# Non-innocent Additives in a Palladium(II)-Catalyzed C−H Bond Activation Reaction: Insights into Multimetallic Active Catalysts

Megha Anand,[†] Raghavan B. Sunoj,*[,‡] and Henry F. Schaefer, III*[,†]

[†]Center for Computational Quantum Chemistry, University of Georgia Athens, Georgia 30602, United States,
[‡]Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

**ⓢ** *Supporting Information*

**ABSTRACT:** The role of a widely employed additive (AgOAc) in a palladium acetate-catalyzed *ortho*-C−H bond activation reaction has been examined using the M06 density functional theory. A new hetero-bimetallic Pd-($\mu$-OAc)$_3$-Ag is identified as the most likely active species. This finding could have far-reaching implications with respect to the notion of the active species in palladium catalysis in the presence of other metal salt additives.

Over the years, a broad range of methodologies has become available for making functionalized aromatic compounds using transition metal-catalyzed C−H bond activation.[1] The approach, in general, involves the use of a suitable transition metal catalyst on substrates bearing a directing group.[2] One of the quintessential examples in this genre is the palladium acetate-catalyzed *ortho*-functionalization of aryl amides as well as 2-phenylpyridines.[3] A quick perusal of literature spanning over a decade reveals that several such methods resort to the use of additives to improve the efficiency of the catalytic processes.[2a,4] Typical additives are metal salts, such as a terminal oxidant, that help regenerate the transition metal catalyst back to its native oxidation state toward the later part of the catalytic cycle.[3a,c,d,5]

It is important to recognize that a large number of C$_{aryl}$−C and C$_{aryl}$−heteroatom bond formation reactions for aryl functionalizations have been achieved using Pd(OAc)$_2$ as the catalyst.[1,2a,b,6] While the examples for C$_{aryl}$−C coupling reactions are available in abundance, reactions for C$_{aryl}$−O and C$_{aryl}$−N coupling remained relatively less reported until recently.[1a,b,5a,6a,7] One of the most recent breakthroughs in direct aryl amination came from the Yu group (Scheme 1).[8] The resulting product aryl amines are known to be useful in many biological processes.[9]

The Yu reaction employs silver acetate and cesium fluoride as additives besides palladium acetate as the catalyst. The use of multiple additives under homogeneous reaction conditions is obviously expected to increase the mechanistic complexities. In particular, the nature of the catalytic species in the presence of such additives could be different from the conventionally proposed monomeric Pd(OAc)$_2$. Clearly, this hypothesis warrants careful scrutiny.

As a part of our continuing investigations toward understanding the mechanisms of transition metal-catalyzed carbon−heteroatom bond formation reactions,[10] we became interested in examining the mechanism of the Pd(OAc)$_2$-catalyzed

**Scheme 1. Palladium Acetate-Catalyzed *ortho*-Amination of N-Arylbenzamide[8]**



**X** = Pd(OAc)$_2$ ; **Y** = CsF ; **Z** = AgOAc       Ar = *p*-(CF$_3$)C$_6$F$_4$
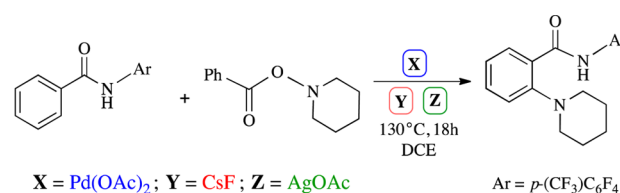
| X | Y | Z | Yield (%) |
|---|---|---|-----------|
| ✓ | ✗ | ✗ | ~40 |
| ✓ | ✓ | ✗ | ~54-70 |
| ✓ | ✓ | ✓ | ~96 |

amination of *N*-arylbenzamides, as shown in Scheme 1.[8] That reaction brings forth some intriguing questions concerning the role of additives such as AgOAc and CsF. However, the molecular origin and the mode of action of such additives in the catalytic cycle still remain to be established. The reaction relies on C−H functionalization, where the amide acts as the directing group for *ortho*-C−H bond activation. In this Communication, we intend to capture the first molecular insights into the potential involvement of some novel multimetallic catalytic species in the vital C−H bond activation step. Our discussion is presented in terms of the Gibbs free energies computed with the M06 density functional theory in 1,2-dichloroethane (DCE) as the continuum solvent.[11]

