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Alkenylation of Phosphacoumarins via Aerobic Oxidative Heck Reactions and Their Synthetic Application to Fluorescent Benzophosphacoumarins

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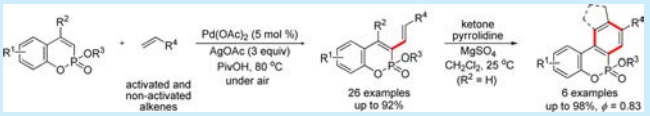
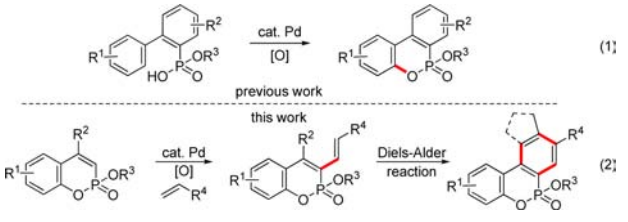
Supporting Information

ABSTRACT: Alkenylation of phosphacoumarins is developed from the reaction of phosphacoumarins with a variety of activated as well as nonactivated alkenes via aerobic oxidative Heck reactions. In addition, 3-alkenylphosphacoumarins undergo an inverse electron demand Diels–Alder reaction (IEDDA) with enamines *in situ* generated from ketone and pyrrolidine followed by 1,2-elimination and a dehydrogenation, producing fluorescent benzophosphacoumarins.



For several decades, organophosphorus compounds have received attention due to applications in diverse fields such as coordination and materials chemistry, homogeneous catalysis, pharmaceuticals, agrochemicals, additives for polymers, and flame retardants.[1] Recently, phosphaheterocyclic compounds have been intensively investigated, because they are one of the most representative privileged organophosphorus compounds.[2] In this regard, we have reported synthetic methods for a wide range of phosphaheterocyclic compounds such as phosphacoumarins, benzophosphacoumarins, phosphaisocoumarins, phosphaisoquinolinones, phospha-γ-lactams, phospha-γ-lactones, phosphaimides, phosphorus-2-pyrons, and phosphaanhydrides.[3] Although benzophosphacoumarins were prepared through C–H activation followed by C–O bond formation, it was limited by a deficiency for substrate variation related to introduction of functional groups (eq 1, Scheme 1).[4]

Scheme 1. Synthesis of Benzophosphacoumarins



Accordingly, a synthetic approach to functionalized phosphacoumarins and benzophosphacoumarins from easily accessible reactants is extremely important. In this context, we were attracted to developing a streamlined method for the synthesis of a myriad of phosphacoumarins and benzophosphacoumarins with the aim of making useful chemical libraries and probes. In addition, the importance of cross-dehydrogenative coupling reactions on Pd-catalyzed direct C–H alkenylation of heteroarenes has been rapidly increased.[5] We then envisaged that the reaction of phosphacoumarins with alkenes would allow the formation of 3-alkenylated phosphacoumarins, which can be employed in a Diels–Alder reaction for the preparation of benzophosphacoumarins (eq 2). Herein we report alkenylation of phosphacoumarins from the reaction of phosphacoumarins with a variety of activated as well as nonactivated alkenes via aerobic oxidative Heck reactions and their synthetic applications to fluorescent benzophosphacoumarins via an inverse electron demand Diels–Alder reaction followed by 1,2-elimination and a dehydrogenation.

We started our investigations by examining the oxidative alkenylation of phosphacoumarin (**1a**) using *n*-butyl acrylate (**2a**) (Table 1). When **1a** was treated with **2a** in the presence of $Pd(OAc)_2$, $Cu(OAc)_2$, and Ag_2CO_3 in acetic acid at 80 °C for 18 h, the desired 3-alkenylated phosphacoumarin **3aa** was gratifyingly obtained albeit in 17% yield (entry 1). Pivalic acid was the best solvent among several reaction media examined (acetic acid, trifluoroacetic acid, and pivalic acid). Among the catalysts screened, $Pd(OAc)_2$ provided **3aa** in 49% yield (entry 3). A number of oxidants such as $Cu(OAc)_2$, AgOAc, and Ag_2CO_3 were tested to reveal that AgOAc was the choice of oxidant (entries 8–10). The best result was obtained from the reaction of **1a** (0.2 mmol, 1 equiv) with **2a** (2 equiv) using $Pd(OAc)_2$ (5 mol %) and AgOAc (3 equiv) in PivOH at 80 °C for 22 h under air, affording **3aa** in 95% yield (entry 12).

