Pd(II)-Catalyzed Phosphorylation of Enamido C(sp^2)–H Bonds: A General Route to β-Amido-Vinylphosphonates

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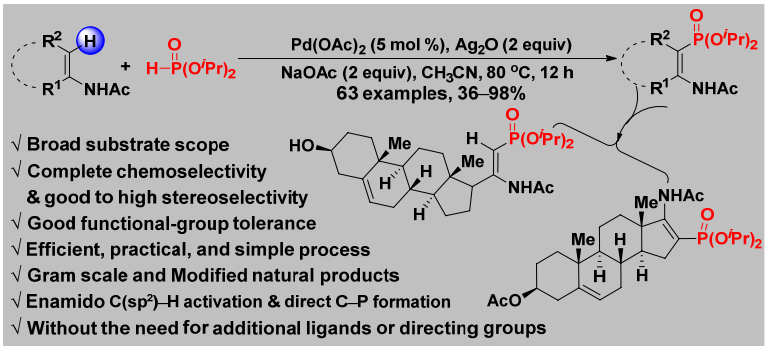
ABSTRACT Organophosphorus compounds are essential structures in modern pharmaceutical, agrochemical, and material sciences. The development of new and efficient methods for the synthesis of C–P bonds has been an important focus of research. We herein report a Pd-catalyzed enamido C(sp^2)–H phosphorylation for direct construction of C–P bonds under simple and convenient conditions without the need for additional ligands or directing groups. The present reaction can tolerate a wide range of functional groups, and furnish a variety of phosphorylation products including tetrasubstituted-vinyl β-aminophosphonates that are otherwise difficult to access. This protocol was also exemplified into the late-stage modification of bioactive natural products and was suitable for large-scale synthesis.



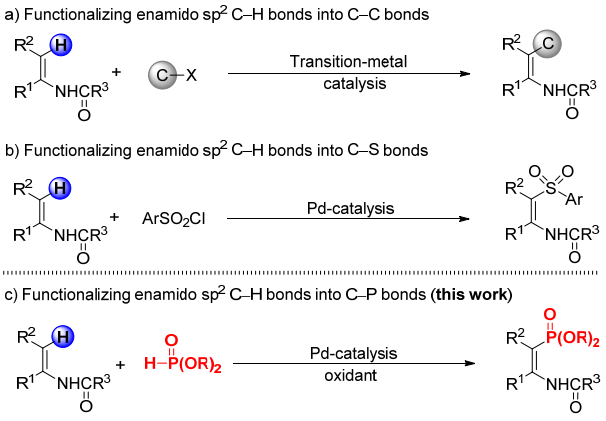
KEYWORDS C-H activation, phosphorylation, palladium catalysis, enamines, late-stage functionalization

Introduction

Organophosphorous compounds have wide applications in organic synthesis, agricultural chemistry, biomedicinal science, and material industries.[1] As a result of their immense usefulness, the construction of C–P bonds has captured the attention of synthetic chemists over the past decades.[2] In this context, the conventional methods involving Michaelis-Arbuzov rearrangement, Hirao cross-coupling, and hydrophosphinylation reactions have been well established for making C–P bonds.[3] Furthermore, many transformations have been successfully applied to the synthesis of agrochemicals and compounds of pharmaceutical significance. Despite these notable advances, the development of new reactions for the construction of C–P compounds is still highly desirable. Direct functionalization of C–H bonds has emerged as an efficient and promising strategy for rapid generation of valuable products from simple starting materials.[4] Recently, several research groups have paid attention to metal-catalyzed phosphorylation of aryl C(sp^2)–H bonds as a late-stage functionalization method for preparing aryl phosphonates.[5] In sharp contrast, direct metal-catalyzed alkenyl C(sp^2)–H activation and phosphorylation remains largely unexplored. Only one example by Murakami and co-workers has addressed the Pd-catalyzed alkenyl C(sp^2)–H phosphorylation by the use of a pyridyl group as the directing group.[5c] This creates the interesting challenge of developing new transition-metal-catalyzed phosphorylation processes to make alkenyl C(sp^2)–P bonds.

