Following Nature's Lead. Designing a Very Simple yet Effective Ligand System Applicable to Pd-Catalyzed Cross Couplings…in Water

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Abstract. A new ligand design based on Nature's use of simple elements is described. This relatively uncommon array of atoms is arrived at in a single step leading to "P3N" ligands, such as "(n-$Bu_2N)_3P$", derived from PCl_3 and three equivalents of n-Bu_2NH. These readily participate in homogeneous, Pd-catalyzed Cu-free Sonogashira and Suzuki-Miyaura couplings. Reliance on low loadings of Pd is documented under aqueous micellar conditions (*i.e.,* in water). Comparisons with several typically used representative ligands, which, by contrast are made in an environmentally egregious fashion, clearly show that this new series of ligands is preferred, cost-wise, synthetically, as well as in terms of their environmental impact.

Introduction

It is hard to imagine Pd-catalyzed transition metal catalysis in the absence of ligands. While there are certainly occasional examples of Pd catalysis run under "ligandless" conditions, by far most reactions, and specifically cross couplings, rely on the judicious choice of ligand. Today, there are seemingly unlimited numbers created for purposes of fine-tuning various properties on the resulting metal catalyst. Unfortunately, they tend to be designed mainly with the end game in mind: that is, a successful ligand assists in accomplishing a targeted synthetic goal, usually independent of the chemistry required to make it or the reaction parameters under which it's to be used. And while this successful approach has predominated for decades, times have changed; there's a growing appreciation of the processes themselves that prepare ligands in terms of their impact on the environment, with new analyses in focus, such as "Life Cycle Assessments" (LCA),[1] "cradle to grave" evaluations,[2] and ultimately, the chemistry's effect on climate change (Figure 1).[3]

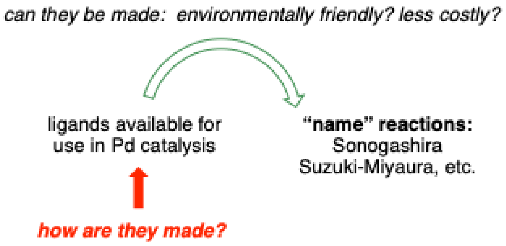


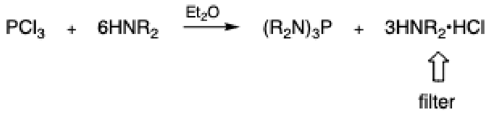
Figure 1. Current awareness of ligand preparation, cost, and sustainability.

Modern Pd catalysis still utilizes (1) organic solvents as reaction medium, notwithstanding their major role in waste-generation, according to the Green Chemistry Institute's Pharma Roundtable;[4] (2) too much energy, in principle needed to drive reactions run in organic solvents to completion, and (3) catalyst loadings of this precious metal that are far too high, leading to up-front expenses as well as costs associated with its removal due to elevated residual levels of Pd in the products. Overall consumption of this limited planetary resource is yet another factor. Most of our efforts have zeroed in on these three reaction parameters, providing technologies that are based on Nature's environmentally responsible solutions to each. Thus, Pd-catalyzed cross couplings can now be done in water under micellar catalysis conditions, thereby avoiding traditional organic solvents.[5] Cross couplings can be run under far milder conditions, with many at room temperature, taking advantage of the high concentrations (*i.e.,* >2 M) characteristic of the inner cores of nanomicelles. And insofar as levels of Pd needed, the proper design of ligands that accentuate lipophilicity (in a "like-dissolves-like" sense, as with EvanPhos[6] and N_2Phos[7]) leading to an increase in residence time inside nanoreactors where catalysis likely occurs. By following these "new rules",[8] roughly ten times less Pd is needed per reaction, essentially solving the long-term availability issue.

Given these advances, the ligand associated with the Pd catalyst becomes the key remaining relatively expensive variable. While water, as well as energy (provided at ambient temperatures), have become virtually cost-free (assuming the available technologies are used), most ligands in use require preparation; in other words, ligand synthesis takes a commitment of time, effort, materials, energy, organic solvents and almost always, several steps to obtain.[9] In this report we describe an unprecedented new series of ligands that is not only trivial to make and done so inexpensively, but also enables Pd catalysis in water using the same low loadings of catalyst.

