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Pd(II)-Catalyzed Phosphorylation of Aryl C−H Bonds

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Supporting Information

ABSTRACT: A Pd(II)-catalyzed C−H phosphorylation reaction has been developed using heterocycle-directed *ortho*-palladation. Both H-phosphonates and diaryl phosphine oxides are suitable coupling partners for this reaction.

Aryl phosphonates and derivatives are an important class of molecules because of their broad application in medicinal chemistry,[1] material chemistry,[2] and catalysis.[3] Since the pioneering work reported by Hirao and co-workers in 1981,[4] palladium catalyzed cross-coupling of aryl halides with H-phosphonates has become a practical method to construct C(sp^2)-P bonds.[5] During the past decade, the scope of the Hirao reaction has been significantly expanded to include aryl triflates, tosylates, diazonium salts, and boronic acids as coupling partners.[6] Copper and nickel complexes were also shown to be effective catalysts for this reaction.[7,8] Encouraged by recent progress toward developing Pd-catalyzed diverse carbon−carbon and carbon heteroatom bond forming reactions via directed C−H activation,[9−13] we embarked on the development of phosphorylation of C−H bonds as a complementary method for making carbon−phosphorus bonds, which remains an unsolved problem due to the strong coordinating property of the phosphorus coupling partners. Takai and co-workers, using a tethered phosphite as a directing group as well as the coupling partner, successfully avoided this problem and established the first example of a Pd(0)-catalyzed C−H phosphorylation reaction in an intramolecular fashion (eq 1).[14−16] Herein we report an intermolecular C−H phosphorylation of C−H bonds with a variety of heterocycles (eq 2). The pyridine and oxazoline containing phophonate products are potentially useful precursors for medicinal chemistry[1] or N,P-bisdendate ligand preparation.[3h]To establish the feasibility of the C−P bond formation from cyclopalladated complexes and H-phosphonates,[17] we treated complexes **I** and **II** with H-phosphonate **2a** under various conditions. We found that stirring **I** or **II** with H-phosphonate **2a** in the presence of 1 equiv 1,4-benzoquinone (BQ) in a range of solvents gave the desired phosphorylation product **3a** and **4** in moderate to excellent yields (eq 3 and eq 4). The use of BQ was found to be essential for the formation of the products. Presumably, BQ promotes the reductive elimination in a similar manner to that observed in the coupling of C−H bonds with organometallic reagents.[18]

On the basis of this reactivity, we proceeded to develop catalytic conditions for this transformation using 2-phenylpyridine **1a** as the model substrate. Not surprisingly, reacting 2-phenylpyridine **1a** with H-phosphonate **2a** in the presence of Pd catalyst in one pot did not give any desired product. Presumably, coordination of the H-phosphonate reagent with Pd(II) catalyst will inhibit the C−H activation step. The tautomeric equilibria of H-phosphonates is well-known and the tricoordinated phosphite can bind strongly to the Pd(II) center with its lone electron pair.[19] To avoid this problem, we added the H-phosphonate **2a** to the reaction dropwise so that the concentration of it is minimized during the reaction course. With 10 mol % $Pd(OAc)_2$ as catalyst, Ag_2CO_3 as oxidant and Na_2CO_3 as base, H-phosphonate **2a** was added dropwise at 100

