EvanPhos. A Ligand for ppm Level Pd-Catalyzed Suzuki-Miyaura Couplings in Either Organic Solvent or Water

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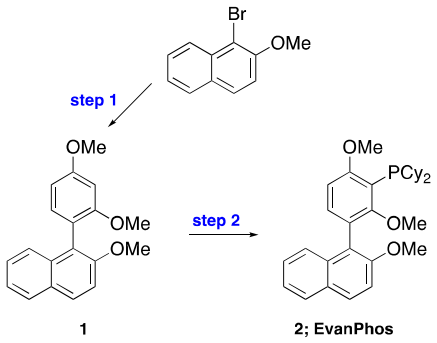
A new biaryl phosphine-containing platform can be constructed in only two steps and that complexes $Pd(OAc)_2$ forming a precursor to a very active catalyst useful for Suzuki-Miyaura cross-couplings of functionalized substrates. By a combination of pre-activation, used together with the uncommon solvent EtOAc, the resulting catalyst system is effective at loadings in the ppm (0.1-0.5 mol %) range with highly functionalized reaction partners. Similar reactions run in water containing nanomicelles are as fast or faster. The derived Pd-complexed pre-catalyst possesses extended bench stability. The resulting technology represents an attractive green synthetic advance in highly valued Suzuki-Miyaura couplings.

Notwithstanding the enormous progress made since the initial disclosure of Suzuki-Miyaura (SM) cross-couplings,[1–4] it now seems reasonable to conclude that no one ligand, nor set of conditions, fits all types of valued Pd-catalyzed Csp^2-Csp^2-type bond constructions. To complicate matters further, with changing times, environmental issues not of consequence back in the 1970's are today of increasing relevance. Moreover, still to be broadly recognized and addressed by chemists worldwide is that the status of many metals routinely used in synthesis, whether precious or otherwise, are endangered, with known lifetimes based on current rates of consumption.[5] Ideally, therefore, efforts leading to the development of catalysts that accommodate several of these important issues would go a long way towards providing more sustainable processes for heavily utilized reactions. It is with this overarching view that we set out to find a new palladium catalyst that meets many of these demands both for today as well as the future of modern organic synthesis, and in particular is applicable to the second most commonly used reaction (*i.e.,* SM couplings) over the past 30 years within the pharmaceutical arena.[6]

A major consideration oftentimes associated with ligand design is that it be easily prepared from readily available and inexpensive starting materials, exhibit extended stability when stored on the bench in the presence of atmospheric oxygen, and preferably be modular in nature such that new variants are readily accessible for future generations based on as yet unforeseen needs. While the recently introduced ligand HandaPhos shows remarkable reactivity as its 1:1 complex with palladium and is useful at ≤0.1 mol % levels (*i.e.,* ≤1000 ppm), its preparation requires ten steps which are characteristic of these oxaphosphole-containing ligands in the BI-DIME series.[7,8] Many popular ligands in the literature (e.g., SPhos, P[*t*-Bu]$_3$, etc.) are typically used in the 1-5 mol % Pd range when in combination with simple Pd pre-catalysts (*e.g.* $Pd[OAc]_2$, $PdCl_2$, $Pd_2[dba]_3$), which is an unsustainable level of Pd usage.[5] Our goal was to devise a readily synthesized, modular ligand architecture that could approach HandaPhos levels of activity for SM couplings in *both* organic solvents as well as under aqueous micellar catalysis conditions. Thus, a new *meta*-biaryl framework **1** (Scheme 1) was envisioned, standing in contrast to the typical *ortho*-biaryl framework that is a key feature of many mono-phosphine ligands for cross-couplings, as a precursor to biarylphosphine **2** that might meet all of these criteria.



step 1: 1-Bromo-2-methoxynaphthalene, 2,4-dimethoxyphenylboronic acid, cat. Pd, K_3PO_4•H_2O, TPGS-750-M (2 wt %), H_2O. 45 °C. 3 h; 88%
step 2: Biaryl **1**, *n*-BuLi, THF. 0 °C, then Cy_2PCl, 0 °C - rt; 77%

Scheme 1. 2-step route to EvanPhos (**2**)

This new biaryl ligand, EvanPhos (**2**; Scheme 1), could readily be fashioned from a simple resorcinol derivative, *O,O*-dimethylresorcinol-4-boronic acid, which smoothly participates in SM cross-couplings with the appropriate bromonaphthol 2-methyl ether to arrive at biaryl **1** (**step 1**). Subsequent metalation at 0 °C with *n*-BuLi in THF followed by quenching with commercially available Cl-PCy_2 afforded the targeted ligand, EvanPhos, **2** (**step 2**). The simplicity of this route, as well as the avoidance of cryogenic (-78 °C) conditions is noteworthy.