Results and discussion

One approach involves a novel arrangement of these atoms into what is commonly referred to as "*P,N*-ligands."[10] These are commonly configured for purposes of metal chelation within 5- or 6-membered rings. However, by forming three *P,N*-bonds via addition of a secondary amine to PCl_3, a new series of "P3N-liands" results. The 3HCl given off is consumed as the salt of the added amine, which is filtered away from the newly generated ligand formed in virtually quantitative yield (Scheme 1).

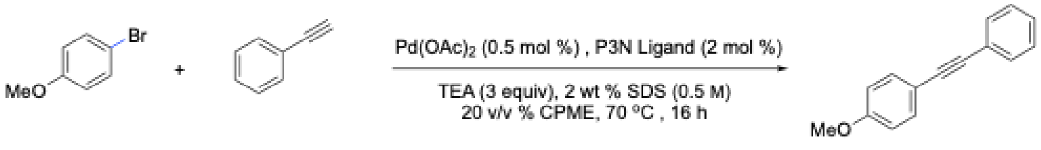


$$PCl_3 + 6HNR_2 \xrightarrow{Et_2O} (R_2N)_3P + \underset{\text{filter}}{\underset{\Uparrow}{3HNR_2{\cdot}HCl}}$$

Scheme 1. 1-Step preparation of P3N-ligands

The simplicity of forming P3N-ligands allowed for several to be constructed the screening of which led to the most effective catalyst following its chelation to a (presumably reduced) palladium(II) salt ($Pd(OAc)_2$). As seen in Table 1, several secondary amines were selected and converted to the corresponding homo- or mixed-P3N ligand (*i.e.,* **L1** – **L7**). A model Sonogashira reaction between aryl halide **1** and alkyne **2** leading to product **3** was used to determine the best match between the ligands in Table 1 and the intended use in Pd-catalyzed couplings. Clearly, (n-$Bu_2N)_3P$ (entry 4) appeared to be the most effective, affording product **3** in high yield.

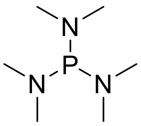
Table 1. Ligand screening



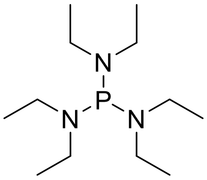
1 **2** (1.2 equiv) **3**

entry	ligand	yield (%)[a]
1	SPhos	77
2	Xphos	58
3	DPPF	79
4	**P(NBu₂)₃**	**92**
5	Ipr	15

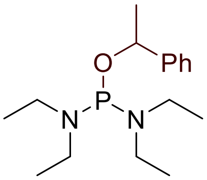
[a] Quantitative NMR yields (using 1,3,5-methoxybenzne as the internal standard)



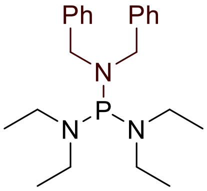
L1
6%



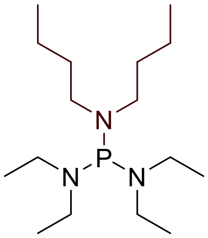
L2
45%



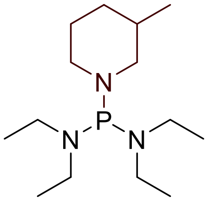
L3
NR



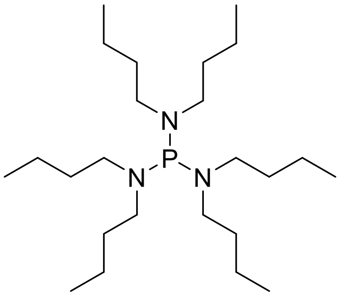
L4
NR



L5
77%



L6
55%



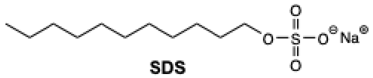
L7
quant

The preparation of (n-$Bu_2N)_3P$ (**L7**), made using this 6:1 ratio of amine to PCl_3 in dry ether (three equivalents of n-Bu_2NH used for removal of the HCl by-product) initially involved a purification via distillation under vacuum and at high temperatures. However, it was soon realized that purification was not needed, as the newly formed ligand was ready for immediate use.

