ORGANIC LETTERS

2005
Vol. 7, No. 6
1011−1014

Proximity Effects in the Palladium-Catalyzed Substitution of Aryl Fluorides

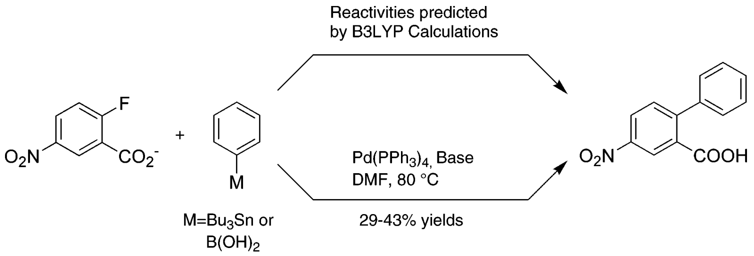
S. Bahmanyar,* Bennett C. Borer, Young Mi Kim, David M. Kurtz, and Shu Yu*

Chemical Research and Development, Pfizer Global R&D-La Jolla,
10578 Science Center Drive, San Diego, California 92121

sami.bahmanyar@pfizer.com; shu.yu@pfizer.com

Received December 16, 2004

ABSTRACT



The aryl fluoride bond has long been considered inert toward Pd-catalyzed insertion reactions. This paper reports for the first time that aryl fluorides bearing an *o*-carboxylate group can undergo Pd-catalyzed couplings. On the basis of this computational study and subsequent experimental verifications of its predictions, we herein report that such reactions are facilitated by stabilization of the transition state by proximal oxyanions.

Carbon−fluorine bond activation has drawn considerable interest in recent years.[1] The aryl fluoride bond has long been considered inert toward Pd-catalyzed insertion reactions. However, recently reported discoveries in our laboratory[2] and others[3] have demonstrated for the first time that *o*-nitro-substituted fluorobenzenes can undergo the Pd(0)-catalyzed amination,[2] Stille coupling, and Suzuki coupling reactions.[2,3] Herein we report for the first time that aryl fluorides bearing a substituent other than an *o*-nitro group can undergo Pd-catalyzed couplings.

To fully understand the role that the *o*-nitro group played in the successful Pd-catalyzed coupling reactions of aryl fluorides, a computational study using hybrid density functional theory was conducted in our laboratory. On the basis of this computational study and subsequent experimental verifications of its predictions, we report that such reactions are facilitated by stabilization of the transition state by proximal oxyanions. This stabilization allowed the prediction of a nonobvious substrate (the carboxylate anion) that could successfully undergo Pd-catalyzed coupling reaction.

Assuming that the Pd(0)-catalyzed coupling reaction proceeds via the oxidative addition/reductive elimination pathway[4] and further assuming that the oxidative addition of Pd(0) onto the aryl fluoride is rate-determining,[5] the addition step of Pd(0) to various aryl halides was modeled

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(1) (a) Clot, E.; Megret, Cl.; Kraft, B. M.; Eisenstein, O.; Jones, W. D. *J. Am. Chem. Soc.* **2004**, 126, 5647−5653. (b) Reinhold: M.; McGrady, J. E.; Perutz, R. N. *J. Am. Chem. Soc.* **2004**, *126*, 5268−5276. (c) Hughes, R. P.; Laritchev, R. B.; Zakharov, L. N.; Rheingold, A. L. *J. Am. Chem. Soc.* **2004**, *126*, 2308−2309. (d) Braun, T.; Noveski, D.; Neumann, B.; Stammler, H.-G. *Angew. Chem., Int. Ed.* **2002**, *41*, 2745−2748. (e) Mazurek, U.; Schroder, D.; Schwarz, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2538−2541.

(2) Kim, Y. M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696−1697.

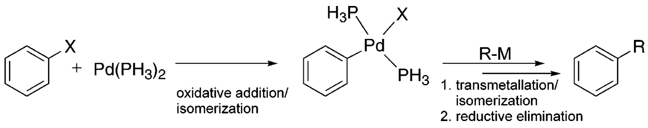
(3) (a) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **2003**, 578−579. (b) Jakt, M.; Johannissen, L.; Rzepa, H. S.; Widdowson, D. A.; Wilhelm, R. *J. Chem. Soc., Perkin Trans. 2* **2002**, 576−581. (c) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **1999**, 2211−2212. (d) Wilhelm, R.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3808−3814. (e) Mikami, K.; Miyamoto, T.; Hatano M. *Chem. Commun.* **2004**, 2082−2083.