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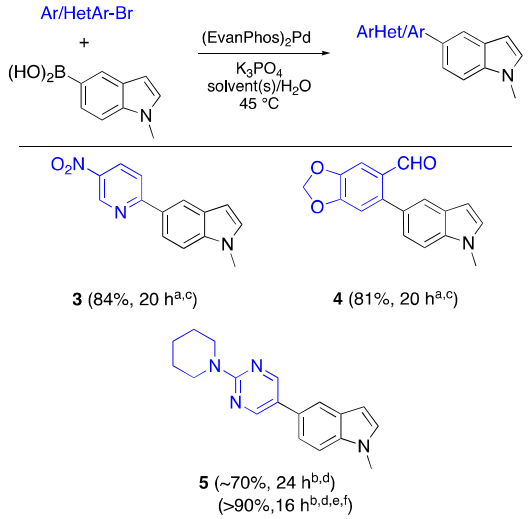
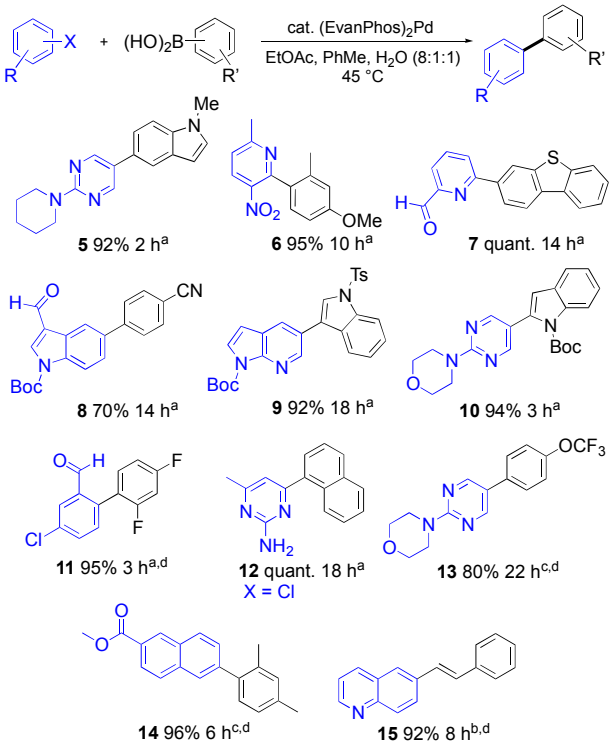
Initial screening of EvanPhos-complexed $Pd(OAc)_2$ (2:1) in SM couplings run in *toluene*, a solvent used quite commonly for state-of-the-art couplings,[9–11] at 45 °C led to good isolated yields of biaryl products **3** and **4**, relying on only 0.1 mol % (1,000 ppm) palladium (Scheme 2). In the specific case of reaction between partners to form product **5**, however, this coupling failed to reach completion with even 0.5 mol % catalyst. By pre-activation, the active Pd(0) catalyst derived from $(EvanPhos)_2Pd(OAc)_2$ increased the extent of conversion to 70%. In our research group's pursuit of greener reaction conditions this coupling was attempted in EtOAc.[12] With this non-obvious solvent switch we noted that the heteroaromatic bromide was fully consumed leading to unsymmetrical biaryl **5** which could be consistently isolated in >90% yield.



Conditions: (EvanPhos) : $Pd(OAc)_2$ 1.5:1 in toluene/H_2O heated with 2 equiv $PhB(OH)_2$ [a] 0.1 mol % Pd. [b] 0.5 mol % Pd; aryl bromide (1.0 mmol), indole-5-boronic acid (1.5 mmol), $K_3PO_4 \cdot H_2O$ (1.5 mmol); 9:1 toluene:water; 1 M relative to bromide; 45 °C. [c] isolated yields. [d] GC/MS conversion. [e] $(EvanPhos)_2Pd$ 1.75 : 1 activated with 2 equiv DIBAL. [f] EtOAc : toluene : H_2O 8:1:1.