In recent years, enamides have been the subject of elegant metal-catalyzed C–H bond functionalization reactions because they allow the direct modification of given substrates without the installation of an additional coordinating functional group (directing group).[6] The transformation of enamido C(sp^2)–H bonds into carbon–carbon bonds has been widely studied by using various C-coupling partners, including arylating, vinylating, alkylating, and acylating reagents (Scheme 1a).[7a–s] In sharp contrast, little progress has been made in the development of carbon–heteroatom bond forming reactions via metal-catalyzed enamido C(sp^2)–H activation, and only one report by Loh and co-workers has described a palladium-catalyzed sulfonylation of enamides for the generation of carbon–sulfur bonds (Scheme 1b).[7t] We surmised that transition-metal catalyzed C–H activation / C–P coupling reactions using enamides as substrates could provide a direct and general method for the preparation of β-amido-vinylphosphonates (β-AVPs).[8] Commonly used methods for the synthesis of β-AVPs include the addition of α-methyl phosphonate carbanions to nitriles,[9] the hydroamination of alkynyl-phosphonates,[10] the hydrophosphonylation of ynamides,[11] and some addition-elimination transformations.[12] However, harsh reaction conditions, limited functional group tolerance, and narrow substrate scopes have restricted these strategies. Therefore, the cross-coupling of enamido C(sp^2)–H bonds with P(O)–H reagents[13] is an unanswered challenge and

Scheme 1. Transition-metal Catalyzed Enamido C(sp^2)–H Functionalization



yet a significant goal from the viewpoint of synthetic applications. Herein, we report such a facile access to β-amido-vinylphosphonates with high chemo- and

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stereoselectivity via palladium-catalyzed phosphorylation of enamido C(sp^2)–H bonds (Scheme 1c). This cross-coupling reaction can be conducted under mild conditions without the need for additional ligands or directing groups. Furthermore, the generality of this newly observed C(sp^2)–H bond functionalization was further demonstrated by phosphorylating α,β-disubstituted and cyclic enamides to provide a wide range of tetrasubstituted-vinyl β-aminophosphonate derivatives that are otherwise difficult to access.

Results and Discussion

Initial Studies and Reaction Optimization Results.

To assess the feasibility of the outlined enamido C(sp^2)–H phosphorylation, we commenced our investigation with the coupling of phenyl enamide **1a** and diisopropyl phosphonate **2a** by using $Pd(OAc)_2$ as a catalyst. After extensive screening of various oxidants [such as $Cu(OAc)_2$, $Mn(OAc)_3$, AgOAc, and $K_2S_2O_8$. See the Supporting Information (SI)], it was found that only AgOAc could deliver the desired phosphorylation product **3a** in 20% yield with high regioselectivity (*Z*/*E*: 7/1). On the basis of this reactivity, we then proceeded to develop catalytic conditions for this transformation (Table 1). Several other silver salts were further examined (entries 1–4), and Ag_2O was found to be the best choice, improving the yield to 66% (entry 4). Exploration of solvents revealed that besides acetonitrile, DMF (*N*, *N*-dimethyl-formamide) also promoted this transformation, whereas the use of chloroform, toluene, *tert*-amylalcohol, DME (dimethoxyethane), or DMSO (dimethyl sulfoxide) led to a significantly lower yield (entries 5–10). The yield of (*Z*)-**3a** was further improved to 88% when the reaction temperature was increased from 60 to 80 °C (entry 11). In addition, a small amount of (*E*)-**3a** could also be isolated in 8% yield. Several bases and palladium species were also examined, but the transformation works well only in the presence of NaOAc as base and $Pd(OAc)_2$ as a catalyst (entries 12–17 *vs* 11). It should be noted that this reaction is also excellently chemoselective, and *N*-phosphorylation side-product was not observed under these reaction conditions.