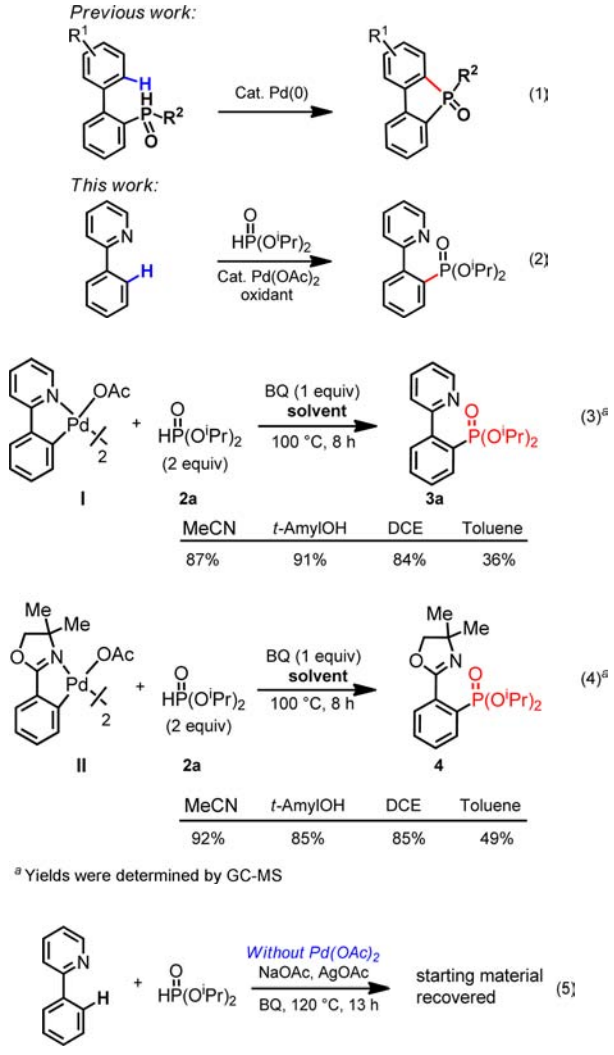

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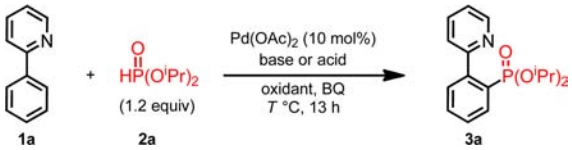
Table 1. Reaction Conditions Optimization[a]

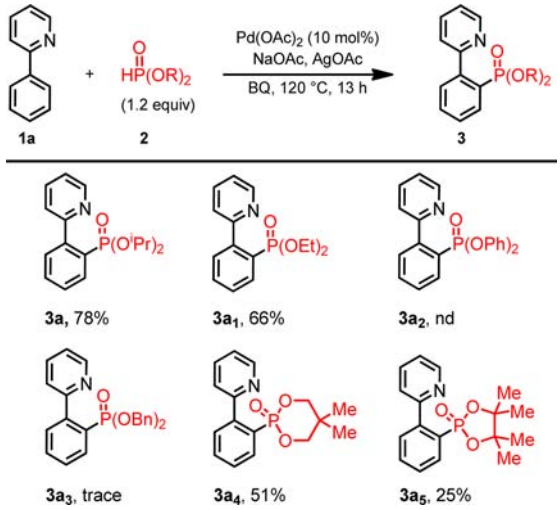


1a 2a 3a

entry	T (°C)	base/acid	oxidant	solvent	yield (%)[b]
1	100	Na_2CO_3	Ag_2CO_3	DCE	19
2	100	Na_2CO_3	Ag_2CO_3	MeCN	22
3	100	Na_2CO_3	Ag_2CO_3	1,4-dioxane	17
4	100	Na_2CO_3	Ag_2CO_3	toluene	34
5	100	Na_2CO_3	Ag_2CO_3	*t*-AmylOH	58
6	100	-	Ag_2CO_3	*t*-AmylOH	29
7	100	PivOH	Ag_2CO_3	*t*-AmylOH	52
8	100	AcOH	Ag_2CO_3	*t*-AmylOH	52
9	100	$NaHCO_3$	Ag_2CO_3	*t*-AmylOH	54
10	100	K_3PO_4	Ag_2CO_3	*t*-AmylOH	0
11	100	NaTFA	Ag_2CO_3	*t*-AmylOH	47
12	100	NaOAc	Ag_2CO_3	*t*-AmylOH	69
13	100	NaOAc	Ag_3PO_4	*t*-AmylOH	73
14	100	NaOAc	AgO	*t*-AmylOH	34
15	100	NaOAc	AgOAc	*t*-AmylOH	79
16	100	NaOAc	$Cu(OAc)_2$	*t*-AmylOH	50
17	100	NaOAc	$K_2S_2O_8$	*t*-AmylOH	44
18	120	NaOAc	AgOAc	*t*-AmylOH	84
19	140	NaOAc	AgOAc	*t*-AmylOH	72