Scheme 2. Initial testing of EvanPhos in Suzuki-Miyaura biaryl couplings

Ethyl acetate is an atypical and non-obvious solvent choice for SM reactions compared to the literature-favored reliance on toluene, dioxane, and other ethereal media.[9,11,13,14] While it has been utilized several times for Sonogashira couplings, its use in SM couplings is limited only to use as a co-solvent in a continuous-flow setting.[15–18] It has many advantages, however, e.g., with regard to known safety issues (such as toxicity, peroxides). Hesitation may well stem from the presence of base and water in the organic medium, suggesting interference by competitive solvent saponification especially for reactions that require heat. Nonetheless, under these mild conditions, cross-couplings take place with most aryl/heteroaryl bromides (except for **12** via the corresponding chloride) quite efficiently using this relatively less environmentally offensive organic reaction medium, and one that can also function directly as the extraction solvent.[19] The effectiveness of this change in solvent may simply reflect its greater polarity relative to others commonly used. Representative couplings performed using these new conditions are illustrated in Scheme 3, and given the nature of several of the heteroatom-rich products, seem to suggest that such conditions are quite general.



Conditions: *a*. $Pd(OAc)_2$ (0.5 mol%), EvanPhos (0.9-1.0 mol %). reduced with DIBAL/PhMe, halide (0.5 mmol), organoboron (0.75 mmol), $K_3PO_4 \cdot H_2O$ (0.75 mmol), EtOAc (0.8 mL), PhMe (0.1 mL from catalyst solution), DI H_2O (0.1 mL). 45 °C. Reaction times not optimized at 0.1 mol % Pd. *b*. $Pd(OAc)_2$ (0.25 mol%) EvanPhos (0.45-0.5 mol %). *c*. $Pd(OAc)_2$ (0.1 mol %), EvanPhos (0.18-0.2 mol %) *d*. no DIBAL

Scheme 3. Cross-couplings in EtOAc using [$Pd(OAc)_2$ + 2EvanPhos]

Low catalyst loadings from this and other studies in our group are typically achieved by transferring an aliquot of a catalyst stock solution of known concentration. HandaPhos has been used in this manner with no affect on reactions regardless of the age of the stock solution. However we have noted that stability can vary widely among other commonly utilized ligands; e.g., a stock solution of SPhos and $Pd(OAc)_2$ (2:1) exhibits a dramatic color change over a 24 hour period when maintained at ambient temperature under an inert atmosphere (Figure 1). A day old solution, therefore, leads to dramatically inferior coupling results (Scheme 4). A reaction to form biaryl **11** is nearly complete (reaction time 1 h for SPhos and 2 h for EvanPhos, respectively) with fresh stock solutions of either catalyst. With SPhos, however, the reaction affords only 34% conversion using a catalyst solution stored for one day. By contrast, a solution of EvanPhos shows no such color change and maintains high catalyst activity. The outcome from its use in a SM coupling corroborates the far greater stability of this new catalyst precursor. Similar sensitivity of other ligands in the presence of $Pd(OAc)_2$ (e.g., XPhos and triphenylphosphine) has been noted previously.[20,21]

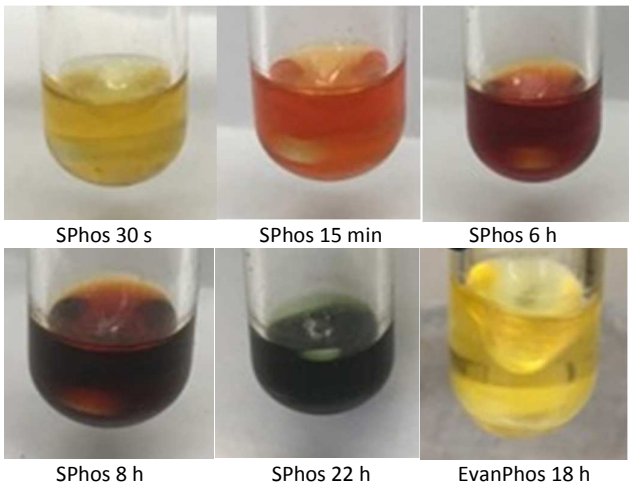
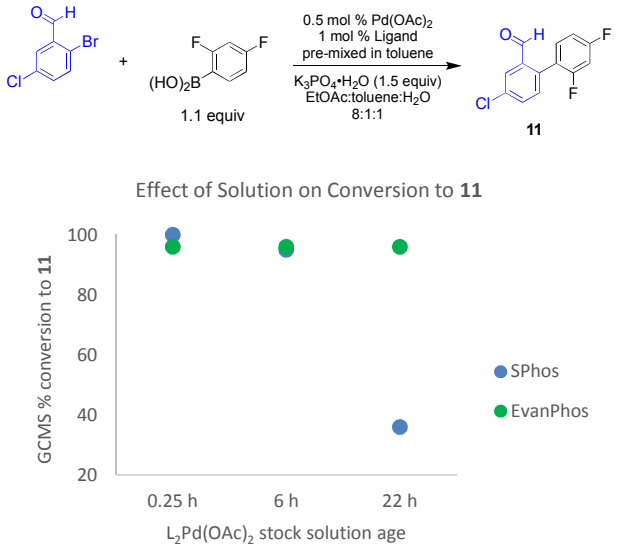


Figure 1: Color changes over time for ligated $Pd(OAc)_2$ pre-catalysts.