(4) Note: at this stage, we still could not completely exclude the possibility of the operation of other mechanisms in those coupling reactions; for direct observation of oxidative addition of Pd(0) to an aryl-fluorine bond, see: Jasim, N. A.; Perutz, R. N.; Whitwood, A. C.; Braun, T.; Izundu, J.; Neumann, B.; Rothfeld, S.; Stammler, H.-G. *Organometallics* **2004**, *23*, 6140−6149.

10.1021/ol047413f CCC: $30.25

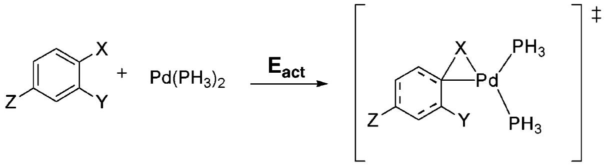
to understand further the role of the nitro substituent in facilitating Pd(0)-catalyzed reactions. Pd(PH$_3$)$_2$ was used as a smaller surrogate of the Pd(PPh$_3$)$_2$ catalyst (Scheme 1).

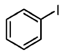
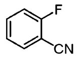
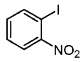
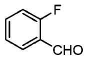
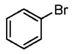
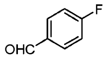
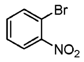
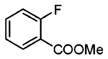
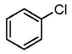
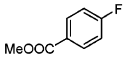
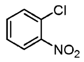
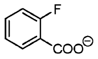
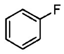
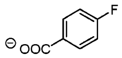
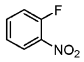
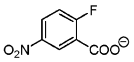
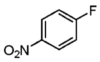
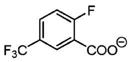
Scheme 1



Gas phase ground state and transition structure geometry optimizations[6] were computed using hybrid density functional theory B3LYP.[7] The 6-31G(d)[8] basis set was used for P, N, O, C, and H and the LANL2DZ[9] effective core potential and its associated basis set was used for the halogens (I, Br, Cl, F) and Pd as implemented in Gaussian 98.[10] The computed activation energies (Table 1) for the addition of Pd(PH$_3$)$_2$ to unsubstituted aryl halides (**1a**−**4a**) agree with the known experimental reactivity of these substrates toward Pd-catalyzed oxidative addition.[11] With the introduction of the *o*-nitro substituent (**1b**−**4b**), the activation energy barriers of the aryl halides decrease as shown in Table 1.[12]

Table 1. Computed Activation Energy Barriers (E_{act}) in Gas Phase ($\epsilon = 1$) and ($E_{act(DMF)}$) in DMF ($\epsilon = 37.2$)



entry	substrate	E_{act} ($E_{act(DMF)}$) kcal/mol	entry	substrate	E_{act} ($E_{act(DMF)}$) kcal/mol
1a		6.7 (12.2)	**5**		32.1 (32.8)
1b		4.2 (9.3)	**6a**		27.5 (26.5)
2a		10.5 (12.1)	**6b**		33.9 (33.9)
2b		6.3 (10.8)	**7a**		30.1 (29.6)
3a		15.8 (15.7)	**7b**		35.0 (35.9)
3b		8.8 (13.5)	**8a**		19.5 (19.9)
4a		37.7 (36.8)	**8b**		41.1 (42.9)
4b		23.3 (21.6)	**8c**		13.9 (15.7)
4c		32.5 (32.0)	**8d**		16.2 (19.3)

The most dramatic change is observed for 1-fluoro-2-nitrobenzene (**4b**). The activation energy barrier decreases to 23.3 kcal/mol when compared to the activation energy for fluorobenzene (**4a**), which is calculated to be 37.7 kcal/mol.[13] However, the computed activation energy barrier for the addition of Pd(0) to 1-fluoro-4-nitrobenzene (**4c**) is only slightly lower (32.5 kcal/mol) than that for fluorobenzene. Similarly, 2-fluorobenzonitrile (**5**) is predicted to have an activation energy barrier close to that of 1-fluoro-4-nitrobenzene. A close examination of the transition structure geometry of TS-**4b** reveals the presence of a very short Pd−O (NO$_2$) distance as shown in Figure 1.