The reaction shown in Scheme 1 can be envisaged to begin with the coordination of the catalyst to the amido nitrogen.[12] The role of different additives has been probed by explicitly including them in the C−H activation transition state. Among the different possibilities considered, energetically the most preferred only are discussed, whereas alternatives are used for cogent comparisons. To begin, a conventional pathway wherein a molecule of Pd(OAc)$_2$ functions as the sole catalyst is examined. Similar to the other known systems, the N−H activation by Pd(OAc)$_2$ is considered as the first step after the combination of catalyst with the substrate.[13] The resulting intermediate is poised to undergo *ortho*-C−H bond activation owing to the proximity between the metal and the aryl C−H bond. The ensuing acetate-assisted C−H activation via **TS1** or **TS2**, as shown in Figure 1, will provide a palladacycle

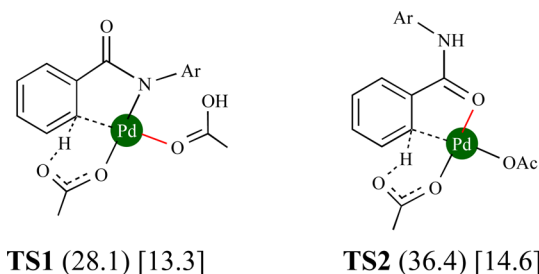**TS1 (28.1) [13.3]**      **TS2 (36.4) [14.6]**

**Figure 1.** C−H activation transition states with a monomeric palladium acetate catalyst. The values in parentheses are the relative free energies (in kcal/mol) with respect to the separated reactants, and those in square brackets are with respect to the preceding intermediate.

intermediate.[6d,e,14] Although the relative Gibbs free energy of this transition state (28 kcal/mol) appears reasonable, the participation of additives is unclear. Hence, the transition-state models are refined by explicit inclusion of AgOAc and CsF. To enable comparison of the computed energetics uniformly across different possible scenarios arising as a result of inclusion of silver and cesium salts in the transition-state models, the relative energies with respect to the infinitely separated reactants are provided.[15] The elementary step barriers are included as well, such that the activation barriers of a given type of transition states (with identical stoichiometry) can be compared.

The inclusion of additives in the transition state is found to help in the deprotonation of the amido group. For instance, the fluoride derived from CsF can lead to the formation of HF, while the acetate of AgOAc can give rise to AcOH. Facilitating the deprotonation of the amido nitrogen may be regarded as the first likely role of CsF.[16] The resulting amidate can now interact with the cesium or the silver ion. The C−H activation in the metal−amidate species is found to be energetically more favored when CsF is involved (**TS3**) as compared to that with AgOAc (**TS4**) (Figure 2).[17] The improved favorability of **TS3**



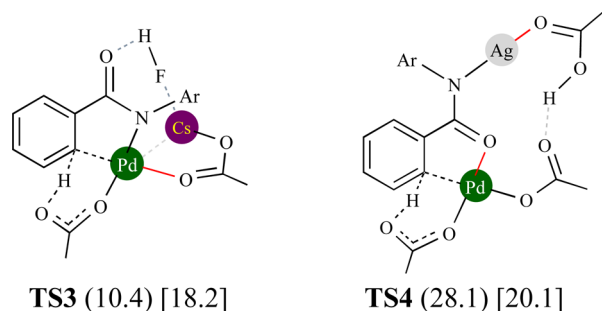**TS3 (10.4) [18.2]**      **TS4 (28.1) [20.1]**

**Figure 2.** C−H activation transition states for cesium (**TS3**) and silver (**TS4**) amidates. The values in parentheses are the relative free energies (in kcal/mol) with respect to the separated reactants, and those in square brackets are with respect to the preceding intermediate.

(10.4 kcal/mol) as compared to **TS1** (28.1 kcal/mol) is in line with the experimental observation of higher efficiency of the reaction when Pd(OAc)$_2$ is used in conjunction with CsF (Scheme 1).

A comparison worth considering at this juncture is that the energy of the transition state with silver bound to the amidate **TS4** is about 18 kcal/mol higher than for the corresponding cesium-bound **TS3** (Figure 2). More interestingly, however,

both of these modes of C−H activation are lower in energy than the conventional transition states (**TS1** and **TS2**) with a monomeric Pd(OAc)$_2$. It is important to note that there could be alternative sites for coordination of the AgOAc to the substrate. We have therefore explored different configurations wherein the catalyst and additives are bound to the substrate while maintaining close proximity between them. Consideration of such geometric propensities can help probe the effect of multimetallic interactions, or even synergism, in the key C−H activation step.

