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Palladium-Catalyzed Phosphorylation of Aryl Mesylates and Tosylates

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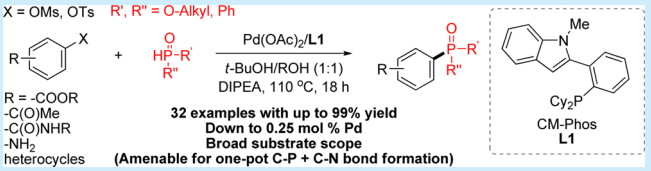
Supporting Information

ABSTRACT: The first general palladium catalyst for the phosphorylation of aryl mesylates and tosylates is reported. The newly developed system exhibits excellent functional group compatibility. For instance, free amino, keto, ester, and amido groups, as well as heterocycles, remain intact during the course of reaction. The mesylated derivatives of biologically active compounds such as 17β-estradiol and 6-hydroxyflavone are also shown to be applicable substrates. A one-pot phosphorylation−amination sequence is described for the facile synthesis of potential pharmacophores.



Organophosphorus compounds such as aryl phosphonates constitute an important class of compound due to their versatile applications in medicinal chemistry,[1] organic synthesis,[2] and material chemistry[3] (Figure 1). Apart from the conventional Grignard or organolithium protocols, the most straightforward method to prepare such compounds is the Pd-catalyzed C−P bond formation pathway between a $R_2P(O)H$ compound and a coupling partner.[4] The pioneering work of Hirao in 1981 has prompted the scientific community's interest in extending the scope of the process.[5] The use of aryl halides,[6] boronic acids,[7] triflates,[8] hydrazines,[9] and triarylbismuths[10] in the Pd-catalyzed C−P bond formation has been well documented. A number of copper[11] and nickel[12] catalysts were also shown to promote the C−P bond-forming reactions.

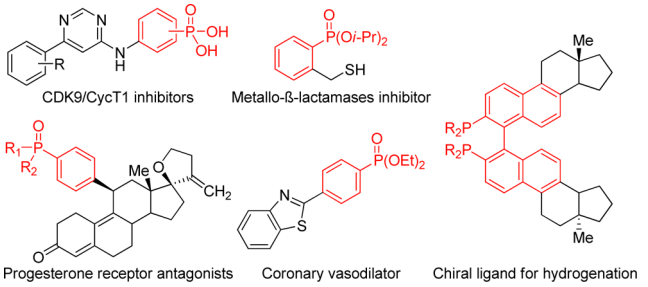


Figure 1. Examples of organophosphorus compounds and their potential applications.

Despite the availability of aryl halides, some unique arenes exist only in phenolic form. In fact, the regioselective halogenation for accessing these particular arene patterns may not be straightforward. For example, biologically active compounds such as estrogenic hormones contain a phenolic moiety, but not the halogenated analog. Although triflating agents could offer a route for transforming phenolic compounds to electrophiles, their high cost and the low hydrolytic stability of aryl triflates have generated application concerns. Indeed, the use of aryl mesylates and tosylates are much more desirable due to their cost-effectiveness[13] and high stability,[14] as well as the environmental friendliness which can be realized by the natural biodegradation of methanesulfonic acid byproducts.[15] However, the chemical inertness of these electrophilic partners makes them prone to the oxidative addition of a Pd(0) species, resulting in lost activity in catalysis. Therefore, the identification of a suitable catalyst to facilitate the aryl mesylate C−P couplings has been proven to be a persistent challenge. Although a nickel catalyst has been reported to use aryl mesylates in the C−P bond forming process,[16] the scope was found not to be general and only moderate product yields were shown. Thus, there is a demand to develop a system for achieving general and versatile C−P bond couplings. Herein, we report the first general Pd catalyst for the phosphorylation of aryl mesylates and tosylates. This new system is applicable to a wide range of functional groups with modest catalyst loadings.