Scheme 4. Effect of catalyst solution age on conversion to biaryl **11**

Although the vast majority of organic synthesis is still performed in organic solvents, we continue to provide examples of important reactions (*e.g.,* peptide couplings,[22,23] S_NAr,[24,25] etc.) that can now be run in water between rt and 45 °C. These are enabled by engineered surfactants (e.g., TPGS-750-M; Figure 2) and their derived environmentally benign nanomicelles that serve as nanoreactors in an aqueous medium. Using this new catalyst system $(EvanPhos)_2Pd(0)$ at the 1000-5000 ppm (0.10-0.50 mol %) level of Pd loading, several challenging cases involving (mainly) aryl bromides and boronic acids were examined under aqueous micellar conditions.[26] These examples leading to products **5**, **6**, **10**, **11,** and **16-24** are illustrated in Scheme 5, and attest to the encouraging functional group tolerance observed, comparing rather well with recently developed HandaPhos technology.[7]

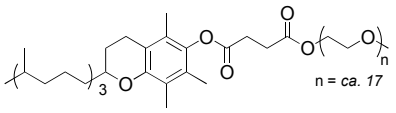
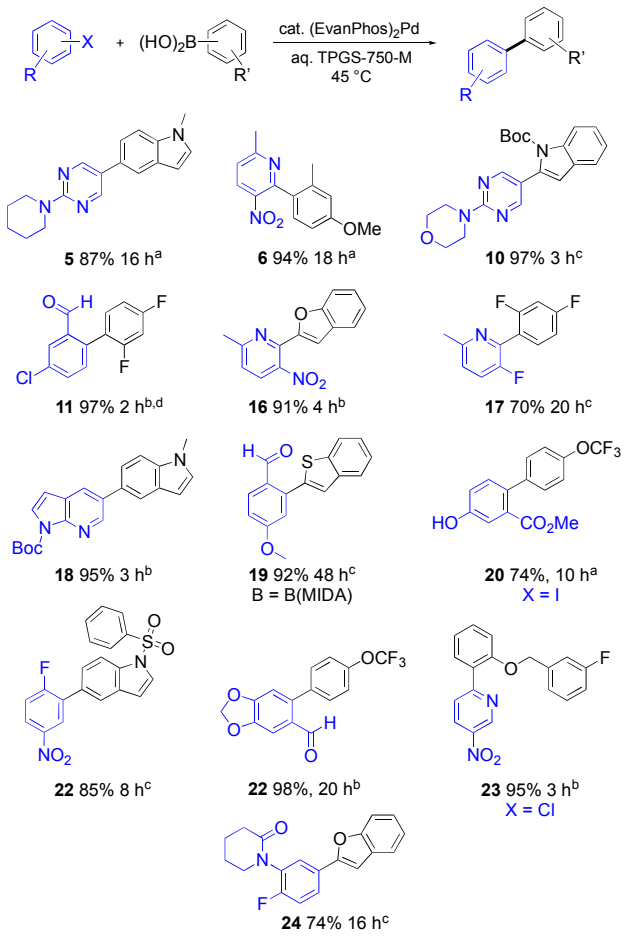


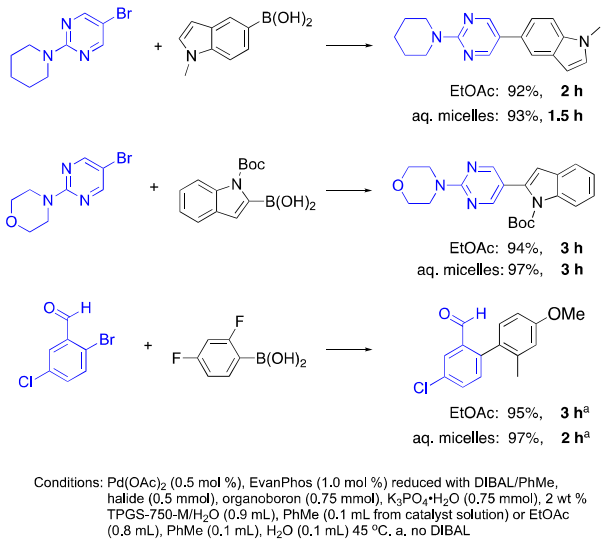
Figure 2. Structure of surfactant TPGS-750-M