To our surprise, a number of interesting transition-state configurations exhibiting multimetallic interactions were identified. To our knowledge, C−H activation transition states exhibiting such hetero-bimetallic interactions are seldom reported.[18] More importantly, **TS5** and **TS6** in this family are energetically lower than all the other transition-state models (Figure 3).[19] For instance, **TS5**, with a Pd−Ag hetero-



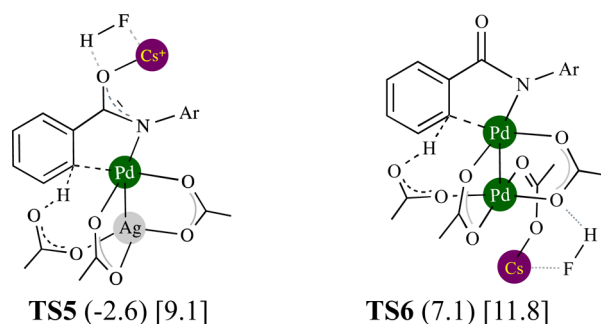**TS5 (-2.6) [9.1]**      **TS6 (7.1) [11.8]**

**Figure 3.** C−H activation TSs exhibiting metal−metal interactions. The values in parentheses are the relative free energies (in kcal/mol) with respect to the separated reactants, and those in square brackets are with respect to the preceding intermediate.

bimetallic interaction, is 30 kcal/mol lower in free energy than **TS1** (with the conventional monomeric Pd(OAc)$_2$) and 13 kcal/mol lower than **TS3** (inclusive of CsF). The geometries of these transition states indicated that the cesium ion interacts with other atoms/groups (oxygen of −CONHAr and −OAc, HF, C$_6$F$_5$CF$_3$ groups shown as Ar for improved clarity) than what is shown in the figures.[20]

The geometry of **TS5** exhibits some interesting features (Figure 4). First, the short contact between Pd and Ag (2.9 Å) indicates a favorable electronic communication.[21] Availability of crystal structures of d$^8$−d$^{10}$ hetero-bimetallic complexes with bidentate acetate bridges provides additional credence to our hypothesis.[22] Besides the direct Pd(II)−Ag(I) interaction, the acetate bridges can augment the intermetallic interaction.[23] While the heterometallic d$^8$−d$^{10}$ interaction in the Pd(II)−Ag(I) system can be viewed as similar to that in Pd(II)−Pd(0), the heterogeneity can offer different cooperative effects in catalysis.[24]

It is also interesting to note that although the C−H activation is facilitated by palladium(II), the proton abstraction is performed by the acetate bound to the silver atom. Interchanging the positions of these two metals, such that silver(I) is closer to the C−H bond while the acetate bound to the palladium abstracts the proton, results in a higher energy transition state.[25] This implies that the Pd(OAc)$_2$ acts as the primary catalyst and hence the reaction is not expected to take place in its absence.

In view of available bimetallic palladium complexes, we have also examined the efficiency of a homo-dimeric Pd$_2$(OAc)$_4$ as
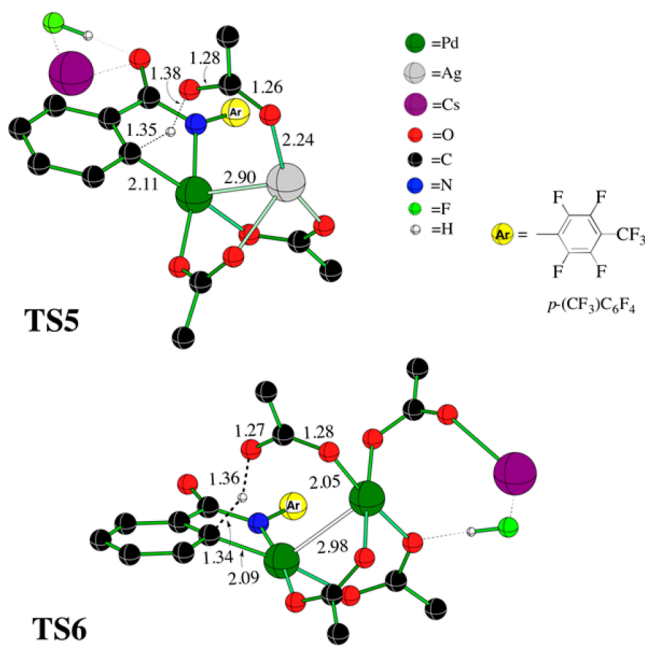
**Figure 4.** Optimized geometries for the C−H activation transition states exhibiting metal−metal interactions.