In our initial investigation, nonactivated 4-*tert*-butylphenyl tosylate and diisopropyl phosphite were selected as the benchmarking substrates (Scheme 1). A series of remarkable ancillary ligands were then evaluated for their efficacy in this C−P bond coupling reaction (Scheme 1). CM-Phos (**L1**)[17] was found to be the best candidate while Mor-DalPhos[18] (**L2**) and XPhos[19] (**L3**) were also suitable ligands albeit with lower yields.

Other state-of-the-art ligand skeletons, including monodentate (**L4**−**L6**, **L11**)[20] and bidentate phosphines[21] (**L7**−**L10**) as well as a N-heterocyclic carbene[22] (**L12**), were also examined. Nevertheless, they were not effective in promoting the catalysis, presumably due to the demanding oxidative

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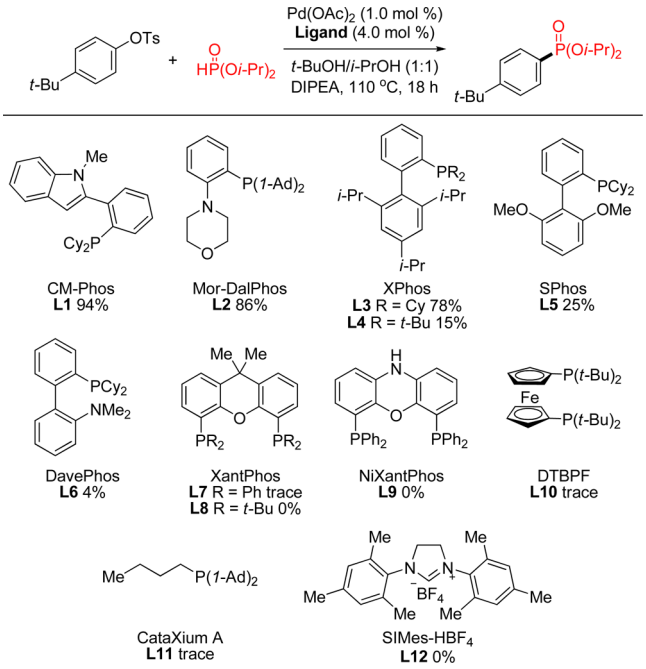
Scheme 1. Evaluation of Ligand Efficacy[a]



[a]Reaction conditions: 4-*tert*-Butylphenyl tosylate (0.3 mmol), DIPEA (0.9 mmol), diisopropyl phosphite (0.45 mmol), *t*-BuOH/*i*-PrOH (1:1, 1.0 mL, 0.3 M), $Pd(OAc)_2$ (1.0 mol %), **Ligand** (4.0 mol %) under nitrogen at 110 °C for 18 h under N_2; calibrated GC yields were reported.

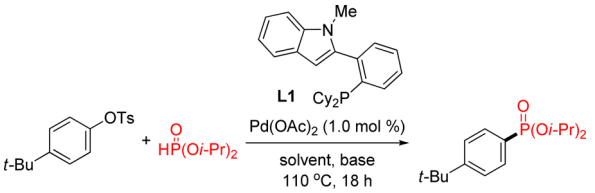
addition of aryl tosylates as suggested by the unreacted remaining starting materials.

Having identified the effective ligand, we next surveyed the reaction conditions for this catalysis (Table 1). *i*-Pr_2NEt (DIPEA) was found to be the best base, whereas inorganic bases such as K_3PO_4 and carbonated bases were inferior (Table 1, entries 1−7). Regarding the solvent screening, *i*-PrOH gave a better result than *t*-BuOH and other solvents (Table 1, entries 8−11). Further solvent investigation showed that *i*-PrOH/*t*-BuOH (1:1) mixtures provided a better product yield (78%) at a concentration of 0.3 M (Table 1, entries 12−14). The best metal-to-ligand ratio was found to be 1:4 (Table 1, entry 15 vs 13). Increasing the amount of diisopropyl phosphite and DIPEA gave a slightly better yield (Table 1, entry 16 vs 15).