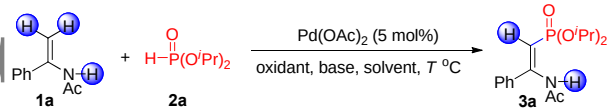


Table 1 Optimization of Catalytic Conditions[a]

entry	Pd catalyst	oxidant	base	*T* (°C)	solvent	yield (%)[b]
1	$Pd(OAc)_2$	AgOAc	NaOAc	60	CH_3CN	20
2	$Pd(OAc)_2$	$AgNO_3$	NaOAc	60	CH_3CN	28
3	$Pd(OAc)_2$	Ag_2CO_3	NaOAc	60	CH_3CN	15
4	$Pd(OAc)_2$	Ag_2O	NaOAc	60	CH_3CN	66
5	$Pd(OAc)_2$	Ag_2O	NaOAc	60	$CHCl_3$	15
6	$Pd(OAc)_2$	Ag_2O	NaOAc	60	toluene	14
7	$Pd(OAc)_2$	Ag_2O	NaOAc	60	*tert*-AmylOH	15
8	$Pd(OAc)_2$	Ag_2O	NaOAc	60	DME	22
9	$Pd(OAc)_2$	Ag_2O	NaOAc	60	DMSO	27
10	$Pd(OAc)_2$	Ag_2O	NaOAc	60	DMF	65
11	$Pd(OAc)_2$	Ag_2O	NaOAc	80	CH_3CN	88
12	$Pd(OAc)_2$	Ag_2O	KOAc	80	CH_3CN	73
13	$Pd(OAc)_2$	Ag_2O	$NaBF_4$	80	CH_3CN	83
14	$Pd(OAc)_2$	Ag_2O	Na_2CO_3	80	CH_3CN	72
15	$PdCl_2$	Ag_2O	NaOAc	80	CH_3CN	22
16	$Pd(TFA)_2$	Ag_2O	NaOAc	80	CH_3CN	68
17	$[Pd(PPh_3)_2Cl_2]$	Ag_2O	NaOAc	80	CH_3CN	31

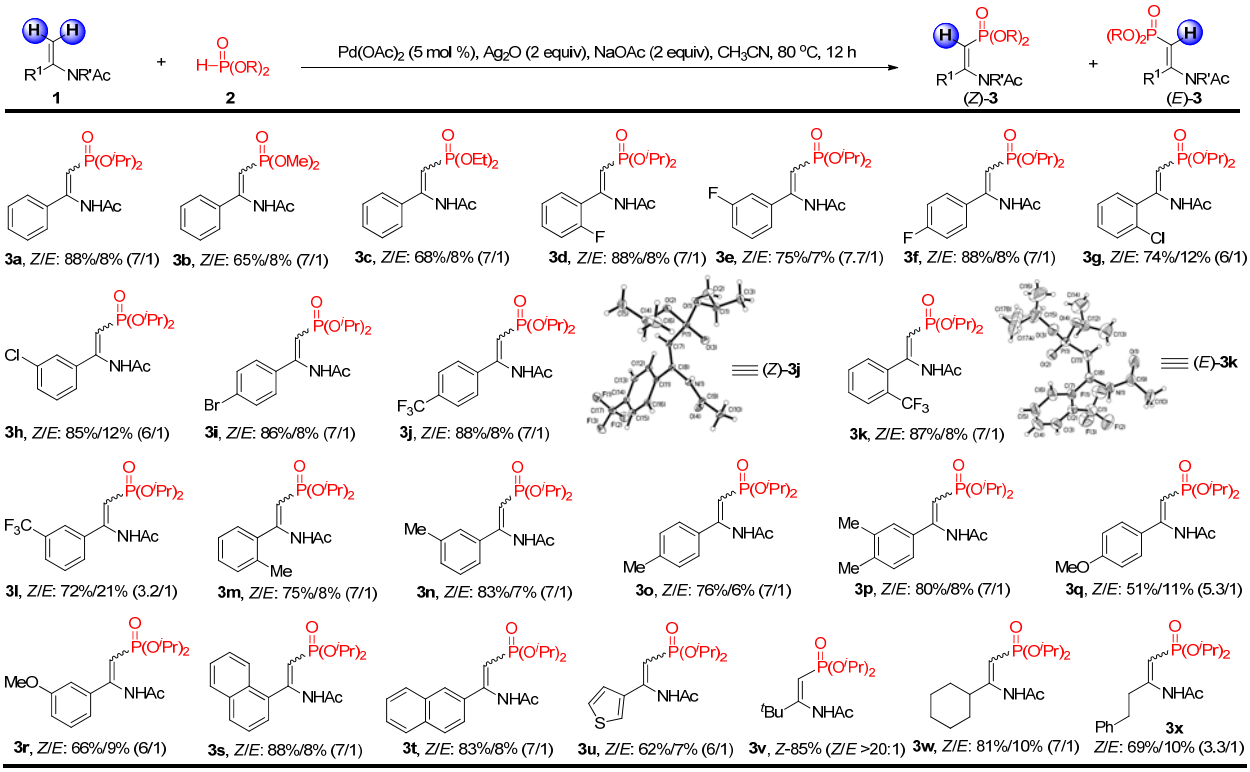
[a] Reaction conditions: Enamide **1a** (97 mg, 0.6 mmol), diisopropyl phosphonate **2a** (50.0 μL, 0.3 mmol), palladium salt (5 mol%), oxidant (0.6 mmol), and base (0.6 mmol) in solvent (4 mL) under the stated temperature for 12 h. Although excess enamide is required for good mono-phosphorylation, the unreacted equivalents could be recovered. [b] Yield shown is the average of two runs based on the phosphonate substrate. The ratio of stereoisomers (*Z*/*E*) was determined by ^{31}P NMR analysis of the crude reaction mixture.