Conditions: *a*. $Pd(OAc)_2$ (0.1 mol %), EvanPhos (0.18-0.2 mol %) reduced with DIBAL/PhMe, halide (0.5 mmol), organoboron (0.75 mmol), $K_3PO_4•H_2O$ (0.75 mmol). 2 wt % TPGS-750-M/H_2O (0.9 mL), PhMe (0.1 mL from catalyst solution) 45 °C. Reaction times not optimized at 0.1 mol % Pd. *b*. $Pd(OAc)_2$ (0.25 mol%), EvanPhos (0.45-0.5 mol %). *c*. $Pd(OAc)_2$ (0.5 mol%, EvanPhos (0.9-1.0 mol %). *d*. no DIBAL

Scheme 5. Representative SM couplings in aqueous nanomicelles

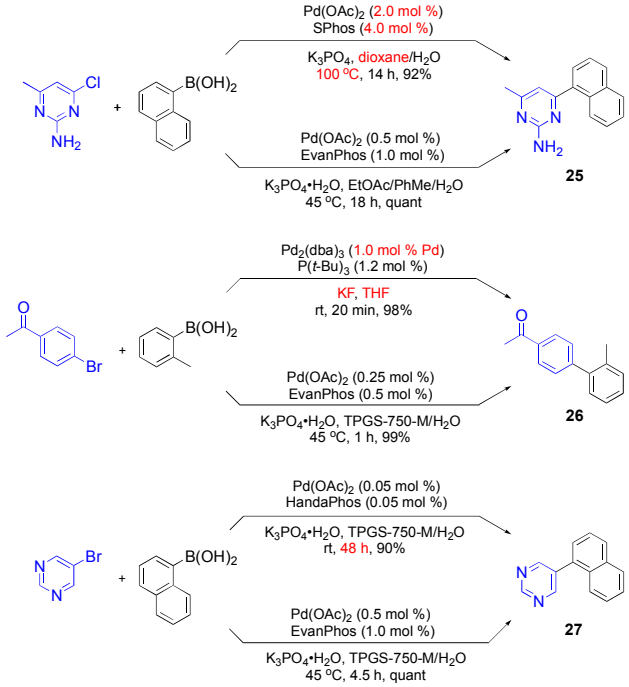
Direct comparison reactions involving $(EvanPhos)_2Pd$ in EtOAc vs. micellar media at the same 0.5 M global concentration were investigated next (Scheme 6). In general, reactions tended to be as fast or faster in aqueous nanomicelles, perhaps not unexpected given the typically higher local concentrations associated with the inner cores of nanomicelles.[27] Thus, these differing reaction media, ethyl acetate and aqueous micelles, provide two excellent options for reactions to be run not only under greener conditions, but also at typically greater rates.



Conditions: $Pd(OAc)_2$ (0.5 mol %), EvanPhos (1.0 mol %) reduced with DIBAL/PhMe, halide (0.5 mmol), organoboron (0.75 mmol), $K_3PO_4 \cdot H_2O$ (0.75 mmol), 2 wt % TPGS-750-M/H_2O (0.9 mL), PhMe (0.1 mL from catalyst solution) or EtOAc (0.8 mL), PhMe (0.1 mL), H_2O (0.1 mL) 45 °C. a. no DIBAL

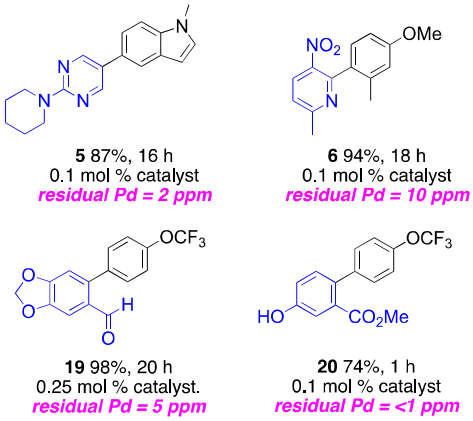
Scheme 6. Comparisons between coupling reactions in EtOAc vs. aqueous nanomicelles