Encouraged by the promising Pd/CM-Phos system, we then turned our attention toward exploring the substrate scope. We first examined a spectrum of aryl tosylates (Scheme 2). The reaction proceeded smoothly with a broad range of substituted aryl tosylates, and mostly 0.5−1.0 mol % of catalyst enabled catalyzing the coupling with complete substrate conversion. Electronically neutral (Scheme 2, **1a**−**1d**), rich (Scheme 2, **1e**−**1g**), and deficient (Scheme 2, **1h**) arenes were well-tolerated. A wide range of heterocycles such as pyridine, thiazole, isoquinolone, thiophene, and pyrrole furnished the desired products in good-to-excellent yields (Scheme 2, **1i**−**1n**). It is worthy to note that particular functional groups including ketone (Scheme 2, **1h**), NH-amide (Scheme 2, **1o**), and an unprotected amino group (Scheme 2, **1p**) was compatible in the system. Dual phosphorylation was also achieved by employing twofold phosphites and DIPEA to give **1q** in 98% yield.

In addition to aryl tosylate, the newly developed catalyst system was capable of facilitating the C−P bond formation of

Table 1. Selected Entries of Reaction Optimization[a]



entry	base	solvent	% yield
1	K_3PO_4	*t*-BuOH (0.2 M)	10
2	K_2HPO_4	*t*-BuOH (0.2 M)	34
3	Na_3PO_4	*t*-BuOH (0.2 M)	37
4	K_2CO_3	*t*-BuOH (0.2 M)	15
5	DABCO	*t*-BuOH (0.2 M)	21
6	NEt_3	*t*-BuOH (0.2 M)	49
7	DIPEA	*t*-BuOH (0.2 M)	52
8	DIPEA	DMF (0.2 M)	trace
9	DIPEA	dioxane (0.2 M)	trace
10	DIPEA	toluene (0.2 M)	trace
11	DIPEA	*i*-PrOH (0.2 M)	63
12	DIPEA	*t*-BuOH/*i*-PrOH (1:1; 0.2 M)	68
13	DIPEA	*t*-BuOH/*i*-PrOH (1:1; 0.3 M)	78
14	DIPEA	*t*-BuOH/*i*-PrOH (1:1; 0.5 M)	71
15	DIPEA	*t*-BuOH/*i*-PrOH (1:1; 0.3 M)	88[b]
16	DIPEA	*t*-BuOH/*i*-PrOH (1:1; 0.3 M)	94[c]

[a]Reaction conditions: 4-*tert*-Butylphenyl tosylate (0.3 mmol), base (0.6 mmol), diisopropyl phosphite (0.36 mmol), solvent, $Pd(OAc)_2$/**L1** = 1:3 under nitrogen at 110 °C for 18 h under N_2; calibrated GC-FID yields were reported. [b]$Pd(OAc)_2$/**L1** = 1:4. [c]$Pd(OAc)_2$/**L1** = 1:4, DIPEA (0.9 mmol), diisopropyl phosphite (0.45 mmol).

aryl mesylates (Scheme 3). Functionalized aryl mesylates containing an ester (Scheme 3, **2e**), an enolizable ketone (Scheme 3, **2d**), a free amine (Scheme 3, **2h**), heterocycles (Scheme 3, **2i**−**2l**), and an *ortho*-substituted arene (Scheme 3, **2d**) were phorsphorylated successfully with good-to-excellent yields. Apart from the *H*-phosphinates, the less electron-deficient ethyl phenylphosphinate was an applicable phosphorus coupling partner as demonstrated by the examples **2l** and **2m**. Organophosphorus compounds have been documented as important functionalities found in many pharmacophores. It would be versatile if our system could directly phosphorylate natural products or biogically active compounds. The mesylated 17β-estradiol and 6-hydroxyflavone were subjected to the reaction. Under the standard conditions, the corresponding products were afforded in moderate (Scheme 3, **2n**) and excellent yields (Scheme 3, **2o**). It is worthy to show that the aliphatic meslyate group in **2n** remained intact during the course of the reaction and can be further functionalized after deprotection strategies. In fact, **2n** can only be prepared from the phenolic derivatives of 17β-estradiol while no corresponding aryl halides were available. The structure of **2n** could also be derived to a bis-steroidal phosphine ligand,[23] which possesses chirality owning to its distinctive carbon framework, with reported synthetic routes.[24]