The coordination of the nitro group oxygen of 1-fluoro-2-nitrobenzene to the Pd metal may be the source of transition state stabilization.[14] In the transition state, the nitro

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(5) It has been proposed that Pd(PPh$_3$)$_4$ dissociates and has two ligands catalyzing the oxidative addition step as discussed by: (a) Fauvarque, J. F.; Pfluger, F.; Troupel, M. *J. Organomet. Chem.* **1979**, *208*, 419−427. (b) Amatore, C.; Pfluger, F. *Organometallics* **1990**, *9*, 2276−2282.

(6) All stationary points were characterized using frequency calculations (reported energies include zero point energy corrections and were scaled by 0.9806. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513). Single point solvation energy calculations for reactants and transition structures were computed using the polarizable continuum solvation model PCM [(a) Miertus, S.; Tomasi, J. *Chem. Phys.* **1982**, *65*, 239−245. (b) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117−129], as implemented in Gaussian 98, with a permittivity of 37.2, the value for DMF. Gas-phase energies in Table 1 are reported as zero point energy corrected electronic energies. The energies computed for structures in solvent include electronic energy plus the solvation energy as reported from PCM.

(7) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(8) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724−728. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257−2261. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213−222.

(9) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270−283.

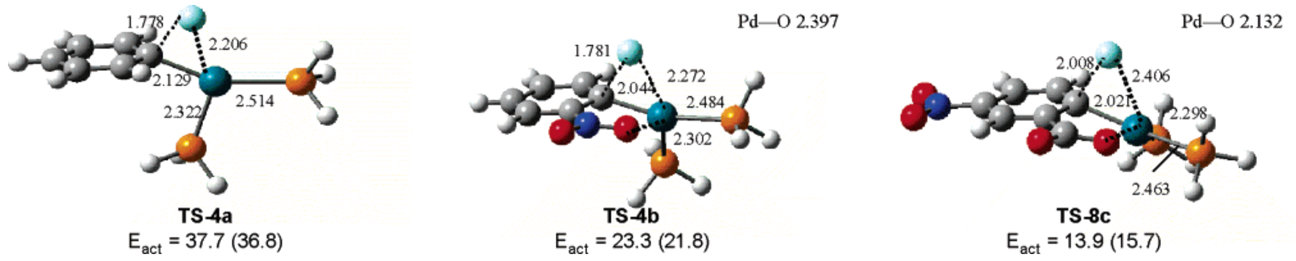
(10) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11; Gaussian, Inc.: Pittsburgh, PA, 1998.

(11) (a) Hegedus, L. S. In *Organometallics in Synthesis: A Manual*; 2nd ed.; Schlosser, M., Ed.; Wiley: New York, 2002; pp 1123−1217. (b) Tsuji, J. In *Palladium Reagents and Catalysts*; Wiley: New York, 1995.

(12) (a) The activation energy barriers computed with B3LYP/6-311+G** basis set for P, N, O, C, H and LANL2DZ effective core potential and its associated basis set for Pd and the halogens (single point energy calculations on fully optimized geometries of structures reported in Table 1) reflect the same general trend as those in Table 1. (b) The use of the LANL2DZ basis set for fluorine was successful in reproducing geometries in crystal structures reported in Chu, Q.; Wang, Z.; Huang, Q.; Yan, C.; Zhu, S. *J. Am. Chem. Soc.* **2001**, *123*, 11069−11070. The comparisons of the calculated and experimental information are provided in Supporting Information.

(13) IRC calculations on transition states **4a** and **4b** lead to intermediates with distorted square planar geometries, supporting a concerted oxidative addition mechanism in the gas phase at this level of theory. Geometries of these intermediates are provided in Supporting Information.

(14) Widdowson et al. made a similar observation as discussed in ref 3a−d.