[a]Reaction conditions: Diisopropyl H-phosphonate **2a** (0.24 mmol) in solvent (2 mL) was added dropwise to a mixture of 2-phenylpyridine **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), base or acid (0.4 mmol) and oxidant (0.4 mmol) in solvent (2 mL) in 13 h. [b]Yields were determined by GC–MS.

Table 2. Evaluation of Different Phosphorylation Reagents[a,b]



1a 2 3

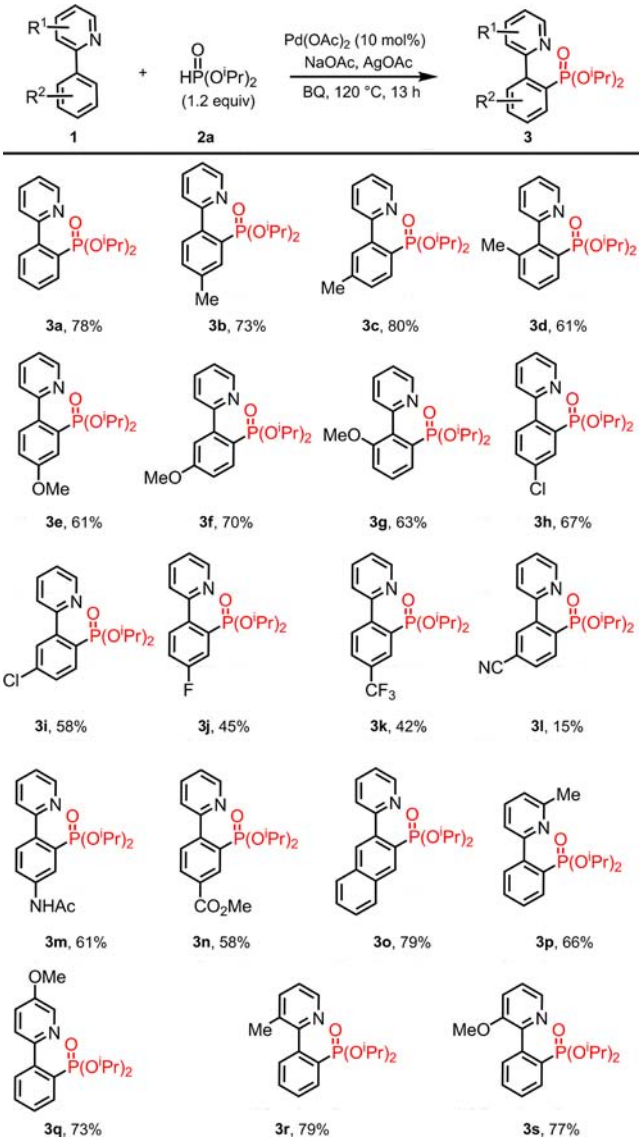
3a, 78% **3a$_1$**, 66% **3a$_2$**, nd

3a$_3$, trace **3a$_4$**, 51% **3a$_5$**, 25%

[a]Same reaction conditions as Table 1 entry 18. [b]Isolated yields.

°C in different solvents (Table 1). To our delight, the desired product was obtained under these reaction conditions, and *t*-AmylOH proved to be the best solvent (entry 5). Both a suitable base and acid promoted the reaction (entries 6–9). While stronger base K_3PO_4 completely inhibited the reaction (entry 10), the use of NaOAc gave product **3a** in 69% yield (entry 12). Several other silver salts were also examined, and AgOAc was found to be the best choice, improving the yield to

Table 3. C–H Phosphorylation of Pyridine Derivatives[a,b]



[a]Reaction conditions: Diisopropyl H-phosphonate **2a** (0.24 mmol) in *t*-AmylOH(2 mL) was added dropwise to a mixture of **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), NaOAc (0.4 mmol), and AgOAc (0.4 mmol) in *t*-AmylOH (2 mL) at 120 °C in 13 h. Unreacted arene substrates were recovered in 90–95%. [b]Isolated yields.