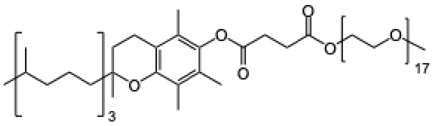
The nature of the surfactant was also screened using this new ligand. Surprisingly, best results were obtained using very inexpensive aqueous sodium dodecylsulfate (SDS; Table 2, entry 6; 2 wt % in water), an anionic surfactant, rather than nonionic amphiphiles (*e.g.,* TPGS-750-M, Savie, etc.) previously found to be the most effective for Sonogashira reactions.

Table 2. Surfactants screened for Pd-catalyzed Sonogashira couplings using (n-$Bu_2N)_3P$

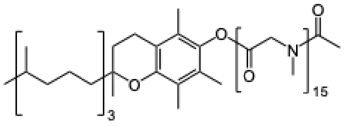
entry	surfactant	**3** (yield, %)
1	H_2O	35
2	TPGS-750-M	71
3	Tween-100	57
4	Savie	61
5	TTAB	73
6	**SDS**	**84**
7	Brij-56	81



SDS

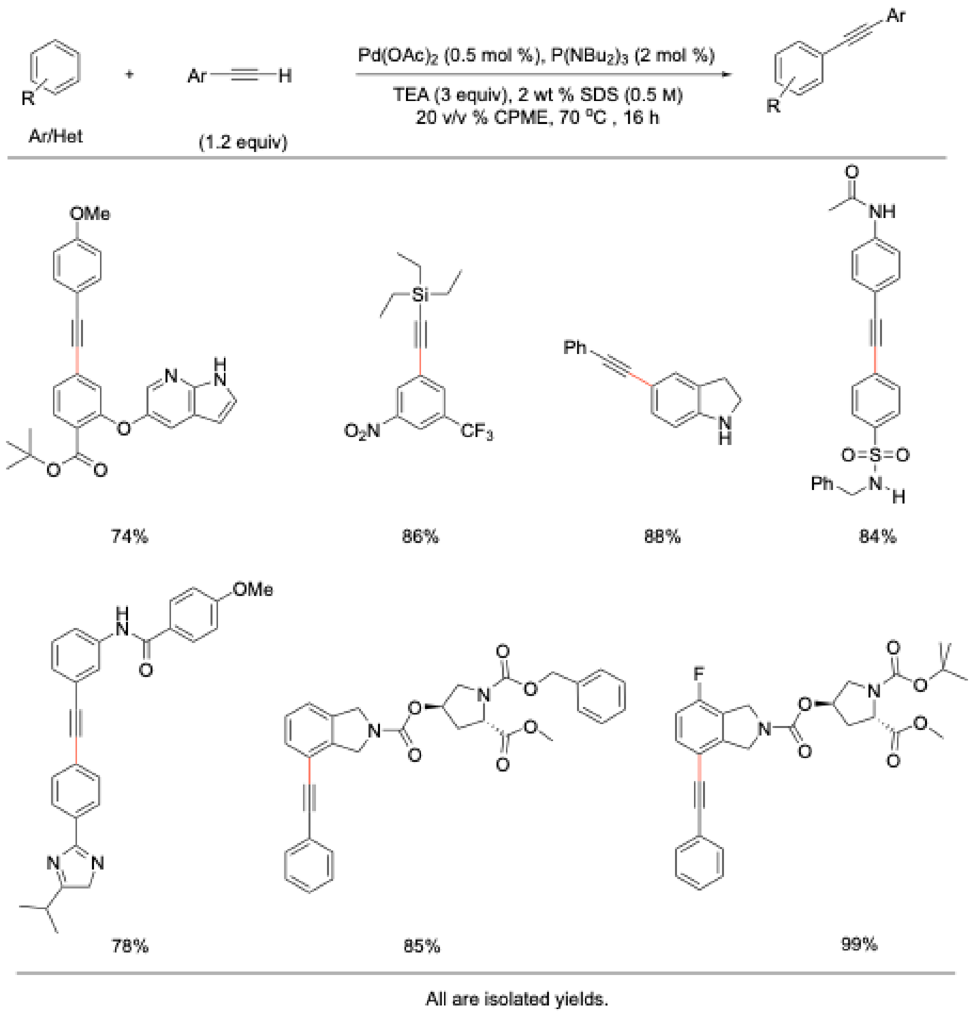


TPGS-750-M



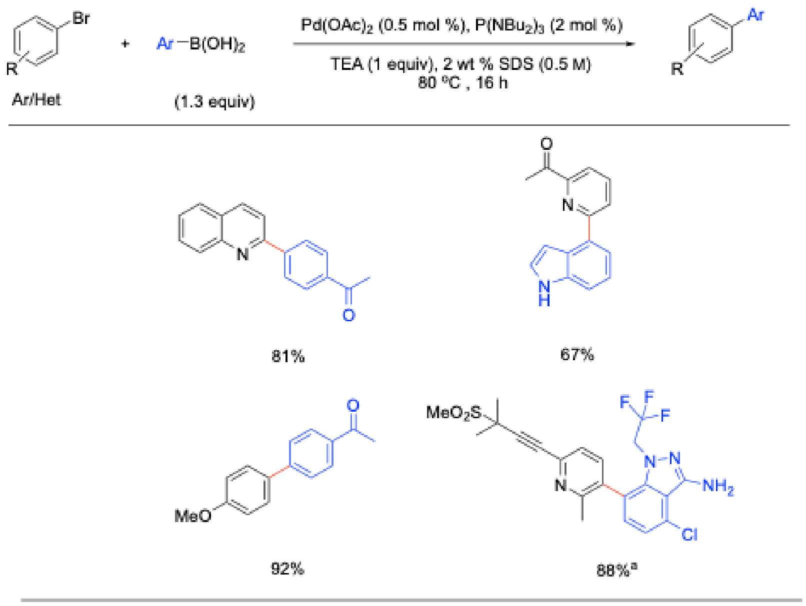
Savie