To realize the capability of the proposed system in the direct synthesis of biologically active compounds, we have designed a one-pot sequential reaction including both C−P and C−N bond formations (Scheme 4). After the first phosphorylation of 3-aminophenyl tosylate, the second electrophile and K_2CO_3 were directly added to the reaction mixture under nitrogen without any additional catalyst or solvent. The mixtures were subjected for an additional 24 h, and **3a** was obtained in

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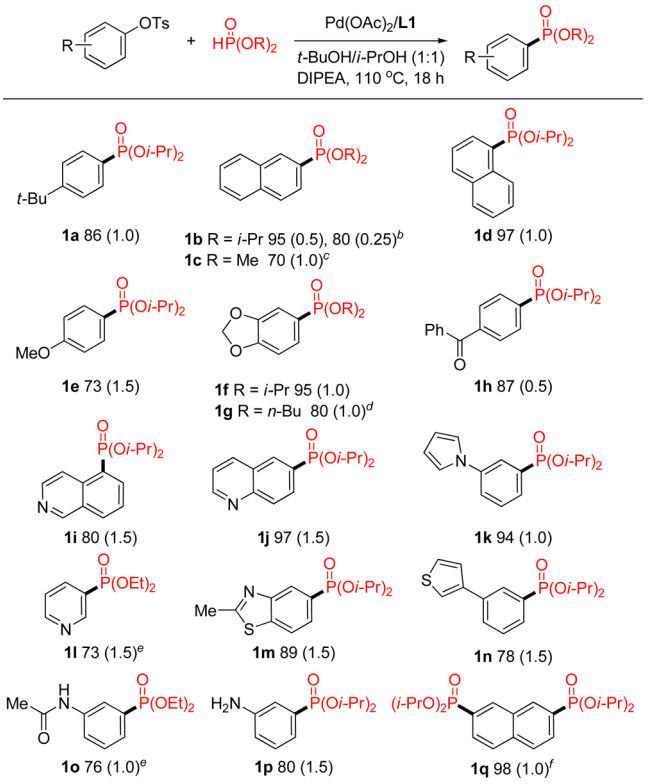
Scheme 2. Pd-Catalyzed Phosphorylation of Aryl Tosylates[a]

