] The derivatization of aromatic compounds by this method found applications in medicine[2] and materials.[3a] Several manifestations of selective activation and functionalization of C−H bonds, particularly using palladium catalysts, have been reported in recent years.[3] Introduction of functional groups at the desired positions by using directing amido or *N*-acyl groups enjoys considerable popularity in contemporary research.[4] While palladium-catalyzed alkylations and arylations continue to remain in the forefront, functionalization by creating a new C−O bond is receiving increasing attention.[5] In one such approach, Wang et al. demonstrated palladium acetate catalyzed direct ortho-acetoxylation of anilides.[6] In a more recent study from the same group, a palladium-catalyzed

(1) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

(2) (a) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177. (b) Potavathri, S.; Kantak, A.; DeBoef, B. *Chem. Commun.* **2011**, *47*, 4679.

(3) (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (b) Bergman, R. G. *Nature* **2007**, *446*, 391. (c) Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(4) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190.

(5) A variety of acetoxylation reactions are recently reported. See: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Fu, Y.; Li, Z.; Liang, S.; Guo, Q.-X.; Liu, L. *Organometallics* **2008**, *27*, 3736. Oxidative functionalization to aryl esters and ethers are also known: (c) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (d) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584. (e) Ye, Z.; Wang, W.; Luo, F.; Zhang, S.; Chen, J. *Org. Lett.* **2009**, *11*, 3974.

(6) Wang, G.-W.; Yuan, T, -T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717.

(7) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476.

(8) (a) For a recent review on acetate-assisted cyclometalations, see: Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 3308. (c) Popp, B. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 4410. (d) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (e) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitec, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (f) Davies, S. S.; Donald, D. L.; A., S. M.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. (f) Steinhoff, B. A.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 11268. (g) Nielson, R. J.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2006**, *128*, 9651. (h) Ziatdinov, V. R.; Oxgaard, J.; Mironov, O. A.; Young, K. J. H.; Goddard, W. A., III; Periana, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 7404.

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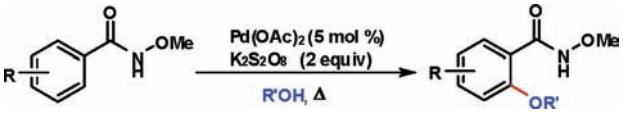
ortho-methoxylation reaction of arenes, as shown in Scheme 1, was reported.[7] Two interesting features of their approach include the use of N-methoxyamide as a directing group and the use of methanol as the solvent as well as the source of methoxide in the reaction.

Scheme 1. Palladium Acetate Catalyzed Direct Alkoxylation of *N*-Methoxybenzamide in Methanol



It has been established that ligands such as an acetate or carbonate additives could exert pivotal effects in cyclometalation reactions.[8] These reactions have offered intriguing mechanistic scenarios such as the involvement of concerted metalation deprotonation (CMD) pathway.[9] In this paper, we intend to convey interesting mechanistic details of methanol as well as acetate-assisted C−H bond activations in the alkoxylation of benzamides. The vital role of solvent is highlighted in several elementary steps in the reaction.

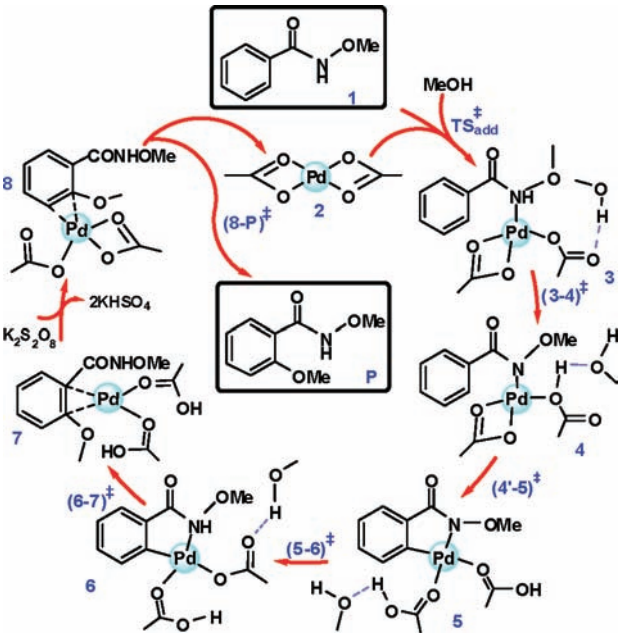
The key steps in the mechanistic cycle involving one molecule of solvent (methanol) are summarized in Scheme 2. The reaction begins by the coordination of Pd(II) acetate to the nitrogen of *N*-methoxybenzamide. This step is accompanied by a change in the coordination pattern of one of the acetate ligands from η^2 to η^1 resulting in intermediate **3**. In the next step, an intramolecular proton transfer from the N−H group to the acetate takes place leading to intermediate **4**. This proton transfer could proceed via a four-membered transition state without methanol or a six-membered transition state involving a methanol. Since a large number of solvent molecules are expected to be in the near vicinity of the solute, as the reaction is conducted in a methanolic medium, the acetic acid bound intermediate **4** could offer another stoichiometrically same intermediate **4′** where the site of methanol attachment is with the acetate ligand. In **4′**, the acetic acid coordination is found to be through the oxygen of the C=O bond as compared to that through −OH in **4** as shown in Figure 1.[10] A concerted metalation deprotonation process can then furnish intermediate **5**.

