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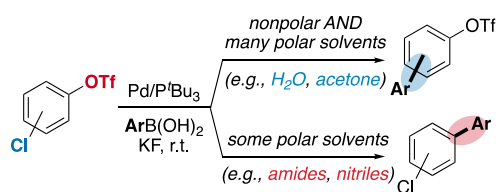
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Solvent Effects on the Selectivity of Palladium-Catalyzed Suzuki-Miyaura Couplings

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TOC Image:



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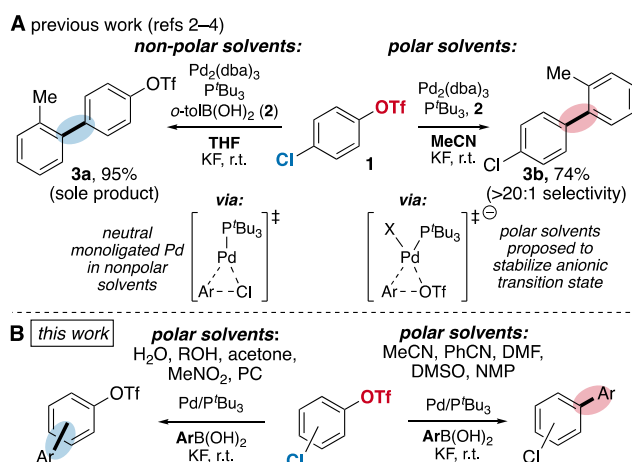
ABSTRACT

The use of polar solvents MeCN or dimethylformamide (DMF) was previously shown to induce a selectivity switch in the Pd/P^tBu₃-catalyzed Suzuki-Miyaura coupling of chloroaryl triflates. This phenomenon was attributed to the ability of polar solvents to stabilize anionic transition states for oxidative addition. However, we demonstrate that selectivity in this reaction does not trend with solvent dielectric constant. Unlike MeCN and DMF, water, alcohols, and several polar aprotic solvents such as MeNO₂, acetone, and propylene carbonate provide the same selectivity as nonpolar solvents. These results indicate that the role of solvent on the selectivity of Suzuki-Miyaura couplings may be more complex than previously envisioned. Furthermore, this observation has the potential for synthetic value as it greatly broadens the scope of solvents that can be used for chloride-selective cross coupling of chloroaryl triflates.

Keywords: Chemoselectivity; Cross-coupling; DFT calculations; Palladium; Solvent effects

Solvents are known to strongly influence the outcome of palladium-catalyzed cross-coupling reactions.^[1] They can play a role in activating precatalysts, stabilizing organometallic reagents and catalysts, and modulating the reactivity of acids and bases. In some cases, solvents can also influence the selectivity of cross couplings. For example, the Pd-catalyzed Suzuki-Miyaura (SM) cross coupling of chloroaryl triflate **1** with *o*-tolylboronic acid in the presence of P^tBu₃ leads to product **3a** in THF or toluene, but to product **3b** in MeCN or DMF (Scheme 1A).^[2,3] DFT studies on this system indicate that the active catalyst in nonpolar solvents is the monophosphine species [Pd(P^tBu₃)].^[4] In contrast, the active catalyst in polar solvents was proposed to be an anionic heteroleptic bisligated complex such as [Pd(P^tBu₃)F]⁻.^[3,5] The observed solvent-induced switch in selectivity was attributed to the ability of polar solvents to stabilize charged palladium species. However, herein we provide evidence that the role of polar solvents in determining selectivity may be more complex than previously thought. We demonstrate that selectivity for reaction at triflate with the Pd/P^tBu₃ system does *not* trend with solvent polarity, and is limited to a few coordinating solvents such as MeCN, DMF, and *N*-methyl-2-pyrrolidone (NMP). With many other polar solvents, the Pd/P^tBu₃-catalyzed SM reaction of chloroaryl triflates gives the same selectivity for reaction at chloride as observed in nonpolar solvents (Scheme 1B).

Scheme 1. Solvent effects on the selectivity of SM cross coupling of **1**.



