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Activation of Aryl Chlorides for Suzuki Cross-Coupling by Ligandless, Heterogeneous Palladium

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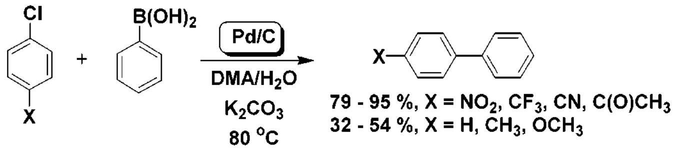
ABSTRACT



We demonstrate that Pd/C without added ligands catalyzes the Suzuki cross-coupling reaction with aryl chlorides. The ability of heterogeneous Pd to activate the C–Cl bond is explained in terms of a synergistic anchimeric and electronic effect that occurs between the Pd surface and the aryl chloride. Furthermore, the importance of selectivity control following C–Cl bond activation is illustrated by the striking role that solvents play in determining homo- vs cross-coupling pathways of the aryl chlorides.

There is great interest in developing catalysts that use aryl chlorides in Suzuki cross-coupling reactions[1,2] because aryl chlorides are readily available, inexpensive, and environmentally strategic reagents. However, they are much more difficult to activate than aryl bromides and iodides. The key to success in homogeneous catalysis[1] and recent examples of Ni/C-catalyzed coupling[3] is the use of ligands that facilitate activation of the C−Cl bond in aryl chlorides. A recently reported ligandless Pd system catalyzes Suzuki cross-coupling with electron-deficient aryl chlorides but fails to work for neutral and electron-rich aryl chlorides.[4] We chose to investigate heterogeneous Pd catalysts to activate aryl chlorides for Suzuki cross-coupling because of their inherent activity toward C−Cl bonds. This inherent activity is manifest in the cleavage of the C−Cl bond of chlorobenzene over a metallic Pd surface at room temperature,[5] hydrodechlorination,[6] and reductive homo-coupling reactions of aryl chlorides over supported Pd catalysts.[7] Furthermore, excellent cross-coupling efficiency is possible over heterogeneous Pd in the cases of aryl bromides and iodides.[8]

We report here that ligandless, heterogeneous Pd catalysts activate C−Cl bonds in aryl chlorides under Suzuki cross-

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coupling reaction conditions. More importantly, with prudent choice of solvent system, we block the homo-coupling pathway of aryl chlorides and selectively obtain the Suzuki cross-coupling product.[9]

A previous study of Pd/C in Suzuki cross-coupling reactions with aryl chlorides reported a 6% yield using EtOH/H_2O as solvent.[8a] Indeed, under similar conditions, we found a disappointing 11% yield of the desired cross-coupling product between phenylboronic acid and *p*-chlorotrifluoromethylbenzene (Figure 1). However, the aryl chloride had completely reacted, producing mainly homo-coupled products. The results were encouraging because they indicated Pd/C is sufficiently reactive to activate aryl chlorides under Suzuki cross-coupling conditions. However, activation itself is not sufficient for high-yielding Suzuki cross-coupling due to the presence of a competing homo-coupling pathway.

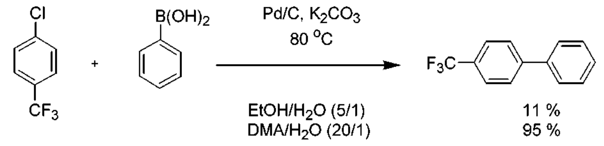

Figure 1. Effect of solvent mixture on cross-coupling yield.

We find that an appropriately chosen solvent system strongly favors the cross-coupling pathway. For example, the cross-coupling yield (Figure 1) increased to 95% in dimethylacetamide (DMA) and water (20/1). The DMA/water volumetric ratio is critical to the success of the cross-coupling reaction. High water concentrations (e.g., DMA/water, 5/1) had a deleterious effect, resulting in significant amounts (74%) of homo-coupling products. Without water, the reaction was highly selective to cross-coupling, but very slow (46% conversion after 24 h). The optimal volumetric ratio was found to be 20/1, under which conditions the cross-coupling proceeded to completion in 1.5 h without observation of homo-coupling product from the aryl chloride.[10] These conditions are generally applicable toward aryl chlorides with electron-withdrawing groups and give 79−95% yields of cross-coupled products (Table 1). Moderate yields are obtained with neutral or electron-rich aryl chlorides which can be improved using greater amounts of catalyst. Thus, a simple change in the solvent system dramatically diverts a reaction pathway that gives almost entirely undesired products to a pathway that gives desired products in high yield.