The explicit acetate-bound methanol in **4′** can help relay the aryl proton in the ensuing C−H bond activation step involving TS(**4′-5**). Subsequently, reprotonation of the amido nitrogen results in a change in coordination of palladium leading to intermediate **6**. In another vital step, the introduction of the methoxy group to the aryl ring by the bound methanol occurs through a reductive elimination of palladium through TS(**6**−**7**). The resulting *o*-methoxybenzamide species **7** with an η^2 coordination with Pd(0)$(AcOH)_2$ can now react with the oxidant to regenerate

(9) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

(10) A transition state for this change of coordination has been located. See Figure S5 in the Supporting Information.

Scheme 2. Key Steps Involved in the Mechanism of Ortho-Alkoxylation of *N*-Methoxybenzamide



the Pd(II) acetate. Upon release of the product, the catalytic cycle continues with $Pd(OAc)_2$ and reactants.

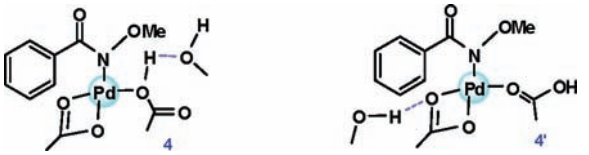


Figure 1. Comparison of intermediates **4** and **4′**.

The computed energetics at the B3LYP/6-31+G** level of theory, obtained both in the gas phase and in the condensed phase (in methanol dielectric continuum) for key elementary steps, are provided in Table 1.[11] The values inclusive of solvent effects obtained at the $SMD_{(MeOH)}$/B3LYP/6-31+G** level of theory are used for discussions herein.

Table 1. The Relative Energies (kcal/mol) of Key Steps Involved in Alkoxylation of Benzamide with and without Explicit Methanol[a]

	no methanol		one methanol	
TS	ΔE	ΔE_{sol}	ΔE	ΔE_{sol}
TS_{add}	14.6	14.7	10.9	14.9
3−**4**	14.6	18.1	1.4	8.7
4′-5	15.0	17.0	4.7	9.9
5−**6**	−6.6	−1.4	−19.2	−9.1

[a] All energies are given in kcal/mol with respect to infinitely separated reactants.

The initial step for the coordination of the substrate to the catalyst is identified to involve a barrier of about 15 kcal/mol. The role of explicit methanol is expected to be minimal in this step. The N−H bond activation and deprotonation of the amido nitrogen can proceed with or without the participation of the explicit methanol. The corresponding transition state TS(**3**-**4**) with methanol, as shown as (i) in Figure 2, is 9.4 kcal/mol lower than the corresponding transition state without methanol, indicating the likely involvement of a relay proton transfer mechanism in this step.[12] A tetracoordinate palladium intermediate **4** is identified in which an acetic acid is coordinated to the palladium through its hydroxyl oxygen. While the methanol molecule can continue to remain attached to the acetic acid fragment, consideration of an alternative possibility wherein the methanol is bound to the acetate ligand, closer to the site of C−H bond activation, was desirable for examining the energetic effects in the subsequent steps. We therefore envisaged another intermediate **4′**, differing in the site of attachment of methanol.

The next step involving the aryl C−H bond activation and concerted metalation deprotonation offers certain remarkable mechanistic features. The CMD step could proceed through C−H activation facilitated either by the acetate or by a molecule of methanol. The energy of CMD transition state TS(**4**−**5**) in the methanol-assisted pathway is found to be lower than the corresponding acetate-assisted mode. The comparison of geometries (iii) and (iv) in Figure 2 implies that the efficiency of direct proton abstraction by the acetate is lower as compared to a relay through the intervening methanol molecule. The proton abstraction in (iii) is more advanced than in (iv) resulting in a shorter Pd−C bond in the transition state in the former case. The methanol-assisted transition state evidently suggests the involvement of a relay proton transfer mechanism in the vital CMD step. This is a significantly interesting observation in view of the use of methanol as a solvent in this reaction. Such roles played by explicit solvent molecules are generally not paid the attention it deserves in mechanistic investigations. The energetics for the formation of the resulting palladacycle intermediate **5** is found to be exothermic, both with and without methanol. This can be readily gleaned from the comparative energy profile diagram provided in Figure 3.