Next, we examined the substrate scope in the reaction of 7-methoxyphosphacoumarin (**1b**) with a variety of terminal alkenes **2** (Scheme 2). When nonactivated aliphatic alkenes such as 3,3-dimethyl-1-butene and 3-phenyl-1-propene were employed in the oxidative alkenylation, the desired products **3bb** and **3bc** were produced in moderate yields under air. Under the optimum conditions, styrene was smoothly transformed to **3bd** in excellent yield. To our delight, a myriad of

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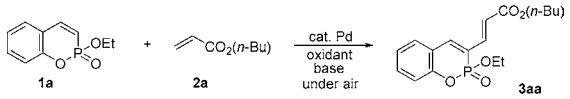
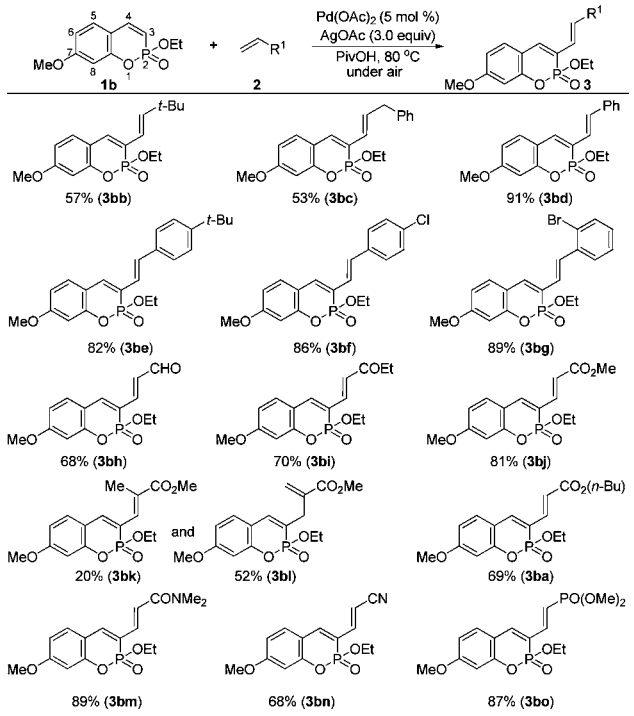
Table 1. Reaction Optimization[a]



entry	cat.	oxidant	base	solvent	yield[b] (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2$	Ag_2CO_3	AcOH	17 (30)
2	$Pd(OAc)_2$	$Cu(OAc)_2$	Ag_2CO_3	TFA	19 (28)
3	$Pd(OAc)_2$	$Cu(OAc)_2$	Ag_2CO_3	PivOH	49 (10)
4	$PdCl_2$	$Cu(OAc)_2$	Ag_2CO_3	PivOH	14 (24)
5	$Pd(TFA)_2$	$Cu(OAc)_2$	Ag_2CO_3	PivOH	15 (10)
6	$Pd(hfacac)_2$	$Cu(OAc)_2$	Ag_2CO_3	PivOH	34
7	$Pd(dba)_2$	$Cu(OAc)_2$	Ag_2CO_3	PivOH	28 (19)
8	$Pd(OAc)_2$	$Cu(OAc)_2$	–	PivOH	6 (73)
9	$Pd(OAc)_2$	AgOAc	–	PivOH	95 (92)[c]
10	$Pd(OAc)_2$	Ag_2CO_3	–	PivOH	50
11	$Pd(OAc)_2$	AgOAc[d]	–	PivOH	57 (21)
12	**$Pd(OAc)_2$**[e]	**AgOAc**	–	**PivOH**	**95 (92)**[c,f]

[a]Reactions were carried out with **1a** (0.2 mmol), Pd catalyst (10 mol %), oxidant (3 equiv), base (3 equiv), and **2a** (2 equiv) in solvent (1.0 mL) at 80 °C for 18 h under air. [b]NMR yield using dibromomethane as an internal standard. Numbers in parentheses are recovery NMR yield of **1a**. [c]Isolated yield. [d]AgOAc (2 equiv) was used. [e]Pd catalyst (5 mol %). [f]22 h.

Scheme 2. Alkenylation of 7-Methoxy Phosphacoumarins with Alkenes[a]

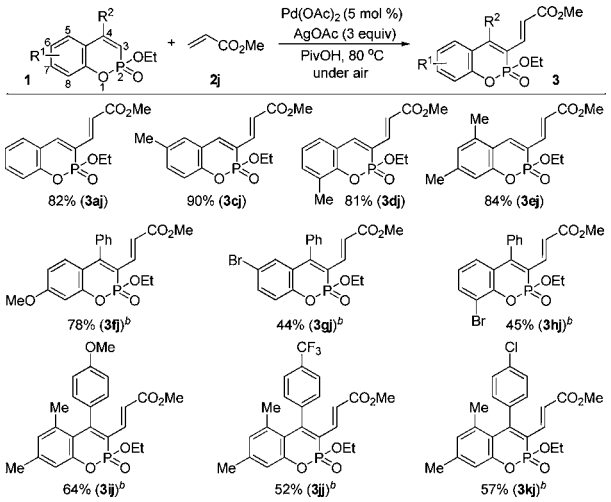


[a]Reactions were carried out with **1b** (0.2 mmol) and **2** (2 equiv) in PivOH (1.0 mL) at 80 °C for 10−48 h under air.