Table 1. Pd/C-Catalyzed Suzuki Cross-Couplings with Aryl Chlorides[9]

entry	*p*-XC_6H_4Cl	*p*-$YC_6H_4B(OH)_2$	yield (%)[a]	convn (%)
1	NO_2	H	93	100
2	CF_3	H	95	100
3	CN	H	83	100
4	$COCH_3$	H	79	100
5	H	OCH_3	45	61
6	OCH_3	H	32	37
7	CH_3	H	36,[b] 54[c]	65,[b] 76[c]

[a] DMA:water (20/1), 80 °C, K_2CO_3 (2 equiv), Pd/C (5 mol %), 24 h. [b] Conditions as cited in (a) except 48 h reaction time was used. [c] 15 mol % of Pd/C, 24 h.

The striking role played by solvents in directing homo- vs cross-coupling pathways highlights the importance of selectivity control following C−Cl bond activation in heterogeneous catalysis. The solvent effect on the cross-coupling efficiency is likely related to the reductive homo-coupling pathway with the alcohol solvent[11] and/or boronic acid[12] as reductive reagent. The use of the nonreducing solvent DMA averts the former problem. The mechanism for the striking sensitivity of cross-coupling selectivity on water concentration is currently under investigation.

In homogeneous Pd chemistry, the choice of the ligand plays a critical role in Suzuki cross-coupling reactions of aryl chlorides.[1] In contrast, the Pd/C catalysts activate aryl chlorides for Suzuki coupling reactions under mild conditions without added ligands. In comparison, a recently reported ligandless catalytic method using homogeneous complexes $PdCl_2(SEt)_2$ or $Pd(OAc)_2$ that also catalyzes Suzuki cross-coupling with electron-withdrawing aryl chlorides “failed” with electron-rich or neutral substrates.[4] Although the Ni/C system is active for Suzuki coupling of aryl chlorides, triphenylphosphine (4 equiv with respect to Ni) is required.[3] In contrast, we find that added phosphines are deleterious to the Pd/C-catalyzed reaction. Addition of phosphines such as $P(t\text{-}Bu)_3$ or PPh_3 in the amount of one equivalent with respect to surface palladium[9] brought the coupling reaction to a halt. Thus, Pd/C is unique in its ability to activate aryl chlorides for Suzuki couplings without added ligands.

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(8) Suzuki coupling: (a) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277−3280. (b) Gala, D.; Stamford, A.; Jenkins, J.; Kugelman, M. *Org. Proc. Res. Dev.* **1997**, *1*, 163−164. (c) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405−3406. (d) Bykov, V.; Bumagin, N. *Russ. Chem. Bull.* **1997**, *46*, 1344−1345. (e) Ennis, D.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G.; Carstairs, A. *Org. Proc. Res. Dev.* **1999**, *3*, 248−252. (f) Kabalka, G. W.; Pagni, R. M.; Hair, C. M. *Org. Lett.* **1999**, *1*, 1423−1425. Heck Coupling: (g) Augustine, R. A.; O’Leary, S. T. *J. Mol. Catal.* **1992**, *72*, 229−242. (h) Eisenstadt, A. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York; pp 415−427. Stille Coupling: (i) Liebeskind, L. S.; Pena-Cabrera, E. *Org. Synth.* **1999**, *77*, 135−140.

(9) **General procedure:** Under a N_2 atmosphere, Pd/C (85.0 mg, 5 wt %, 5 mol % total Pd vs aryl chloride, obtained from PMC, 20% Pd dispersion), phenylboronic acid (120 mg, 0.96 mmol), K_2CO_3 (221 mg, 1.60 mmol), 5 mL of solvent and water at a desired v/v ratio, and a magnetic stir bar were combined. This mixture was degassed with 5 vacuum/N_2 purge cycles and the reaction initiated by the addition of the aryl halide (0.8 mmol) and placed in an oil bath at 80 °C for 24 h. The catalyst was filtered off and washed with 75 mL of acetonitrile. The filtrate and wash were combined and diluted for HPLC yield analysis. All products had the same retention time as authentic materials and the correct mass by GC/MS. All products were isolated and their ^1H NMR were identical to authentic samples.

(10) A small amount of biphenyl identified in the reaction correlates with the number of surface palladium atoms and suggests that the phenylboronic acid plays a role in reducing the surface palladium. Thus, reactions are performed with a 20% excess of aryl boronic acid.