Scheme 2 provides several representative examples resulting from the use of (n-$Bu_2N)_3P$ together with a relatively low loading of a Pd(II) salt in Sonogashira couplings. These include several examples featuring late-stage functionalization and attest to the not only the effectiveness of this catalyst and the environmental friendliness of the conditions involved (*i.e.,* in water), but also the far less costly nature of this new ligand system.



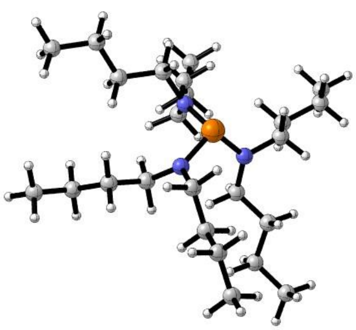
Scheme 2. Representative examples of Sonogashira couplings using (n-$Bu_2N)_3P$ as the ligand on Pd

Similar uses of the same Pd complex of (n-$Bu_2N)_3P$ in Suzuki-Miyaura couplings, as illustrated in Scheme 3, also gave good levels of cross coupling products. In addition to relatively straightforward cases, an example of a highly substituted substrate underwent an efficient coupling affording the product in 88% yield.

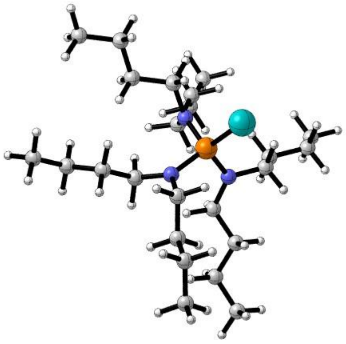


All isolated yields. [a] 0.5 mol % of $Pd(OAc)_2$ was used.