Substrate scope for palladium-catalyzed direct phosphorylation of enamides with H-phosphonates.

With these interesting results in hand, we examined the scope of this catalytic phosphorylation using a broad array of enamides and P(O)–H hydrogen phosphoryl compounds under the optimal reaction conditions (Scheme 2). In most cases, both *Z*- and *E*-isomers of the desired β-amido-vinylphosphonates could be easily separated through flash column chromatography (FCC). This Pd-catalyzed direct phosphorylation also took place efficiently with dimethyl and diethyl phosphonates under our standard reaction conditions to afford the corresponding products **3b** and **3c** in high yields. In the case of aryl enamides, the phosphorylation reaction tolerates various substitution patterns and a range of different substituents on the aryl ring. Alkyl, alkoxy-, halo-, and trifluoromethyl-substituted phenyl enamides all undergo the desired reaction to give the phosphorylated products **3d–r** in 62–97% yields with good to high stereoselectivities. Furthermore, the major isomer of **3j** and the minor isomer of **3k** proved to be suitable crystallines, thus allowing the determination of the stereochemistry of C=C double bond to be (*Z*)-**3j** and (*E*)-**3k** by means of X-ray crystallographic analysis (see the SI). 1-Naphthyl-, 2-naphthyl-, and 3-thiophenyl-substituted enamides were also found to be good substrates, delivering the desired β-amido-vinylphosphonates **3s–u** in 69–96% yields with good stereoselectivities. In addition, several alkyl-substituted enamides were also prepared and subjected to this cross-coupling process under the same conditions. For example, *tert*-butyl-substituted enamide underwent a clean conversion and the corresponding β-amido-vinylphosphonate **3v** was obtained in 85% yield with excellent stereoselectivity. Cyclohexyl- and phenethyl-substituted enamides furnished *Z*- and *E*-isomers of the phosphorylated products **3w** and **3x** in total yields of 91% and 79%, respectively.