79% (entry 15). $Cu(OAc)_2$ and $K_2S_2O_8$ can also been used as oxidant albeit less effective compared to silver salt oxidants (entries 16 and 17). The reaction yield was further improved to 84% when the reaction temperature was raised from 100 to 120 °C (entry 18). The use of other diaryl H-phosphonates and cyclic H-phosphonates did not improve the reaction yields (Table 2).

With these optimized reaction conditions in hand, we examined the scope of arenes using coupling partner **2a** and obtained the isolated yields with substrates **1a–s** (Table 3). Arenes with electron-donating *p*- and *m*-methyl substitution gave yields of 73% and 80% respectively (**3b** and **3c**), while the *o*-methyl substituted arene afforded a lower yield of 61% (**3d**) due to the buttressing effect of the biphenyl. Similar trends in yields were observed with MeO substituted arenes (**3e–3f**). Introduction of moderately electron-withdrawing Cl on the *para*-position of arene was well tolerated and the product was

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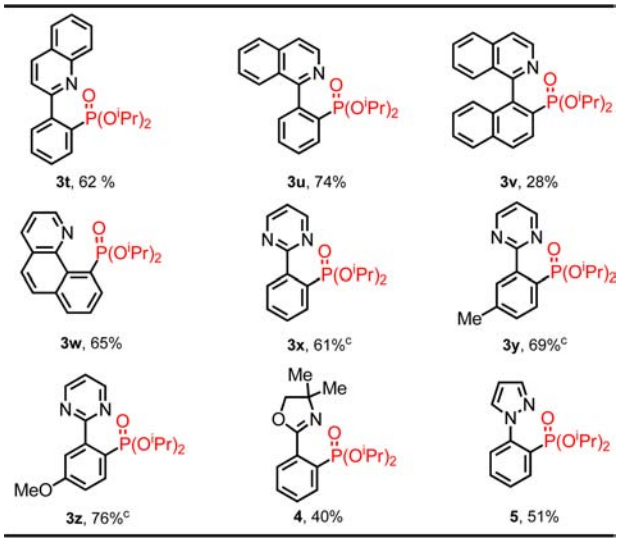
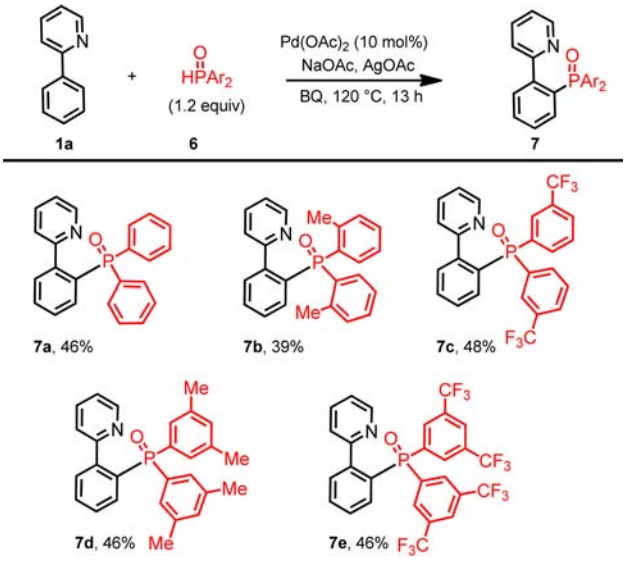
Table 4. C−H Phosphorylation with Diverse Heterocycles[a,b,c]



[a]Same reaction condition as Table 3 unless otherwise noted. [b]Isolated yields. [c]Ag_3PO_4 (0.2 mmol) was used as oxidant instead of AgOAc.