an active species for the C−H activation (**TS6**).[26] However, the computed energies are found to be higher (∼10 kcal/mol) than those for the hetero-bimetallic Pd(OAc)$_3$Ag analogue (**TS5**). This suggests the existence of cooperativity between the catalyst Pd(OAc)$_2$ and the additive (AgOAc). In addition, transition states consisting of more than one molecule of AgOAc and CsF are examined. These possibilities, however, are of higher free energies as compared to what has herein been presented.[27]

In conclusion, explicit consideration of silver acetate and cesium fluoride in the key C−H activation transition states led to the identification of a new hetero-bimetallic Pd-($\mu$-OAc)$_3$-Ag species as the most likely active catalyst in a palladium acetate-catalyzed *ortho*-amination reaction. The results reported herein are expected to have broad mechanistic implications for other transition metal-catalyzed reactions employing metal salts as additives.

## ■ ASSOCIATED CONTENT

**ⓈSupporting Information**

Complete ref 11 and additional citations related to refs 17, 21, and 22; total electronic energies; optimized Cartesian coordinates for all the transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

**Corresponding Authors**

sunoj@chem.iitb.ac.in

qc@uga.edu

**Notes**

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

## ■ REFERENCES

(1) (a) Hartwig, J. F. *Nature* **2008**, *455*, 314. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Bergman, R. G. *Nature* **2007**, *446*, 391. (d) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (e) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (f) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824. (g) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749.

(2) (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (d) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041 and references cited therein.

(3) (a) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476. (b) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428. (c) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (d) Feng, C.-G.; Ye, M.; Xiao, K.-J.; Li, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 9322.

(4) (a) Ceccarelli, S.; Piarulli, U.; Gennari, C. *J. Org. Chem.* **2000**, *65*, 6254. (b) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (c) Weibel, J.-M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149. (d) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (f) Feng, C.-G.; Ye, M.; Xiao, K.-J.; Li, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 9322.

(5) (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. and references cited therein (c) Muehlhofer, M.; Strassner, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1745. (d) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180.

(6) (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (b) McGlacken, G. P.; Fairlamb, I. J. S. *Eur. J. Org. Chem.* **2009**, 4011. (c) Li, Hu.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (d) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (e) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.

(7) (a) Suzuki, A. *Chem. Commun.* **2005**, 4759. (b) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* **2012**, *44*, 1778. (c) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864. (d) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901.

(8) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652.

(9) Chenna, B. C.; Shinkre, B. A.; King, J. R.; Lucius, A. L.; Narayana, S. V. L; Velu, S. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 380.

(10) (a) Anand, M.; Sunoj, R. B. *Org. Lett.* **2011**, *13*, 4802. (b) Anand, M.; Sunoj, R. B. *Organometallics.* **2012**, *31*, 6466. (c) Parija, A.; Sunoj, R. B. *Org. Lett.* **2013**, *15*, 4066.

(11) All computations were performed using the Gaussian09 suite of programs: Frisch, M. J. et al. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009. The PCM$_{DCE}$/M06/6-31+G**, LANL2DZ(Pd,Ag,Cs)//PCM$_{DCE}$/B3LYP/6-31G**,LANL2DZ (Pd,Ag,Cs) level of theory has been used. See computational methods in the Supporting Information for full details.

(12) The coordination through the carbonyl oxygen resulted in higher energy transition states (Figure 1).

(13) The energy of the TS without the deprotonation of −NHAr is found to be 13.1 kcal/mol higher than that of **TS1**. See Figure S1 in the Supporting Information for more details. The amidic N−H activation prior to the C−H bond activation was earlier noted in other reactions as well.[10a,b]

(14) Such transition states involving acetate-assisted C−H activation have been proposed in the cases of different substrates: (a) Davies, L. D.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. (b) Ess, D. H.; Bischof, S. M.; Oxgaard, J.; Periana, R. A.; Goddard, W. A., III *Organometallics* **2008**, *27*, 6440.