Encouraged by these results, we moved to examine the phosphorylation of α,β-disubstituted enamides. As shown in Scheme 3, when α,β-disubstituted (*E*)-enamide **4a** was employed under the current reaction conditions, not surprisingly, the phosphorylation of enamido C(sp^2)–H bond was observed to produce the expected (*Z*)-amido-vinylphosphonate **5a** in 59% yield (Scheme 3a). In contrast, when α,β-disubstituted (*Z*)-enamide **4a** was exposed to the optimized conditions, (*Z*)-**5a** was obtained in very low yield (Scheme 3b). Subsequently, a series of α,β-disubstituted enamides were investigated and the results are listed in Scheme 4. Three (*E*)-enamides **4b–d** bearing α-phenyl and β-alkyl substituents were readily transformed into the corresponding (*Z*)-amido-vinyl-phosphonates **5b–d** in 57–64% yields. The (*Z*/*E*)-mixtures of dialkyl-substituted enamides **4e–g** were also subjected to this Pd-catalyzed phosphorylation process

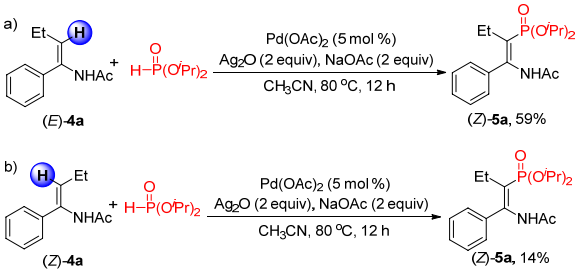
Scheme 2 Pd-Catalyzed Direct Phosphorylation of Enamides [a-c]



[a] Reaction conditions: Enamide **1** (0.6 mmol), phosphonate 2 (0.3 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol%), Ag_2O (137.2 mg, 0.6 mmol), and NaOAc (49.2 mg, 0.6 mmol) in CH_3CN (4 mL) under the stated temperature for 12 h. [b] Isolated yields based on the phosphonate substrates. [c] The values in parentheses were determined by ^{31}P NMR analysis of the crude mixtures.

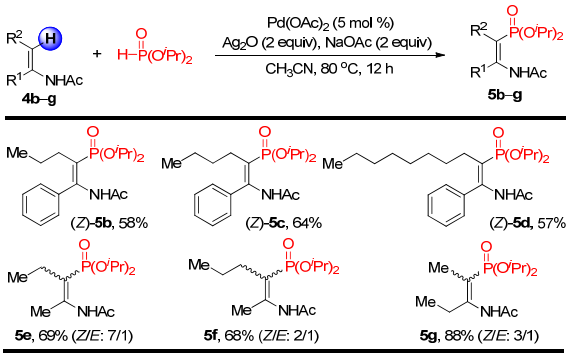
to afford the desired products **5e–g** in good yields with moderate to good stereoselectivities.

Scheme 3 Pd-Catalyzed Phosphorylation of α,β-disubstituted (*E*) and (*Z*)-Enamides **4a**