Comparison couplings between Pd-complexed EvanPhos and three alternative catalyst systems are illustrated in Scheme 7.[7,28,29] Biaryl **25** demonstrates the effectiveness of switching from an SPhos-based catalyst used in hot dioxane to an EvanPhos-complexed Pd-driven coupling in EtOAc. As with this first example, compound **26** highlights the significant drop in catalyst loading using EvanPhos technology, and eliminates use of a water-miscible organic solvent. To arrive at biaryl **27**, although HandaPhos technology allows for a catalyst loading of only 500 ppm, the reaction time required (48 h) can be shortened considerably using the readily prepared and stable catalyst, $(EvanPhos)_2Pd$.



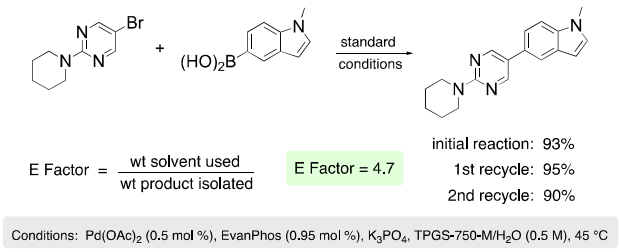
Scheme 7. Comparison SM reactions between Pd-complexed EvanPhos and other ligands

Use of $(EvanPhos)_2Pd$ in the 1000-2500 ppm range leads to low levels of residual palladium as found within the biaryl products. This is an especially important consideration within the pharmaceutical arena, as it relates to the U.S. F.D.A. allowed level of 10 µg (i.e., 10 ppm) palladium/g drug/day for residual palladium.[30] ICP-MS analyses on products **5, 6**, **19** and **20** showed ≤10 ppm Pd in each case (Scheme 8). Catalyst loadings of 0.5 mol %, on the other hand, resulted in residual Pd levels between 150-250 ppm (see SI).



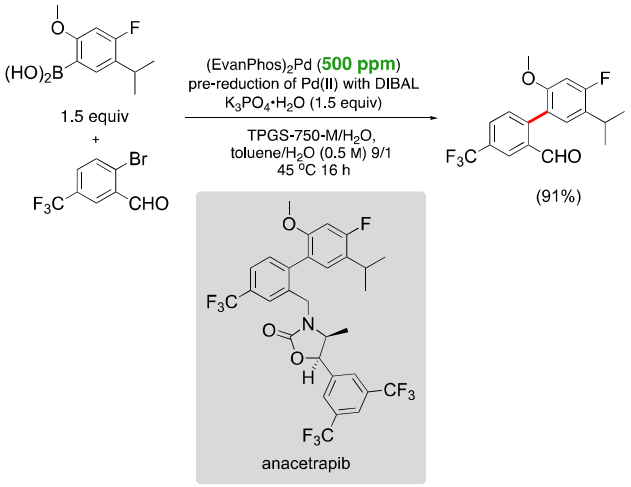
Scheme 8. Analysis of residual palladium in biaryl products

Recycling of the reaction mixture containing TPGS-750-M in water, albeit with additional $(EvanPhos)_2Pd$ (0.5 mmol in this case) being added for each cycle, could be readily achieved by simple in-flask extraction of the aqueous medium with MTBE. The yields for each of two additional recycles did not vary significantly, while the E Factor associated with this coupling, based on organic solvent used, was quite low as compared with those values typically seen for such reactions in the literature (Scheme 9).[31]



Scheme 9. Recycling study and E Factor determination.

As a representative example of the potential of this new technology in the pharmaceutical space, synthesis of an intermediate towards Merck's CETP inhibitor anacetrapib could be achieved with $(EvanPhos)_2Pd$ under micellar conditions, with a loading as low as *500 ppm* (0.05 mol %) (Scheme 10).[31] Use of toluene (10% by volume) as co-solvent leads to a very freely stirring, well-behaved emulsion and is highly suggestive that such couplings at these low catalyst loadings can be easily scaled.[32]



Scheme 10. Use of catalyst $(EvanPhos)_2Pd$ at the 500 ppm level to prepare an intermediate *en route* to anacetrapib.