(15) The use of infinitely separated reactants as the common reference point is the most widely employed approach in literature in mechanistic problems of varying complexities. (a) Cheng, G.-J.; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-Y.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J.-Q.; Wu, Y.-D. *J. Am. Chem. Soc.* **2014**, *136*, 894. (b) Yang, Y.-F.;

Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344. (c) Zhang, S.; Shi, Li.; Ding, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20218. (d) Balcells, D.; Nova, A.; Clot, E.; Gnanamgari, D.; Crabtree, R. H.; Eisenstein, O. *Organometallics* **2008**, *27*, 2529. (e) Nova, A.; Balcells, D.; Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H.; Eisenstein, O. *Organometallics* **2010**, *29*, 6548.

(16) In **TS3**, we also observed a weak palladium—cesium (Pd—Cs distance is 3.81Å) interaction, and its energy is lower than the similar TS where the cesium ion is far from palladium (Figure S2(i) in the Supporting Information).

(17) Interestingly, Yu and co-workers have reported an X-ray structure of a similar cesium ion-bound intermediate under similar reaction conditions. However, silver acetate was not used in this analogous reaction. Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948. See Figure S2 in the Supporting Information for analogous transition states with different modes of coordination between palladium and the substrate.

(18) There are some qualitative proposals wherein homo-bimetallic palladium dimers are suggested to be the active catalyst rather than their monomeric analogue. However, no transition states or details of the potential energy surfaces were reported. (a) Paton, R. S.; Brown, J. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 10448. (b) Powers, D. C.; Ritter, T. *Nature* **2009**, *1*, 302. (c) Christmann, U.; Pantazis, D. A.; Benet-Buchholz, J.; McGrady, J. E.; Maseras, F.; Vilar, R. *J. Am. Chem. Soc.* **2006**, *128*, 6376. (d) Cotton, F. A.; Gu, J.; Murillo, C. A.; Timmons, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 13280.

(19) See Figure S2 in the Supporting Information for other possible higher energy C—H activation transition states. We were also able to locate a few low energy C-H activation transition states having trimetallic (Pd—Pd—Ag) interaction as the active catalyst (Figure S4).

(20) Additional possibilities with one and two molecules of solvent DCE bound to the cesium ion are computed to be of higher energy. See Figure S3 in the Supporting Information.

(21) The Pd—Ag bond distance is 2.9 Å, comparable to a normal palladium—silver single bond length. (a) Braunstein, P.; Frison, C.; Oberbeckmann-Winter, N.; Morise, X.; Messaoudi, A.; Bénard, M.; Rohmer, M.-M.; Welter, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 6120. (b) Kickham, J. E.; Loeb, S. J. *Organometallics* **1995**, *14*, 3584.

(22) (a) Canty, A. J.; Koten, G. V. *Acc. Chem. Res.* **1995**, *28*, 406. (b) Kozitsyna, N. Y.; Nefedov, S. E.; Klyagina, A. P.; Markov, A. A.; Dobrokhotova, Z. V.; Velikodny, Y. A.; Kochubey, D. I.; Zyubina, T. S.; Gekhman, A. E.; Vargaftik, M. N.; Moiseev, I. I. *Inorg. Chim. Acta* **2011**, *370*, 382.

(23) Direct metal—metal interaction has been noted in many crystal structures of homo-/hetero-bimetallic complexes and has also been studied using computational methods. (a) Chaudret, B.; Delavaux, B.; Poilblanc, R. *Coord. Chem. Rev.* **1988**, *86*, 191. (b) Richardson, D. E.; Taube, H. *Coord. Chem. Rev.* **1984**, *60*, 107. (c) Adams, R. D.; Captain, B.; Zhu, L. *J. Am. Chem. Soc.* **2006**, *128*, 13672. (d) Álvarez, R.; de Lera, A. R. *Organometallics* **2007**, *26*, 2799. (e) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (f) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (g) Giri, R.; Lan, Y.; Liu, P.; Houk, K. N.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 14118.

(24) (a) Murahashi, T.; Kurosawa, H. *Coord. Chem. Rev.* **2002**, *231*, 207. (b) Petretto, G. L.; Rourke, J. P.; Maidich, L.; Stoccoro, S.; Cinellu, M. A.; Minghetti, G.; Clarkson, G. J.; Zucca, A. *Organometallics* **2012**, *31*, 2971.

(25) See Figure S5 in the Supporting Information.

(26) See Figure S6 in the Supporting Information for other higher energy C—H activation transition states with homodimeric Pd$_2$(OAc)$_4$ as the active catalyst.

(27) See Figure S7 in the Supporting Information. Attempts to locate C—H activation TSs with two CsF failed to converge even after repeated attempts, perhaps indicating that the optimum number of CsF could just be one.