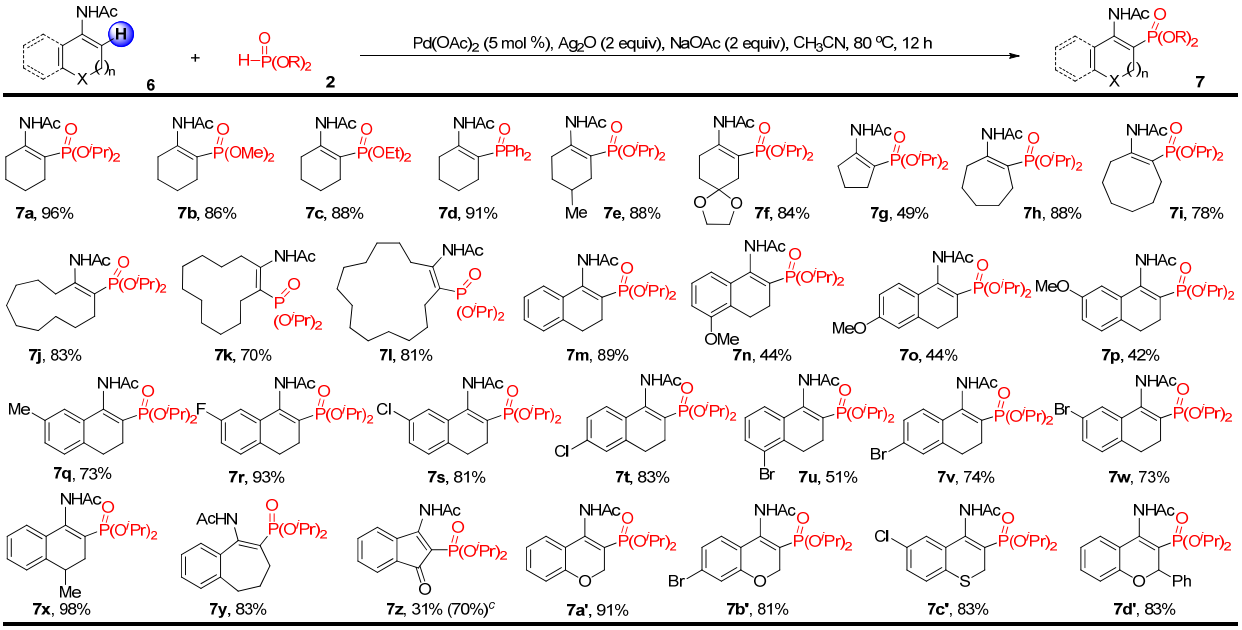
Further extension of our protocol to various cyclic enamides **6** was also generally successful, and the results are summarized in Scheme 5. We found that cyclohexanone-derived enamides readily participated in this Pd-catalyzed phosphorylation to deliver the corresponding β-amido-vinylphosphonates **7a–f** in high yields. The phosphorylation of cyclopentanone-derived enamide gave the desired product **7g** in relatively lower yield. Cycloheptanone- and cyclooctanone-derivated enamides also furnished the corresponding products **7h** and **7i** in 88% and 78% yields, respectively. Several large-ring *E*-enamides were also viable substrates, affording β-amido-vinylphosphonates **7j–l** in good yields. Subsequently, a series of cyclic enamides derived from 1-tetralones were tested. It appeared that electron-neutral, -donating, and -withdrawing substituents on the phenyl ring can be tolerated, and moderate to high yields were observed for the products **7m–x**. 1-Benzosuberone-derived cyclic enamide was also compatible with the current reaction conditions to give the functionalized product **7y** in 83% yield. 1-Indanone-derived enamide was simultaneously oxidized and

Scheme 4 Pd-Catalyzed Phosphorylation of α,β-disubstituted Enamides **4b–g** [a]



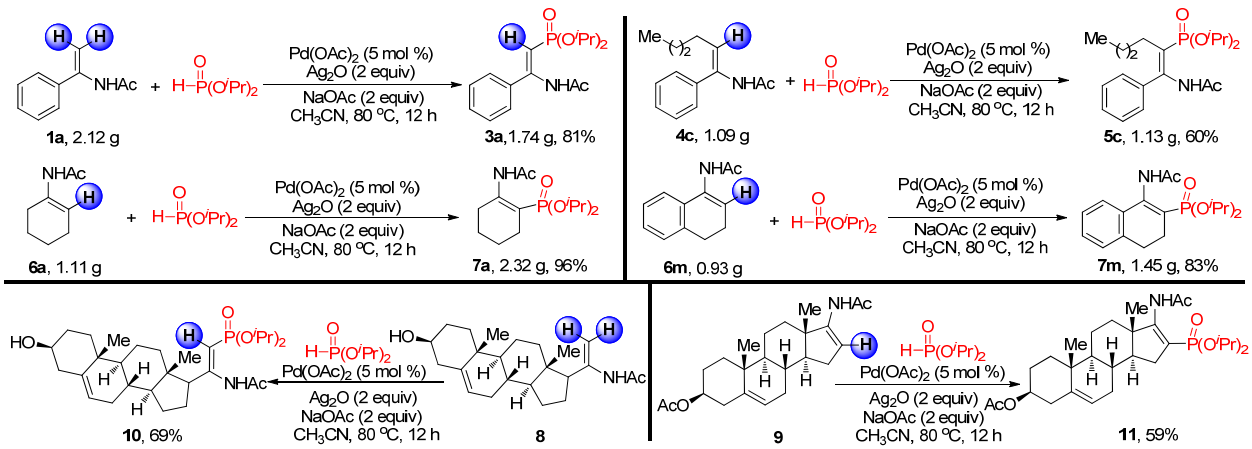
[a] Reaction conditions: Enamide **4** (0.3 mmol), diisopropyl phosphonate **2** (50.0 μL, 0.3 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol%), Ag_2O (137.2 mg, 0.6 mmol), and NaOAc (49.2 mg, 0.6 mmol) in CH_3CN (4 mL) under the stated temperature for 12 h. [b] Isolated yields based on the enamide substrates. [c] (*Z*/*E*)-isomers of **5e–g** could not be isolated by the FCC, and the values in parentheses were determined by ^{31}P NMR analysis of the isolated products.