While trying to reproduce the reaction shown in Scheme 1A using THF, we initially obtained only trace yield of cross coupled product (Table 1, entry 1). These results can be rationalized in part by the problems associated with using Pd₂(dba)₃: commercial sources of this Pd(O) precatalyst are notoriously variable in purity.^[6,7] The percent yield of product **3a** was improved slightly by using Buchwald's convenient air-stable P^tBu₃ Pd G4^[8] precatalyst instead of Pd₂(dba)₃/P^tBu₃ (entry 2). To increase yields further, we anticipated that it might be beneficial to add water (our lab operates in a particularly dry, high-altitude climate). Trace water not only helps solvate inorganic salts,^[9] but is also needed for efficient transmetalation in the absence of a hydroxide base.^[10,11] However, because polar solvents were previously reported to favor reaction at triflate using Pd/P^tBu₃, we were concerned that added water could erode selectivity for reaction at chloride. Gratifyingly, small amounts of H₂O greatly improved conversion and were not detrimental to selectivity (entries 3–5). The highest yield of **3a** was obtained with 99.1% THF : 0.9% H₂O (1 molar equiv H₂O relative to **1**, entry 4). To our surprise, the reaction also remained selective for coupling at chloride with larger amounts of H₂O, and even in neat H₂O (entries 6–10). These results are a counterexample to the prior generalization that polar solvents favor reaction at triflate using Pd/P^tBu₃. The Pd source is not a factor in this selectivity: both Buchwald's Pd G4 catalyst (entry 10) and Pd₂(dba)₃/P^tBu₃ (entry 11) exclusively provide **3a** in H₂O.

Table 1. Effect of water on the selectivity of the Pd/P^tBu₃-catalyzed SM coupling of **1**.

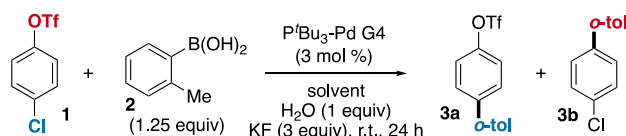
| entry | THF (%) ^a | H ₂ O (%) ^a | cat. ^b | 3a (%) ^c | 3b (%) ^c |
|-------|----------------------|-----------------------------------|-------------------|-------------------------------|-------------------------------|
| 1 | 100 | 0 | A | 1 | n.d. |
| 2 | 100 | 0 | B | 11 | n.d. |
| 3 | 99.6 | 0.4 | B | 27 | n.d. |
| 4 | 99.1 | 0.9 | B | 95 (52%) ^d | n.d. |
| 5 | 98.2 | 1.8 | B | 93 | n.d. |

| | | | | | |
|----|----|-----|----------|----|------|
| 6 | 90 | 10 | B | 88 | n.d. |
| 7 | 80 | 20 | B | 89 | 1 |
| 8 | 50 | 50 | B | 74 | 1 |
| 9 | 20 | 80 | B | 67 | n.d. |
| 10 | 0 | 100 | B | 59 | n.d. |
| 11 | 0 | 100 | A | 14 | n.d. |

^aPercent of total solvent volume. ^bCatalyst system **A** = Pd₂(dba)₃ (1.5 mol %), P^tBu₃ (3 mol %). Catalyst system **B** = P^tBu₃ Pd G4 (3 mol %). ^cGC yields calibrated against undecane as an internal standard. n.d. = not detected. ^dIsolated yield.

We further explored the effect of other solvents on the chemoselectivity of this transformation (Table 2). Consistent with the previously described trends, nonpolar solvents give high selectivity for cross coupling at chloride (**3a**, entries 1-6), and some polar aprotic solvents (nitriles, amides, and DMSO) effect the opposite selectivity for reaction at triflate (**3b**, entries 10, 12, 14, 16, 17). However, protic solvents as well as several polar aprotic solvents [acetone, MeNO₂, propylene carbonate (PC)] provide the same selectivity as nonpolar solvents (entries 7–9, 11, 13, 15, 18, 19). It is clear from these results that selectivity does not trend with solvent dielectric constant.^[12]

Table 2. Cross-coupling selectivity in diverse nonpolar and polar solvents.