styrene derivatives could be employed in the oxidative alkenylation. Electronic variation of substituents on the aryl ring of styrene did not affect the reaction efficiency. For example, styrene derivatives **2** having electron-donating *tert*-butyl as well as electron-withdrawing 4-chloro and 2-bromo groups on the phenyl ring underwent the oxidative alkenylation, providing the desired phosphacoumarins (**3be**, **3bf**, and **3bg**) in good yields ranging from 82% to 89%. In addition, the oxidative alkenylations of phosphacoumarin **1b** with a wide range of electron-deficient alkenes **2** were conducted to examine the scope of the present method. Acroleins and ethyl vinyl ketones were reacted with **1b** to afford the desired **3bh** (68%) and **3bi** (70%). The present method worked equally well with methyl acrylate and *n*-butyl acrylate, producing the corresponding phosphacoumarins **3bj** (81%) and **3ba** (69%). Treatment of **1b** with methyl methacrylate afforded the two isomeric phosphacoumarins **3bk** (20%) and **3bl** (52%). When **1b** was subjected to the oxidative alkenylation with *N*,*N*-dimethyl acrylamide, the alkenylated product **3bm** was isolated in 89% yield. We were pleased to obtain **3bn** in 68% yield from acrylonitrile. Vinyl phosphate (**2o**) turned out to be compatible with the present reaction conditions.

With these results in hand, the efficiency and scope of the oxidative alkenylation of various phosphacoumarins (**1**) with methyl acrylates (**2j**) were explored under the optimum conditions (Scheme 3). When **1a** was reacted with **2j** in the presence of a Pd catalyst, the desired product **3aj** was obtained in 82% yield. 6- and 8-Methylphosphacoumarins **1c** and **1d** underwent the oxidative alkenylation with methyl acrylate to furnish the corresponding products **3cj** and **3dj** in excellent yields. 5,7-Dimethylphosphacoumarin (**1e**) also worked well. 7-Methoxy-4-phenylphosphacoumarin (**1f**) was treated with methyl acrylate (5 equiv), producing **3fj** in 78% yield. However, 4-phenylphosphacoumarins having 6- or 8-bromo groups underwent the oxidative alkenylation in slightly lower yields. Electronic variation of substituents on the aryl ring at the 4-position of 4-aryl-5,7-dimethylphosphacoumarins were examined. An electron-donating methoxy group on the aryl ring did not significantly influence the oxidative alkenylation, and thus, the desired product **3ij** was obtained in 64% yield. However, phosphacoumarins having electron-withdrawing trifluoromethyl and chloro groups on the aryl ring were slightly less reactive than **3i**.

Scheme 3. Alkenylation of Phosphacoumarins with Methyl Acrylates[a]



[a]Reactions were carried out with **1** (0.2 mmol) and **2j** (2 equiv) in PivOH (1.0 mL) at 80 °C for 10−80 h under air. [b] Methyl acrylate (5 equiv) was used.

An H/D exchange experiment was conducted in order to explain the initial interaction of the oxidative alkenylation of

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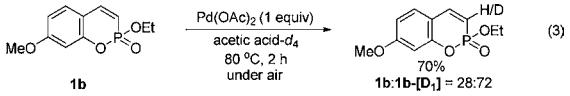
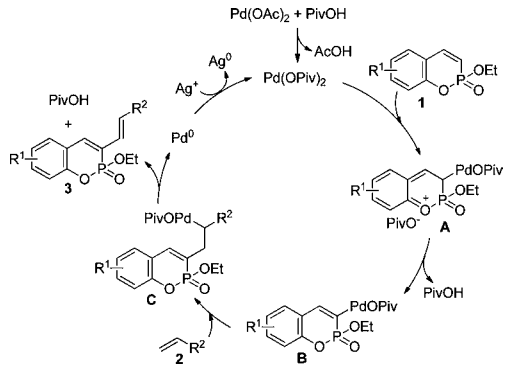
phosphacoumarin **1b** with a Pd catalyst. When **1b** in the presence of $Pd(OAc)_2$ in acetic acid-d_4 was heated at 80 °C for 2 h without use of an alkene, deuterium incorporation (72% D) was largely detected at the 3-position of phosphacoumarin (**1b**) (eq 3).