TS-4a
E_{act} = 37.7 (36.8)

TS-4b
E_{act} = 23.3 (21.8)

TS-8c
E_{act} = 13.9 (15.7)

Figure 1. Transition structure geometries (labeled according to entries in Table 1) and activation energy barriers for the addition of Pd(PH_3)$_2$ to fluorobenzene (TS-**4a**), 2-fluoronitrobenzene (TS-**4b**), and 2-fluoro-5-nitrobenzoate (TS-**8c**). All energies are reported in kcal/mol and distances are reported in angstroms.

and cyano substituents stabilize negative charge buildup in the aryl ring,[15] but the Pd−O coordination plays an equally important (if not more important) role in transition state stabilization and lowering of the activation energy barrier.

To explore further the extent of transition state stabilization via Pd−O coordination, the activation energy barriers for the addition of Pd(0) to 2-fluorobenzaldehyde, methyl 2-fluorobenzoate, and the 2-fluorobenzoate carboxylate anion (**6a**−**8a**) were computed. These substrates were selected on the basis of their varying amount of formal negative charge density on the oxygen atom. The gas phase activation energy barriers for addition to **6a**, **7a**, and **8a** are predicted to be 27.5, 30.1, and 19.5 kcal/mol, respectively, as shown in Table 1. The transition state geometries illustrate that the carbonyl oxygen of the formyl and methyl ester are only weakly coordinated (Pd−O ~2.5−2.7 Å) to the Pd metal.[16]

On the other hand, in the transition state the negatively charged carboxylate oxygen of 2-fluorobenzoate (**8a**) has a much stronger coordination to the Pd metal, as observed in the Pd−O distances (Pd−O 2.171 Å). With the presence of additional electron-withdrawing substituents on the ring, the computed activation energy barriers are 13.9 kcal/mol for 2-fluoro-5-nitrobenzoate (**8c**) and 16.2 kcal/mol for 2-fluoro-5-trifluoromethylbenzoate (**8d**). The transition structure geometries illustrate that the charged carboxylate oxygen has a stronger Pd−O coordination when compared to the nitro group (Pd−O distances for TS-**4b**, 2.397 Å and for TS-**8c**, 2.132 Å) as shown in Figure 1.[17] These are approaching Pd−O distances in Pd(II) complexes, which are considered to be covalent,[18] and this stabilizing interaction in the transition state lowers the activation energy barrier and should make these substrates susceptible to palladium-catalyzed oxidative addition.

When the calculated activation energies for **6a**−**8a** are compared to their *para*-substituted counterparts **6b**−**8b**, it can be concluded that the transition state stabilization originates mainly from Pd−O coordination and not just the electron-withdrawing ability of the substituent. Thus, the decrease in the activation energy barrier for Pd(0) addition to substituted fluorobenzenes can be due to two main factors: the electron-withdrawing ability of the substituents on the ring, and the ability of the proximal oxygen atom of the substituent at the *ortho* position to donate charge to the Pd metal in the transition state. Both of these factors are required to facilitate the oxidative addition of Pd(0) to the aryl-fluorine bond. These computational data and the resulting conclusions were supported experimentally by study of the reactivity of appropriately substituted aryl fluorides.

Stille coupling reactions have been demonstrated to be useful model reactions due to the lack of non-Pd-catalyzed background reactions.[2] The experimental results of our current studies are summarized in Table 2.

As previously reported, 2-fluoro-5-nitrobenzaldehyde and 2-fluoro-5-nitrobenzonitrile underwent Stille coupling with ease (entries 1, 3, 7, and 9).[2] When the positions of the activating groups were switched, 4-fluoro-3-nitrobenzaldehyde and 4-fluoro-3-nitrobenzonitrile were not reactive under the same reaction conditions or at higher temperatures (entries 2, 4, 8, and 10). These results demonstrated the importance of the proximity of the nitro group and were in good agreement with the computational rationale. As the computed activation energy barriers suggested, 2-fluoro-5-nitrobenzoate indeed underwent Stille coupling in fair yields (entries 5 and 11). The control experiments (entries 6 and 12) demonstrated that the coupling reaction required the presence of palladium.