Scheme 5 Pd-Catalyzed Direct Phosphorylation of Cyclic Enamides **6** [a, b]



[a] Reaction conditions: Enamide **6** (0.3 mmol), phosphonate **2** (0.3 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol%), Ag_2O (137.2 mg, 0.6 mmol), and NaOAc (49.2 mg, 0.6 mmol) in CH_3CN (4 mL) under the stated temperature for 12 h. [b] Isolated yields based on the enamide substrates. [c] The yield in parenthesis was based on 1,3-indanedione-derived enamide.

Scheme 6 Scaled-up Version of Pd-Catalyzed Phosphorylation, and Synthesis of Prasterone- and Prasterone-based β-Amido-vinylphosphonates



phosphorylated to afford the product **7z** in 31% yield,[14] whereas the phosphorylation of 1,3-indanedione-derived enamide furnished the same product **7z** in good yield. Additionally, four 4-chromanone-based cyclic enamides could also undergo direct phosphorylation to give the corresponding AVPs **7a'–d'** in 81–91% yields.

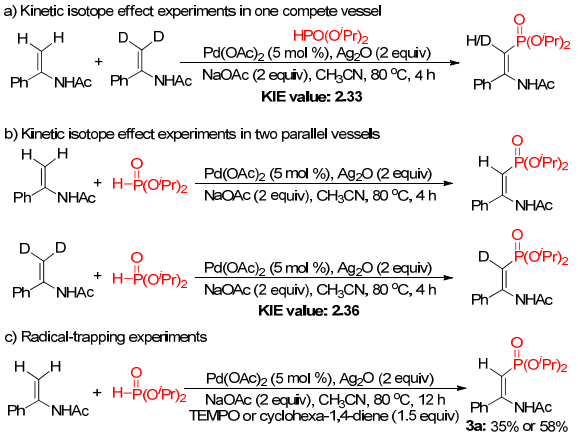
Scaled-up version of Pd-catalyzed phosphorylation and synthetic applicability.

To evaluate this catalytic system on a gram-scale, the phosphorylation of enamides **1a**, **4c**, **6a**, and **6m** with diisopropyl phosphonate **2a** was repeated over one grams and the reaction delivered the desired products **3a**, **5c**, **7a**, and **7m** with results almost identical to that of the model reaction. Although 2.0 equivalents of Ag_2O was used in this phosphorylation reaction, the excess Ag_2O and the resulting silver species could be recovered and recycled conveniently by filtration and treatment with nitric acid and NaOH. The regenerated Ag_2O could still promote this phosphorylation in comparable yield without loss of activity (see the SI). In addition, the applicability of our protocol to the facile modification of complex natural products is a highly desirable feature, as analogues of bioactive molecules could be constructed without the need for de novo synthesis. For example, two enamides **8** and **9** derived from natural pregnenolone and prasterone were subjected to the current phosphorylation process to afford the corresponding products **10** and **11** in 69% and 59% yields, respectively (Scheme 6). These syntheses exemplify the potential utility of the current phosphorylation method for the rapid and efficient construction of important β-amnio-phosphonate targets.[15]

Mechanistic discussion.