An X-ray determination of the $(CH_3CN)_2PdCl_2$-derived 2:1 complex, $(EvanPhos)_2PdCl_2$, is illustrated in Figure 3. While the related complex $(EvanPhos)_2Pd(OAc)_2$ could be isolated, obtaining crystals suitable for single-crystal X-ray analysis proved elusive. Nonetheless, both isolated pre-catalysts in their powdered form were bench-stable and catalytically active. Two interesting features noted from the crystal structure showing Ci symmetry are (1) the orientation of the biaryl bond being rotated such that the majority of the naphthyl substituent, rather than the less bulky pendant methoxy group, is oriented towards the palladium center, and (2) the weak 3.076 Å coordination between the palladium center and the methoxy oxygen on the resorcinol ring. DFT calculations on $(EvanPhos)_2PdCl_2$ reveal that rotating about the biaryl bond such that the methoxy substituent on the naphthalene system is closer to Pd yields a structure that is 1.72(4.36) kcal/mol (B3LYP/6-31G(d)-SDD and MN15/6-31+G(d,p)-SDD) higher in free energy at 298K.[33] Opposite to the orientation observed in the X-ray structure. The bond distances and angles for $(EvanPhos)_2PdCl_2$ from B3LYP/6-31G(d)-SDD and MN15/6-31+G(d,p)-SDD level calculated geometries compare favorably with values from the experimental X-ray structure (see Supporting Information). The more recent MN15 functional gives substantially better agreement with experimental geometries, suggesting that energies at this level of theory might also be more reliable.

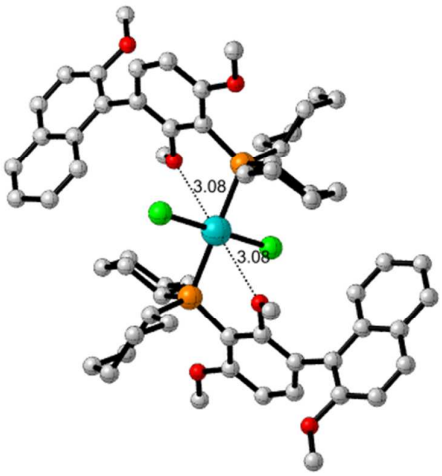


Figure 3. X-ray structure of $EvanPhos_2PdCl_2$. Hydrogens omitted for clarity

The structures and energies of the pre-reductive elimination intermediate (Figure 4) and the reductive elimination transition state (Figure 5) for the Suzuki reaction to form biphenyl as the coupling product were calculated using DFT methods to help understand how EvanPhos functions, and how it might be improved in future catalysts. The pre-reductive elimination intermediate prefers a conformation with the methoxy substituent on the naphthalene system closer to Pd, while the transition state shows a negligible free energy difference. The intermediate structure reveals a square planar complex with a C-Pd-C angle of 87.68° and a short 2.330 Å bond to a methoxy oxygen on the resorcinol ring. Another conformation of the intermediate with a planar T-structure at Pd (C-Pd-C angle 162°) and weak methoxy coordination (C-Pd distance 3.05 Å) from above the Pd plane is 20.43 kcal/mol higher in free energy (B3LYP/6-31G(d)-SDD), indicating the importance of methoxy coordination. The transition state structure is also roughly square planar in nature, but with a C-Pd-C angle of 60.25° and a longer 2.936 Å distance to the methoxy oxygen. The free energy of activation for reductive elimination is calculated to be 14.1 kcal/mol at 298 °K in toluene (to mimic a micellar environment)[MN15/6-31+G(d,p)-SDD)]. Without the methoxy group on the naphthyl ring the free energy of activation is predicted to be 12.7 kcal/mol (see Supporting Information for further details and discussion of computational work).

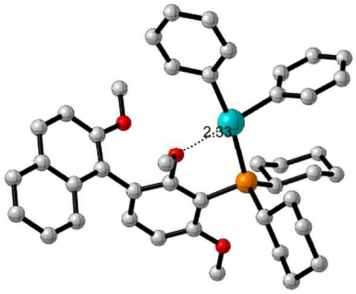


Figure 4. Calculated structure of $(EvanPhos)PdPh_2$ pre-reductive elimination intermediate. Hydrogen atoms omitted for clarity.