Considering that methyl 2-fluoro-5-nitrobenzoate was unreactive (entry 13), the reactivity of the parent 2-fluoro-5-nitrobenzoate must stem from the coordinating power of the carboxylate anion to Pd. Since the computational studies suggested the reactivity of 2-fluorobenzoate, extensive efforts were made to verify the predictions. Unfortunately, all attempts to date have failed (entry 14). From an experimental standpoint, these results appear to suggest that the proximity of an oxyanionic coordinating group is necessary but alone not sufficient to activate the fluorobenzene; it requires the

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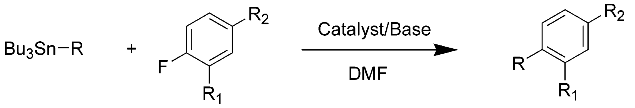
[15] Experimentally it has also been shown that the reactivity of aryl halides towards Pd(0) addition increases with electron-withdrawing substituents on the ring as discussed by Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287−291.

[16] Transition structure geometries (TS-**6a**, TS-**7a**, and TS-**8a**) are provided in Supporting Information.

[17] Transition structure geometry (TS-**8d**) is provided in Supporting Information.

[18] (a) Adam, S.; Bauer, A.; Timpe, O.; Wild, U.; Mestl, G.; Bensch, W.; Schlögl, R. *Chem. Eur. J.* **1998**, *4*, 1458−1469. (b) Quintal, S. M. O.; Nogueira, H. I. S.; Fèlix, V.; Drew, M. G. B. *New J. Chem.* **2000**, *24*, 511−517. (c) Shi, P.-Y.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T. *Organometallics* **2002**, *21*, 3203−3207.

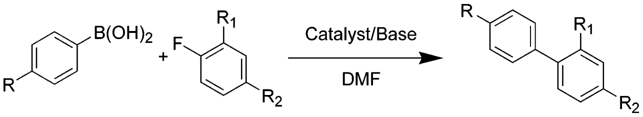
Table 2. Stille Coupling of Aryl Fluorides



entry	R	R_1	R_2	base	catalyst $Pd(PPh_3)_4$	temp (°C)	yield (%)
1	Ph	NO_2	CHO		10%	65	65[a]
2	Ph	CHO	NO_2		10%	65	*b*
3	Ph	NO_2	CN		10%	65	56[a]
4	Ph	CN	NO_2		10%	65	*b*
5	Ph	CO_2H	NO_2	Triton B	10%	80	29
6	Ph	CO_2H	NO_2	Triton B	40% PPh_3	80	*c*
7	vinyl	NO_2	CHO		10%	65	45[a]
8	vinyl	CHO	NO_2		10%	65	*b*
9	vinyl	NO_2	CN		10%	65	28[a]
10	vinyl	CN	NO_2		10%	65	*b*
11	vinyl	CO_2H	NO_2	Triton B	10%	80	36[a]
12	vinyl	CO_2H	NO_2	Triton B	40% PPh_3	80	*c*
13	vinyl	CO_2CH_3	NO_2		10%	80	*b*
14	vinyl	CO_2H	H	Triton B	10%	80	*b*

[a] The reactions were carried out using 2.7 mmol of organotin compound, 1.5 equiv of fluorobenzene derivative, and 1.5 equiv of Triton B for entries 5, 6, 11, 12, and 14 in 25 mL of DMF; the amount of the catalyst, ligand, and temperature are indicated. The reaction mixtures were degassed three times by alternately connecting to house vacuum and nitrogen prior to heating. All reactions were carried out at the listed temperature for at least 24 h. [b] No product was detected at higher temperatures. [c] Control experiment in the absence of Pd source. No product was detected.