| entry | solvent | ϵ^a | 3a (%) ^b | 3b (%) ^b |
|-------|------------------------------------|--------------|-------------------------------|-------------------------------|
| 1 | dioxane | 2.2 | 22 | n.d. |
| 2 | toluene | 2.4 | 76 | n.d. |
| 3 | CHCl ₃ | 4.8 | 11 | n.d. |
| 4 | THF | 7.5 | 95 | n.d. |
| 5 | CH ₂ Cl ₂ | 8.9 | 65 | n.d. |
| 6 | PhCF ₃ | 9.2 | 42 | n.d. |
| 7 | ⁱ PrOH | 20.2 | 94 | n.d. |
| 8 | acetone | 21.0 | 83 | 2 |
| 9 | EtOH | 25.3 | 71 | n.d. |
| 10 | PhCN | 25.9 | 9 | 62 |
| 11 | CF ₃ CH ₂ OH | 27.7 | 82 | 1 |
| 12 | NMP | 32.6 | 9 | 37 |
| 13 | MeOH | 33.0 | 55 | 2 |
| 14 | CH ₃ CN | 36.6 | 0 | 81 |

| | | | | |
|----|---------------------------------|------|-----------|-----------|
| 15 | CH ₃ NO ₂ | 37.3 | 84 | 2 |
| 16 | DMF | 38.2 | 9 | 45 |
| 17 | DMSO | 47.2 | 1 | 61 |
| 18 | PC | 66.1 | 71 | 11 |
| 19 | H ₂ O | 80.1 | 59 | n.d. |

^aDielectric constant of solvent from ref 12. ^bGC yield calibrated against undecane as an internal standard.

To examine the generality of these solvent effects, we next evaluated other substrate substitution patterns and arylboronic acids. We chose to focus on THF, alcohols, and MeCN as representative of nonpolar solvents that favor reaction at chloride, polar solvents that favor reaction at chloride, and polar solvents that favor reaction at triflate, respectively. The divergent behavior of alcohol solvents and MeCN that we observed in the coupling of **1** with **2** is maintained in other SM cross couplings (Table 3). The *meta*- and *ortho*-chlorophenyl triflates (**4** and **5**) undergo selective cross coupling at chloride in MeOH to give products **4a** and **5a**. These products are identical to those obtained in the nonpolar solvent THF. However, the use of MeCN leads to selective cross coupling at triflate to give **4b** and **5b**. Both electron-rich (**2**, **6**, **9**) and electron-deficient (**7**, **8**, **10**) arylboronic acids react selectively with **1** at either chloride (in alcohols or THF) or at triflate (in MeCN).

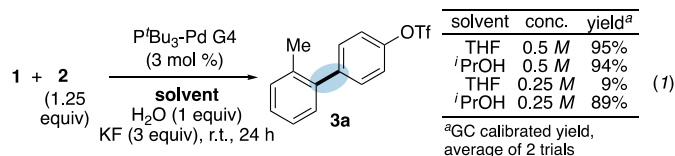
Table 3. Generality of solvent trends to other chloroaryltriflates and arylboronic acids.

| substrate | boronic acid | solvent | major product | isolated yield (GC yield) ^a | selectivity ^b (a : b) | sub- strate | boronic acid | solvent | major product | isolated yield (GC yield) ^a | selectivity ^b (a : b) |
|-----------|--------------|-------------------|---------------|--|----------------------------------|----------------|--------------|-------------------|---------------|--|----------------------------------|
| 4 | 2 | MeOH | 4a | 61% ^c | 17 : 1 | 1 | 7 | MeOH | 7a | 60% | 30 : 1 |
| | | MeCN | 4b | 52% ^c | <1 : 50 | | MeCN | 7b | 93% | <1 : 50 | |
| | | THF | 4a | (≥99%) | 50 : <1 | | THF | 7a | (70%) | 50 : <1 | |
| 5 | 2 | MeOH | 5a | 81% | 50 : <1 | 1 | 8 | MeOH | 8a | 49% | 15 : 1 |
| | | MeCN | 5b | 57% ^{c,d} | 1 : 22 | | MeCN | 8b | 91% | <1 : 50 | |
| | | THF | 5a | (90%) | 50 : <1 | | THF | 8a | (44%) | 50 : <1 | |
| 6 | 1 | MeOH | 6a | 90% | 11 : 1 | 1 | 9 | ⁱ PrOH | 9a | 87% | 50 : <1 |
| | | MeCN | 6b | 89% | <1 : 50 | | MeCN | 9b | 80% | <1 : 50 | |
| | | THF | 6a | (74%) | 50 : <1 | | THF | 9a | (69%) | 50 : <1 | |
| 10 | 1 | ⁱ PrOH | 10a | 53% ^c | 44 : 1 | 1 | 10 | ⁱ PrOH | 10a | 53% ^c | 44 : 1 |
| | | MeCN | 10b | 79% | 1 : 35 | | MeCN | 10b | 79% | 1 : 35 | |
| | | THF | 10a | (48%) | 20 : 1 | | THF | 10a | (48%) | 20 : 1 | |