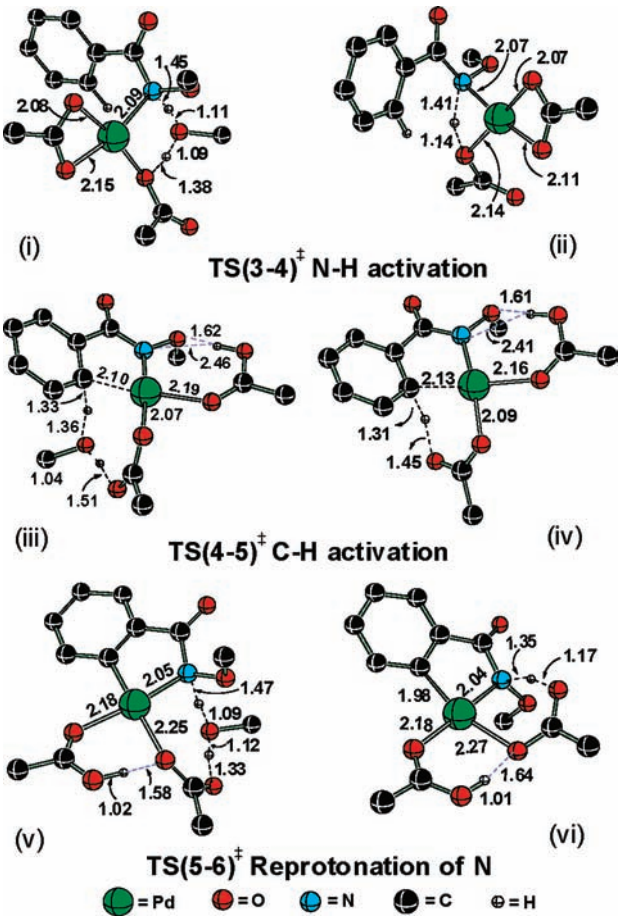


Figure 2. Transition-state geometries for important mechanistic steps with (i, iii, v) and without (ii, iv, vi) explicit methanol.

In the next step, reprotonation of amido nitrogen is examined. The corresponding transition state for the conversion of **5** to **6** is identified as more stable when a methanol-assisted relay proton transfer operates, as shown in (v) in Figure 2. A direct comparison between the methanol-assisted and the unassisted pathway can be performed with the help of Figure 3. The largest stabilization due to explicit methanol participation is noticed for the N−H activation step which is 9.4 kcal/mol, while the C−H activation and reprotonation of amido nitrogen exhibited stabilizations of the order of about 7 kcal/mol.

The subsequent steps in the reaction are common to both pathways, with or without methanol, as the role of methanol now is to act as a source of methoxy group. The geometry of the transition state for the reductive elimination step, TS(**6**−**7**), is shown in Figure 4. It can be noticed that the proton abstraction from methanol is performed by the acetate ligand. As the methoxide gets bound to the ortho carbon of the aryl ring the Pd−C bond elongates, eventually leading in an η^2 aryl complex. The transition state for this step is found to occupy the highest point on

(11) (a) All calculations were performed using Gaussian09 suite of programs. Firsch, M. J. et al. Gaussian 09 Revision A.02; Gaussian, Inc.: Wallingford, CT, 2004. See computational methods provided in the Supporting Information for further details. (b) The B3LYP functional are generally known to be good for mechanistic studies on palladium catalyzed reactions. See: Braga, A. A. C.; Ujaque, G.; Maseras, F. *Organometallics* **2006**, *25*, 3647. Garcia-Fandino, R.; Gulias, M.; Castedo, L.; Granja, J. R.; Mascarenas, J. L.; Cardenas, D. J. *Chem.—Eur. J.* **2008**, *14*, 272. Ananikov, V. P.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **2002**, *124*, 2839.