To cast some light on the mechanism, the kinetic isotope effect (KIE)[16] and radical-trapping experiments were conducted (Scheme 7). The significant kinetic isotope effect was observed in the reaction of the deuterated and the protonated enamides with diisopropyl phosphonate (Scheme 7a and 7b). These results show that the enamido C(sp^2)–H cleavage could occur during the rate-determining step. In addition, when 1.5 equivalent of TEMPO or cyclohexa-1,4-diene was employed under the normal reaction conditions, the desired product **3a** was obtained in 35% and 58% yields (Scheme 7c). Thus, this phosphorylation transformation might not involve a radical process.

Scheme 7 Kinetic Isotope Effect and Radical-trapping Experiments



Based on the above experimental studies and the previous observations that the Pd-catalyzed vinylation[7g] and acylation[7o] of enamides involve a six-membered palladacycle, the following mechanistic scenario was proposed (Figure 1). Enamido C(sp^2)–H activation forms cyclopalladate species **A**, which undergoes anionic ligand exchange with P(O)–H compounds to give the intermediate **B**. The reductive elimination of the complex **B** yields the phosphorylation products. Then oxidation of Pd(0) with the Ag(I) salt regenerates the Pd(II) catalyst to complete the catalytic cycle.

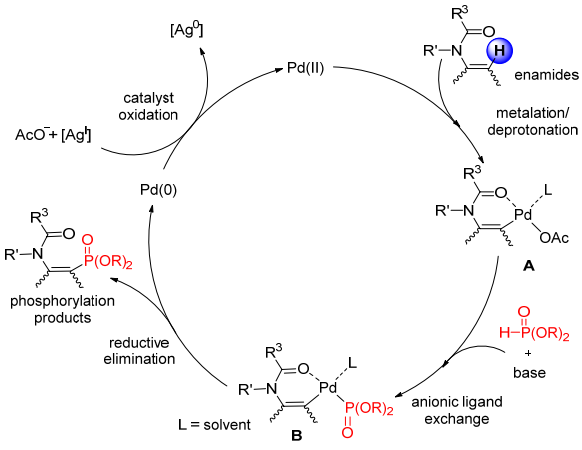


Figure 1 A plausible mechanism for palladium-catalyzed phosphonation of enamides.

Conclusions

In summary, we have successfully developed a Pd-catalyzed direct and efficient phosphorylation of enamido C(sp^2)–H bonds with P(O)–H reagents to access a wide range of β-amido-vinylphosphonates without the need for additional ligands or directing groups. This new cross-coupling reaction displayed high functional-group tolerance and proved to be a quite general methodology. Furthermore, this system was found to be applicable to the late-stage modification of bioactive natural products and was suitable for gram-scale synthesis. The expansion of this strategy to other substrates and further transformation of these compounds prepared here into β-aminophosphonic acids are currently under way and will be reported in due course.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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Title Pd(II)-Catalyzed Phosphorylation of Enamido C(sp^2)–H Bonds: A General Route to β-Amido-Vinylphosphonates

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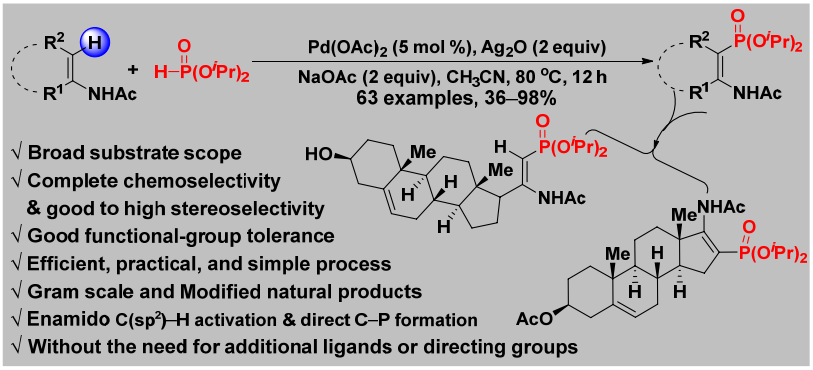

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