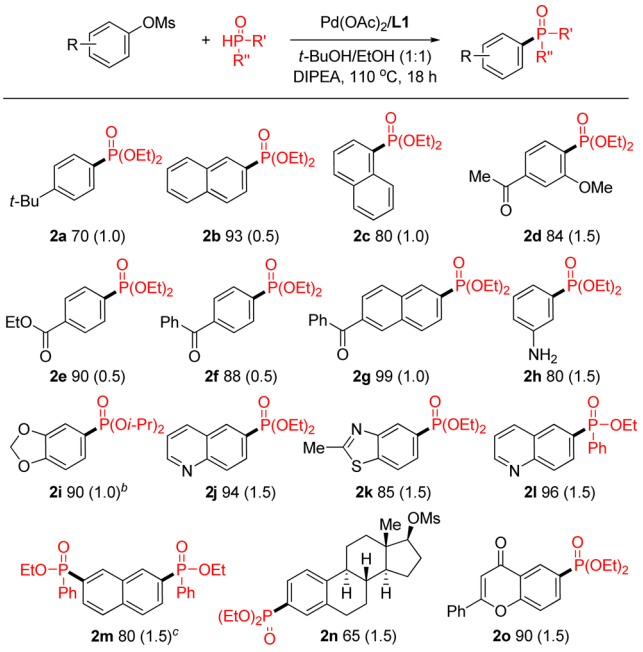


[a]Reaction conditions: ArOTs (0.3 mmol), DIPEA (0.9 mmol), dialkyl phosphite (0.45 mmol), *t*-BuOH/*i*-PrOH (1:1, 1.0 mL, 0.3 M), $Pd(OAc)_2$/**L1** = 1:4 under nitrogen at 110 °C for 18 h under N_2; isolated yields were reported. Catalyst loading was reported in parentheses as mol % of Pd with respect to ArOTs. Reaction times were not optimized for each substrate. [b]Reaction time = 36 h. [c]*t*-BuOH was used as solvent. [d]*t*-BuOH/*n*-BuOH (1:1) was used as solvent. [e]*t*-BuOH/EtOH (1:1) was used as solvent. [f]DIPEA (1.8 mmol), diisoproyl phosphite (0.9 mmol).

moderate yield. Particularly noteworthy is that the 3-(heteroarylamino)phenylphosphonate is a key functionality of the potential CDK9/CycT1 inhibitors.[25]

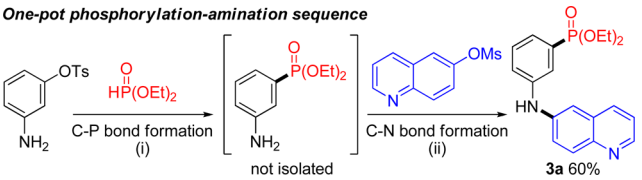
In summary, the transformation of naturally abundant phenolic derivatives to their corresponding phosphorus-containing compounds via an electrophilic pathway has been a challenge. Here, we show the first general palladium catalyst for the phosphorylation of aryl mesylates and tosylates with *H*-phosphonates and *H*-phosphinate esters. The chemoselectivity of the Pd/**L1** system was demonstrated by a wide spectrum of compatible functional groups including an enolizable ketone, ester, amide, unprotected amine, and heterocycles. Phenolic derivatives from biologically active compounds also underwent the reaction smoothly. The one-pot two-step phosphorylation−amination sequence provides a facile and direct synthesis of attractive phosphorus-containing pharmcophores. Due to the attractiveness of the aryl mesylates/tosylates and the above-mentioned amenability, we believe this new Pd catalyst will provide efficient access to a variety of synthetically useful and pharmaceutically attractive organophosphorus compounds. Future efforts will focus on the synthesis of novel phosphine ligands using the proposed system.

Scheme 3. Pd-Catalyzed Phosphorylation of Aryl Mesylates[a]



[a]Reaction conditions: ArOMs (0.3 mmol), DIPEA (0.9 mmol), *H*-phosphonate or *H*-phosphinate ester (0.45 mmol), *t*-BuOH/EtOH (1:1, 1.0 mL, 0.3 M), $Pd(OAc)_2$/**L1** = 1:4 under nitrogen at 110 °C for 18 h under N_2, isolated yields were reported. Catalyst loading was reported in parentheses as mol % of Pd with respect to ArOMs. Reaction times were not optimized for each substrate. [b]*t*-BuOH/*i*-PrOH was used as solvent. [c]DIPEA (1.8 mmol), ethyl phenylphosphinate (0.9 mmol).

Scheme 4. One-Pot Sequential Integration of Aryl Phosphonate[a]



[a]Reaction conditions: (i) 3-Aminophenyl tosylate (0.3 mmol), DIPEA (0.9 mmol), diethyl phosphite (0.45 mmol), *t*-BuOH/EtOH (1:1, 1.0 mL, 0.3 M), $Pd(OAc)_2$ (2 mol %), **L1** (8 mol %) under nitrogen at 110 °C for 18 h under N_2. (ii) 6-Quinolinyl mesylate (0.45 mmol), K_2CO_3 (0.75 mmol) were added under N_2, and the reaction mixtures were stirred at 110 °C for an additional 24 h.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03104.

Detailed experimental procedures; ^1H, ^{13}C, ^{31}P NMR spectra; and characterization data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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