(12) (a) We, as well as others, have earlier highlighted the importance of assisted proton-transfer processes as capable of offering effective lowering of activation barriers. See: Patil, M. P.; Sunoj, R. B. *Chem.—Eur. J.* **2008**, *14*, 10472. Patil, M. P.; Sunoj, R. B. *J. Org. Chem.* **2007**, *72*, 8202. Roy, D.; Sunoj, R. B. *Chem.—Eur. J.* **2008**, *14*, 10530. Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. Liang, Y.; Zhou, H.; Yu, Z.-X. *J. Am. Chem. Soc.* **2009**, *131*, 17783. (b) The transition state for direct proton transfer involving a six-membered geometry is found to be lower than the corresponding four-membered geometry. Additional details for this process is provided in Figures S3 and S4 in the Supporting Information.

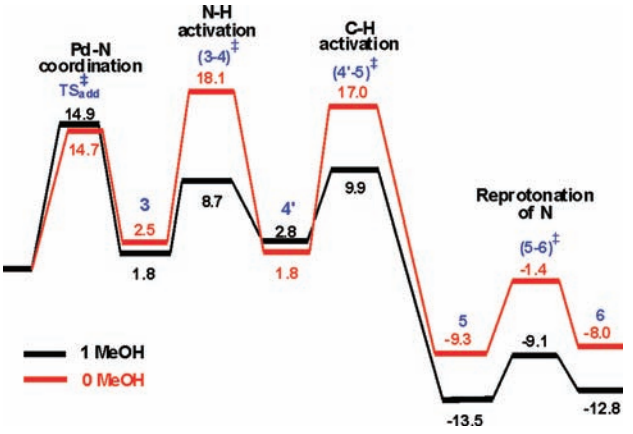


Figure 3. Comparative energy profile obtained at the $SMD_{(MeOH)}$/B3LYP/6-31+G** level of theory for the key mechanistic steps involved in the alkoxylation of benzamide.

the potential energy profile, which is 25 kcal/mol with respect to the reference point (separated reactants), indicating that the reductive elimination step could determine the rate of overall reaction. In the resulting intermediate **7**, two molecules of acetic acid are coordinated to the palladium center, suggesting a Pd(0) state. Upon action of the oxidant ($K_2S_2O_8$), a product complex **8** can be formed wherein the palladium acetate is bound to product ortho-methoxybenzamide. The oxidation step is computed to be mildly endothermic by 4.7 kcal/mol.[13] The energy of the transition state (**8-P**) for the product release from the penultimate intermediate **8** revealed a low barrier process. The overall reaction between *N*-methoxybenzamide and methanol giving rise to *o*-methoxy-substituted *N*-methoxybenzamide is computed to be exothermic by 6.4 kcal/mol.[14]

A comparison of energetics in the gas phase with that obtained using the continuum solvent effects, as summarized in Table 1, reveals a broad consensus. The trends, such as a higher energy addition transition state and a facile reprotonation of amido nitrogen, continues to remain similar with and without methanol inclusion as well.

(13) (a) Calculated as the energy difference between **8** + $2KHSO_4$ and **7** + $K_2S_2O_8$. The similar role of $K_2S_2O_8$ is reported in: (b) Muehlhofer, M.; Strassner, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1745.

(14) The value is computed as the heat of reaction **1** + MeOH + $K_2S_2O_8$ → **P** + $2KHSO_4$ at $SMD_{(MeOH)}$/B3LYP/6-31+G**//6-31G* level of theory.

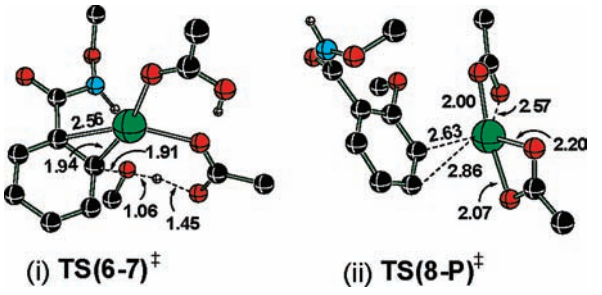


Figure 4. Transition-state geometries for (i) alkoxylation and (ii) product release.

In conclusion, the explicit participation of methanol in the vital elementary steps in the mechanism of ortho-alkoxylation of benzamides has been found to be significant. Since the stabilization of the transition states for the initial N−H activation and subsequent concerted metalation deprotonation step are high, a prominent role of solvent methanol is expected in this reaction.

The findings could have wider implications in the way the mechanism of C−H activation reactions in polar protic solvents is generally perceived. Further studies are currently underway to arrive at sufficient generalizations of possible relay proton transfer in bond-activation reactions.

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Supporting Information Available. Full details of computational methods, optimized Cartesian coordinates for all stationary points, and other pertinent information as referred in the text. This material is available free of charge via the Internet at http://pubs.acs.org.