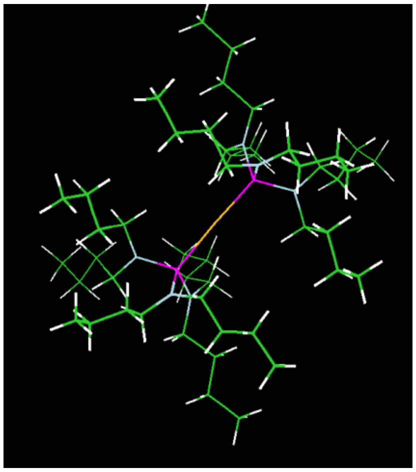
Additional information regarding the new ligand array (n-$Bu_2N)_3P$ was also obtained using DFT calculations. Its structure was optimized at the B3LYPD3BJ/6-31+G(d,p) level of theory with a symmetrical C3 conformation **A** and an all-*anti* arrangement of the *n*-butyl groups chosen to have the groups arranged to have a minimum steric energy keeping these alkyl groups away from the phosphine, thereby allowing binding to palladium, as well as oxidative addition of a substrate. Introduction of Pd into conformer **A** led to **PdA**, optimized at the B3LYPD3BJ/6-31+G(d,p) and B3LYPD3BJ/6-31+G(d,p)/SDD(Pd,Br) level of theory. Similarly, a second ligand on the Pd gave **PdA2**. Oxidative addition of bromobenzene to **PdA** and **PdA2** gave intermediates **PdAPhBr** and **PdA2PhBr**. The **PdA2PhBr** structure, when optimized at the B3LYPD3BJ/6-31G(d)/SDD(Pd,Br) level of theory did not lead to a minimum with both phosphine ligands bound to Pd; rather, it spontaneously cleaved to give a structure with only a single phosphine ligand bound to Pd. Calculations showed that formation of this oxidative addition complex bearing two ligands, **PdA2PhBr,** was uphill thermodynamically relative to the mono-ligated species **PdAPhBr** and **A,** or from **PdA2** and **PhBr**. Thus, these calculations show that only two ligands can be accommodated around each Pd, while one must be lost in order for the catalytic cycle involving an initial oxidative addition to take place.



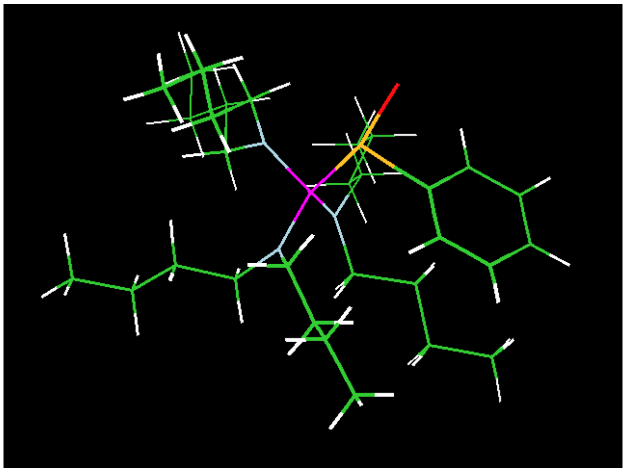
A [(n-Bu$_2$N)$_3$P]



PdA [(n-Bu$_2$N)$_3$P-Pd]



PdA2 [(n-Bu$_2$N)$_3$P-Pd-P(n-Bu$_2$N)$_3$]



PdAPhBr [(n-Bu$_2$N)$_3$P-Pd(Ar)(Br)]

In summary, a new, very inexpensive yet effective P3N ligand system derived from the simple addition of a secondary amine to PCl_3 has been disclosed. The leading ligand is derived from (n-Bu$_2$N and affords (n-Bu$_2$N)$_3$P, which can be used in both Suzuki-Miyaura and Sonogashira cross couplings, under aqueous micellar catalysis. In side-by-side comparison reactions, (n-Bu$_2$N)$_3$P has been found to outperform several of the most commonly used ligands. Moreover, each of these traditional ligand arrays requires several steps to prepare that require conditions that are typically environmentally egregious. All these factors lead to a far more costly ligand and yet, less effective ligand system than (n-Bu$_2$N)$_3$P. The bottom line is that Nature wins again.

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