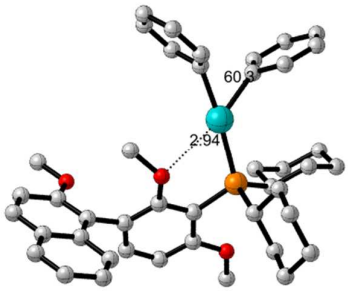


Figure 5. Calculated structure of $(EvanPhos)PdPh_2$

Attempts to isolate an analogous acetate complex with the di-*t*-butyl EvanPhos ligand provided an unexpected result. Recrystallization of the isolated yellow powder revealed a dimer of (*t*-BuEvanPhos)Pd(OAc) wherein a methoxy group adjacent to the P(*t*-Bu)$_2$ group of the ligand was demethylated *in situ* under neutral conditions, yielding a *P,O*-bidentate ligand (Figure 6). Analysis of the ESI-MS data reveals that the major species in the powder is actually the monomer. The dimer was only observed in the MS at exceedingly high concentrations. Analysis of the crude NMR of the isolated powder even after rinsing with hexanes and vacuum filtration unambiguously revealed the presence of residual methyl acetate. Several substrate combinations revealed that the reactivity of the *monoligated* *t*-BuEvanPhos-derived catalyst (i.e., (*t*-BuEvanPhos)Pd) is at least equal to that of (EvanPhos)$_2$Pd, while requiring half the amount of ligand (Scheme 11) and to the best of our knowledge this represents the first example of an anionic P,O bidetante ligand utilized for SM couplings in the literature. We envision that this complex arises from Lewis acid-mediated demethylation, where the nucleophile is the atypical but mechanistically plausible acetate ion (Scheme 12).

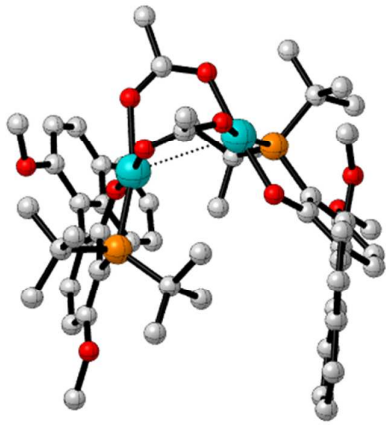
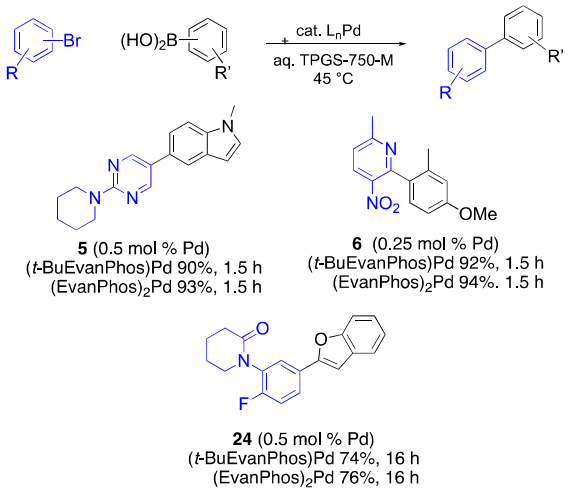
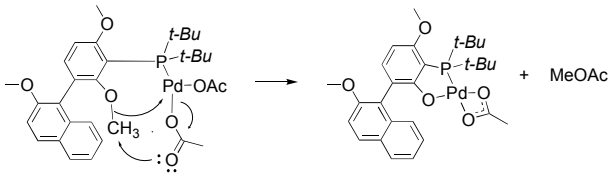


Figure 6. X-ray structure of (*t*-BuEvanPhos)$_2$Pd$_2$(OAc)$_2$. Hydrogens omitted for clarity.



Scheme 11. Comparison of *t*-BuEvanPhos vs. EvanPhos



Scheme 12. Proposed mechanism for bidentate P,O-complex formation.

Conclusions

In summary, a newly designed ligand, EvanPhos, is described that when combined with palladium as a ca. 2:1 complex serves as a pre-catalyst for SM couplings in either EtOAc or under micellar conditions in water with equal efficiency. It can be prepared in two simple steps from either $(CH_3CN)PdCl_2$ or $Pd(OAc)_2$, and is readily converted to a highly active Pd(0) species. This catalyst is even more reactive in the atypical organic medium EtOAc, rather than in commonly used toluene or ethereal solvents, and functions with loadings in the 0.05-0.5 mol % range of Pd. Making the switch to aqueous micellar media, the rates of reactions can be even faster. EvanPhos is also resistant to common intermolecular redox processes, indicative of forming a stable pre-catalyst in the presence of $Pd(OAc)_2$.Given the modular nature associated with the synthesis of biaryls represented by EvanPhos (cf. Scheme 1), the search for even more effective ligands based on this biaryl platform that are readily prepared as described herein are under active investigation.

Conflicts of interest

The authors declare that a patent application on EvanPhos has been submitted by the University of California.

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Crystallographic data

CCDC deposition numbers 1823687 and 1823688 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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