Table 3. Suzuki Coupling of Aryl Fluorides



entry	R	R_1	R_2	base	catalyst $Pd(PPh_3)_4$	temp (°C)	yield (%)
1	H	NO_2	CHO	Cs_2CO_3	10%	80	86[a]
2	H	CHO	NO_2	Cs_2CO_3	10%	80	*b*
3	H	NO_2	CN	Cs_2CO_3	10%	80	64[a]
4	H	CN	NO_2	Cs_2CO_3	10%	80	*b*
5	H	CO_2H	NO_2	Triton B, Cs_2CO_3	10%	80	43
6	H	CO_2H	NO_2	Triton B, Cs_2CO_3	40% PPh_3	80	*c*
7	CH_3O	NO_2	CHO	Cs_2CO_3	10%	65	33[a]
8	CH_3O	CHO	NO_2	Cs_2CO_3	10%	65	*b*
9	CH_3O	NO_2	CN	Cs_2CO_3	10%	65	49[a]
10	CH_3O	CN	NO_2	Cs_2CO_3	10%	65	*b*
11	CH_3O	CO_2H	NO_2	Triton B, Cs_2CO_3	10%	80	30[a]
12	CH_3O	CO_2H	NO_2	Triton B, Cs_2CO_3	40% PPh_3	80	*c*
13	CH_3O	CO_2CH_3	NO_2	Cs_2CO_3	10%	80	*b*
14	CH_3O	CO_2H	H	Triton B, Cs_2CO_3	10%	80	*b*

[a] The reactions were carried out using 2.7 mmol of the boronic acid, 1.5 equiv of fluorobenzene, 2.25 equiv of base (as well as 1.5 equiv of Triton B for entries 5, 6, 11, 12, and 14) in 25 mL of DMF; the amount of the catalyst, ligand and temperature are indicated. The reaction mixtures were degassed three times by alternately connecting to house vacuum and nitrogen prior to heating. All reactions were carried out at the listed temperature for at least 24 h. [b] No product was detected at higher temperatures. [c] Control experiment in the absence of Pd source. No product was detected.

combination of a properly positioned strong electron-withdrawing group as well as the proximity of a coordinating group to activate the system toward palladium-catalyzed coupling.[19]

The Suzuki coupling is another useful transformation to study the reactivity of fluorobenzenes. The reactivity of fluorobenzenes toward phenylboronic acid and 4-methoxyphenylboronic acid was studied, and the results are summarized in Table 3. A very similar reactivity pattern (to Stille coupling) was observed, i.e., fluorobenzenes need to be doubly activated to undergo the Suzuki coupling reaction. The substrates that afforded Suzuki coupling products (Table 3, entries 1, 3, 5, 7, 9, and 11) all contain at least one properly positioned strong electron-withdrawing group, such as nitro, formyl, or cyano, as well as a good coordinating group (nitro or carboxylate) at the *ortho* position. These results provided further evidence for the necessity of the combination of a properly positioned strongly electron-withdrawing group and a proximal oxyanionic coordinating group to activate fluorobenzenes.

In summary, our computational predictions and the experimental verification confirm that fluorobenzenes with an *o*-carboxyl and *para* electron-withdrawing substituents, similar to 2-fluoronitrobenzene, are activated toward Stille and Suzuki couplings. To the best of our knowledge, this is the first report on Pd-catalyzed coupling reactions of fluorobenzenes that do not have an *o*-nitro group. We predict that the enhanced reactivity observed for these fluorobenzenes is a general effect and will be observed for other fluorobenzenes with a proximal anionic group and electron-withdrawing substituents on the ring. The generality of this effect and the extent in activating other aryl halides toward Pd-catalyzed coupling reactions is currently under investigation in our laboratory and will be reported in due course.

Acknowledgment. The authors would like to thank Professors Stephen L. Buchwald, E. J. Corey, Kendall N. Houk, Tomas Hudlicky, Larry Overman, and Dean J. Tantillo for helpful discussions and suggestions. Special thanks are extended to Drs. Kim Albizati, Mark Guzman, and Robert Scott for insightful discussions. D.M.K. and Y.M.K. thank Drs. Melissa Rewolinski, Wolfgang Notz, Qingping Tian, and the Pfizer summer internship program for financial support.

Note Added after ASAP Publication. The calculated activation energies for **6a−8a** were incorrectly listed as **6a−6b** in the text below Figure 1 in the version published ASAP February 24, 2005; the corrected version was published ASAP February 25, 2005.

Supporting Information Available: Experimental procedures and spectral data for all of the new compounds and Cartesian coordinates for all structures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047413F

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(19) To date, the reactivity of 2-fluorobenzoate has not been observed experimentally. Further screening of experimental conditions is underway in our laboratory, and results will be reported in due course.