(11) (a) 2-Propanol is used as reducing reagent in homo-coupling of aryl halides. See: Hassan, J.; Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793−13804. (b) Postreaction NMR of the ethanol solvent revealed a complex mixture including the presence of aldehydic protons (δ 9.74, q, $J = 2.5$ Hz) indicating oxidation of ethanol.

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On the basis of findings from surface science studies, we hypothesize that the extraordinary reactivity of the ligandless heterogeneous Pd catalyst results from a property unique to heterogeneous catalysts, i.e., synergistic anchimeric and electronic effects occurring upon adsorption of aryl chlorides on Pd surfaces. In contrast to the single-site Pd catalysts employed in homogeneous catalysis, heterogeneous Pd catalysts have reactive sites adjacent to one another. Surface science studies show that aryl chlorides adsorb on Pd(111) surfaces mainly via π-electrons, resulting in a nearly parallel orientation of the ring with the surface.[13] Adsorption of the aryl moiety to the Pd surface serves as an anchor, enhancing the chemical interaction of the C−Cl bond with a separate but nearby Pd site (i.e., an anchimeric effect). Furthermore, the adsorption of aryl chlorides influences the electronic properties of the catalytic surface. It leads to a decrease in the work function of the metal surface,[14] implying a net electron flow from the adsorbed aryl group to the Pd surface.[15] The Pd surface acts effectively as an electron-withdrawing substituent on the aryl ring which facilitates C−Cl bond activation.[16] The corresponding increase in electron density on Pd, in turn, facilitates C−Cl bond activation. These cooperative anchimeric and electronic effects are absent with single-site homogeneous catalysts, which explains the excellent reactivity of heterogeneous Pd catalysts, even with electron-rich aryl chlorides.

A salient advantage of heterogeneous catalysts is the ease with which they are separated from the reaction products. The Suzuki reaction is often used in the last steps in convergent synthesis of bioactive molecules. That it is difficult to remove both the residual metal and ligands of homogeneous catalysts often presents a significant practical problem. Extra chromatographic, precipitation, or extraction steps are often required.[17] However, after catalyst filtration we observe less than 1.0 ppm Pd (<0.10% loss based on the initial palladium) in the reaction mixtures, which lends support that the reaction is heterogeneously catalyzed.[18] Because added ligands are unnecessary, product isolation is simplified and potential side reactions between aryl groups of the phosphines and the boronic acid[19] are eliminated.

In summary, we demonstrate the first high-yielding use of ligandless Pd/C as an effective catalyst for Suzuki cross-coupling using aryl chlorides. A synergistic anchimeric and electronic effect, indigenous to heterogeneous catalysts, is proposed to be responsible for the high reactivity. We also show that activating the C−Cl bond is not sufficient, but prudent selection of reaction medium is essential for the cross-coupling pathway. Potential applications of this synergistic effect will be further explored, and efforts to understand the reaction mechanism and to improve the cross-coupling efficiency for electron-neutral and -rich aryl chlorides are in progress.

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(15) Work function is defined as the minimum work that must be done to remove an electron from the metal at 0 K. See: (a) Lang, N. D.; Kohn, W. *Phys. Rev. B* **1971**, *3*, 1215−1223. (b) Somorjai, G. A. *Introduction to Surface Chemistry*; Wiley: New York, 1994; Chapter 5.

(16) This is analogous to the acceleration of oxidative addition of aryl chlorides to Pd(0) via coordination of an electron-withdrawing tricarbonylchromium group to the arene ring. See: Uemura, M.; Nishimura, H.; Kamikawa, K.; Nakayama, K.; Hayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 1909−1912.

(17) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995.

(18) For the reaction of *p*-chloronitrobenzene with phenylboronic acid at 80 °C with 5 mol % of Pd/C, after filtration through 0.45 mm filter, we found 1.0 ppm of palladium by atomic absorption spectroscopy. If the reaction were to occur exclusively on palladium that leached into solution, a turnover number (TON) of 16 000 would be required. Catalytic palladium-catalyzed cross-couplings with TON greater than 10 000 have only been demonstrated in few cases ((a) Murray, W. V. *Chemtracts-Org. Chem.* **1993**, *6*, 263−284. (b) Hsieh, K.-H.; Hsieh; LaHann, T.; Speth, R. *J. Med. Chem.* **1989**, *32*, 898−903. (c) Williams, D.; Kannan, R. *J. Org. Chem.* **1987**, *52*, 5435−5437) and those which utilize aryl chlorides to the best of our knowledge are nonexistent.

(19) O'Keefe, D.; Dannock, M.; Marcuccio, S. *Tetrahedron Lett.* **1992**, *33*, 6679−6680.