Table 5. Coupling With Several Diarylphosphine Oxides[a,b]

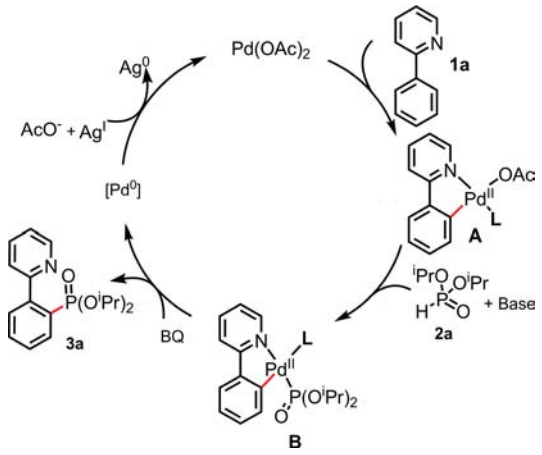


[a]Same reaction conditions as Table 3. [b]Isolated yields.

obtained in 67% yield (**3h**). However, Cl on the *meta*-position (**3i**), and strongly electron-withdrawing F (**3j**), CF_3 (**3k**), CN (**3l**), and CO_2Me (**3n**) groups at the *para* position decreased the yields to 58%, 45%, 42%, 15%, and 58%, respectively. The reaction of 2-naphthalene also proceeded smoothly and gave highly selective *β*- phosphorylation product in 79% yield (**3o**). Moderate to good yields (66−79%) were obtained when the pyridine rings were substituted by methyl or MeO groups at various positions (**3p**−**3s**).

To expand the utility of this methodology, several other nitrogen-based heterocycle scaffolds were examined (Table 4). Both quinoline- and isoquinoline-directed phosphorylation of **1t** and **1u** occurred to give the corresponding products **3t** and **3u** in 62% and 74% yields, respectively. Phosphorylation of isoquinoline **1v** gave the desired product **3v** in only 28% yield due to steric hindrance. We were delighted that 7,8-benzoquinoline was phosphorylated in 65% yield to give a potentially useful ligand scaffold **3w**. Phosphorylation of 2-phenylpyrimidines gave corresponding products in 61−76% yields (**3x**−**3z**). We also attempted to use this reaction to prepare the PHOX type ligands,[3a] but only in 40% yield (**4**). Pyrrazole substrate was also phosphonated to give **5** in 51% yield.

Scheme 1. Proposed Reaction Mechanism



Reactions of these phophonates with ArMgX readily afford triarylphosphine oxides which can be reduced to give triarylphophine ligands.[3h,i] Alternatively, we also demonstrated the feasibility of preparing diarylphosphine oxide precursors directly by coupling C−H bonds with various diaryl phosphine oxides (Table 5), albeit giving moderate yields under current conditions.

In light of the previous observation that Ag(I)-mediated phosphorylation of indoles with H-phosphonates proceeds via a radical pathway,[15d] we performed a control experiment in the absence of Pd catalyst (eq 5). We found that this reaction did not proceed without the palladium catalyst. Since the palladocycles **I** and **II** were shown to react with H-phosphonate **2a** to give the phosphorylation products (eq 1), we believe that our reaction proceeds through directed palladation and subsequent coupling with phosphate coupling partners.[20] C−H activation of 2-phenylpyridine **1a** generates cyclopalladate species **A**, which undergoes anionic ligand exchange with H-phosphonate **2a** to provide complex **B**.[20] The reductive elimination of complex **B** facilitated by BQ affords the desired phosphorylation product. The Ag(I) oxidant reoxidizes Pd(0) to Pd(II) to close the catalytic cycle (Scheme 1). In terms of redox chemistry, this reaction differs from the Takai's intramolecular reaction in which Pd(0) inserts into the P−H bonds to form the P−Pd−H species that cleaves C−H bonds.[14]

In summary, a Pd(II)-catalyzed intermolecular C−H activation/phosphorylation reaction has been developed for the first time. A variety of heterocyclic substrates were phosphorylated to give N−P bisdentate compounds that are potentially useful in medicinal chemistry and catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes
The authors declare no competing financial interest.

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