^aGC yields calibrated against undecane as an internal standard. ^bSelectivity based on GC yields prior to purification. ^cWith 3 mol % P^tBu₃-Pd G4. ^dProduct is ~82% pure by ¹H NMR due to difficulties with isolation.

The ability to selectively react at chloride in alcohol solvents may be particularly valuable in cases where poor conversion is obtained in nonpolar solvents. For example, moderate yield of **9a** is detected by GC with boronic acid **9** in THF. The polar aprotic solvent MeCN leads to good conversion, but this solvent favors reaction at triflate (**9b**). However, the use of ⁱPrOH results in selective cross coupling at chloride to give **9a** in very good isolated yield compared to the use of THF. Additionally, we have found that chloride-selective cross couplings can be run at lower concentrations in alcohols than in THF (eq 1). The ability to conduct reactions at low

concentration is valuable for small-scale high throughput screening in which stock solutions of reagents must be prepared.



As described above, the selectivity for reaction at C—OTf in some polar solvents has been attributed to stabilization of an anionic transition state for oxidative addition.^[3] In MeCN, oxidative addition is proposed to involve $[\text{Pd}(\text{P}^t\text{Bu}_3)\text{X}]^-$ (X = anionic ligand such as fluoride or $[\text{ArB}(\text{OH})\text{O}]^-$). Our own DFT studies using an implicit solvent model (CPCM) are able to reproduce prior results, that oxidative addition of **1** at $[\text{Pd}(\text{P}^t\text{Bu}_3)\text{F}]^-$ is favored at C—OTf over C—Cl in MeCN (Table 4; **TS11b** is lower in energy than **TS11a**). However, DFT predicts that $[\text{Pd}(\text{P}^t\text{Bu}_3)\text{F}]^-$ should also favor reaction at C—OTf in other solvents, including water and MeOH. This result is consistent across several DFT methods including those with dispersion (Mo6L, Mo6, ωB97XD) and without (B3LYP). Because reaction at C—Cl is observed experimentally in water and MeOH, these results suggest that anionic $[\text{Pd}(\text{P}^t\text{Bu}_3)\text{X}]^-$ may not be the active catalyst in these polar solvents. Alternatively, the mechanism for oxidative addition may be more complex than currently understood. We are continuing to explore the relevance of solvent coordinating ability on the selectivity of this transformation.

Table 4. Effect of solvent and DFT method on predicted relative energies of anionic transition structures for oxidative addition at chloride and triflate.

| Method ^b | $\Delta\Delta G^\ddagger$ (TS11a-TS11b) ^a | | | |
|---------------------|--|------|------------------|-----|
| | MeCN | MeOH | H ₂ O | THF |
| A | 2.4 | 1.8 | 1.7 | 4.3 |
| B | 2.2 | 2.3 | 2.2 | 3.8 |
| C | 6.9 | 7.1 | 6.1 | 6.5 |

D 6.7 5.8 5.7 9.4

^aGibbs free energies in kcal mol⁻¹. ^bOptimized in indicated solvent. ECP for Pd in geometry optimizations is LANL2DZ. A = CPCM-Mo6L/6-31+G(d). B = CPCM-B3LYP/6-31+G(d). C = CPCM- ω B97XD/6-31+G(d). D = CPCM-Mo6/6-311++G(2d,p)/SDD(Pd)//CPCM-Mo6L/6-31+G(d).

In summary, we have described that several polar solvents give unexpected selectivity in the Pd/P^tBu₃-catalyzed Suzuki-Miyaura cross coupling of chloroaryl triflates. We show that water, alcohols, and some polar aprotic solvents including acetone, MeNO₂, and PC favor selective reaction at C–Cl. However, in line with previous reports, some polar solvents such as MeCN, DMF, and DMSO favor coupling at C–OTf. Polar solvents were previously proposed to stabilize oxidative addition transition states involving anionic palladium, leading to preferential reaction at triflate. Our results suggest that oxidative addition may not proceed through the same mechanism in all polar solvents. Further studies to elucidate the origin of divergent selectivity with different classes of polar solvents are ongoing in our lab.

EXPERIMENTAL SECTION

Representative Procedure. P^tBu₃-Pd G4 catalyst (1.8-7.0 mg, 0.003–0.012 mmol, 0.75–3 mol %), KF (69.7 mg, 1.2 mmol, 3 equiv), and boronic acid (0.44-0.6 mmol, 1.1-1.5 equiv) were weighed out in air and combined in a 1 dram vial equipped with a magnetic stir bar. Chloroaryl triflate substrate (0.40 mmol, 1 equiv) was added followed by a stock solution of water in the desired reaction solvent (0.80 mL of solution, corresponding to 0.40 mmol, 1 equiv of water). The reaction mixture was immediately degassed by sparging with N₂ for 1 min. The vial was immediately sealed with a PTFE-lined cap and the reaction was stirred at room temperature for 24 h. The reaction mixture was diluted with Et₂O or acetone, filtered through celite, concentrated, and purified by recrystallization or flash column chromatography.

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REFERENCES

- [1] For a recent review, see Sherwood, J.; Clark, J. H.; Fairlamb, I. J. S.; Slattery, J. M. *Green Chem.* **2019**, *21*, 2164.
- [2] Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
- [3] Proutiere, F.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 8192.
- [4] Schoenebeck, F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 2496.
- [5] Proutiere, F.; Schoenebeck, F. *Synlett* **2012**, *23*, 645.
- [6] Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302.
- [7] The yield is also improved by using **2** that has been recrystallized from water, as described in ref 2.
- [8] Friis, S. D.; Skrydstrup, T.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 4296.
- [9] For evidence that water solvates halide byproducts, preventing them from interfering with catalysis, see Yan, N.; Yang, X.; Fei, Z.; Li, Y.; Kou, Y.; Dyson, P. J. *Organometallics* **2009**, *28*, 937.
- [10] For evidence supporting the involvement of a palladium hydroxide catalytic intermediate, see (a) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116; (b) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492; (c) Hirakawa, T.; Uramoto, Y.; Yanagisawa, S.; Ikeda, T.; Inagaki, K.; Morikawa, Y. *J. Phys. Chem. C* **2017**, *121*, 19904; (d)

Molloy, J. J.; Seath, C. P.; West, M. J.; McLaughlin, C.; Fazakerley, N. J.; Kennedy, A. R.; Nelson, D. J.; Watson, A. J. B. *J. Am. Chem. Soc.* **2018**, *140*, 126.

[11] For evidence supporting the involvement of a boronate species in transmetalation, see (a) García-Melchor, M; Braga, A. A. C.; Lledós, A.; Ujaque, G.; Maseras, F. *Acc. Chem. Res.* **2013**, *46*, 2626 and referenes therein, (b) Ortuño, M. A.; Lledós, A.; Maseras, F.; Ujaque, G. *ChemCatChem* **2014**, *6*, 3132; (c) Lima, C. F. R. A. C.; Rodrigues, A. S. M. C.; Silva, V. L. M.; Silva, A. M. S.; Santos, L. M. N. B. F. *ChemCatChem* **2014**, *6*, 1291.

[12] Wohlfarth, C. "Permittivity (Dielectric Constant) of Liquids" in *CRC Handbook of Chemistry and Physics, Internet Version 2005*, Lide, D. R., ed., <<http://www.hbcpnetbase.com>>, CRC Press, Boca Raton, FL, 2005