A plausible reaction mechanism for the formation of 3-alkenylphosphacoumarins (**3**) from the reaction of phosphacoumarins (**1**) with alkenes (**2**) is shown in Scheme 4. Because

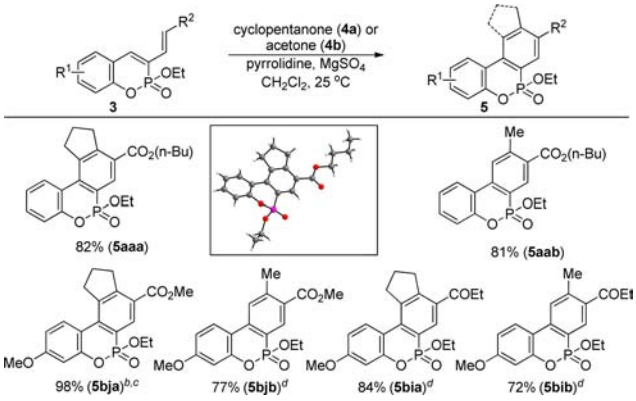
Scheme 4. A Plausible Mechanism



the 3-position on phosphacoumarin is nucleophilic, C3-palladation in the presence of the Pd catalyst occurs to provide the intermediate **B**, which inserted into the alkenes to produce the intermediate **C**. The subsequent β-hydride elimination afforded the alkenylated phosphacoumarins **3** and a Pd(0) catalyst, which is reoxidized by AgOAc to regenerate the Pd(II) catalyst to complete the catalytic cycle.

Because 3-alkenylphosphacoumarins (**3**) could be serviced as a diene system, we envisioned that an inverse electron demand Diels–Alder reaction (IEDDA) of **3** with enamines *in situ* generated from ketones and pyrrolidines followed by 1,2-elimination and a dehydrogenation would allow the formation of fluorescent benzophosphacoumarins (**5**) (Scheme 5).[6] For example, when phosphacoumarin **3a** was treated with cyclo-

Scheme 5. Synthesis of Benzophosphacoumarins[a]



[a]Reactions were carried out with 3 (0.2 mmol), ketone (5 equiv), pyrrolidine (0.5 equiv), and $MgSO_4$ (2 equiv) in solvent (1.0 mL) at 25 °C for 12–60 h. [b] 80 °C. [c] DCE/CH_3CN = 1:4. [d] 40 °C.

pentanone (**4a**) and pyrrolidine in the presence of $MgSO_4$ in dichloromethane at 25 °C, the desired benzophosphacoumarin **5aaa** was produced in 82% yield. The structure of **5aaa** was unambiguously determined by X-ray crystallography (see the Supporting Information).[7] Enamine *in situ* generated from acetone (**4b**) and pyrrolidine works equally well to produce **5aab** in 81% yield. 7-Methoxyphosphacoumarins (**1b**) having methyl acrylate and ethyl vinyl ketone moieties at the 3-position smoothly underwent an IEDDA, producing the desired benzophosphacoumarins in good to excellent yields ranging from 72% to 98%.

Because 3-alkenylphosphacoumarins (**3**) and benzophosphacoumarins (**5**) were fluorescent, their optical properties in CH_2Cl_2 solution were examined (Table 2). The phosphacou-

Table 2. Photophysical Properties of Phosphacoumarins and Benzophosphacoumarins[a]

compd	$\lambda_{max,abs}$ (nm)	$\lambda_{max,em}$ (nm)	ε ($M^{-1}\cdot cm^{-1}$)	ϕ
3bd	355	435	69,998	0.03
3be	358	423	132,271	0.04
3bf	357	433	47,392	0.03
3bg	348	435	50,071	0.03
3bj	346	436	48,572	0.01
3cj	306	424	44,484	0.02
5aaa	281	355	20,128	0.08
5aab	278	361	23,458	0.10
5bja	322	370	21,679	0.83
5bjb	316	372	25,287	0.83

[a]Absorption peaks ($\lambda_{max,abs}$) and molar extinction coefficients (ε) were measured in CH_2Cl_2 (10^{-5} M). Full spectra are given in the Supporting Information.

marin fluorophores showed Stokes shifts ranging from 48 to 118. Extinction coefficients were variable from 20,128 to 132,271 $M^{-1}\cdot cm^{-1}$. The presence of methoxy as well as methoxycarbonyl groups on the benzophosphacoumarins is essential to the high quantum yields (**5bja** and **5bjb**), which are an attractive property for biological probes (see the Supporting Information).

In conclusion, we have developed an alkenylation from the reaction of phosphacoumarins with a wide range of activated as well as nonactivated alkenes via aerobic oxidative Heck reactions. Moreover, 3-alkenylphosphacoumarins undergo inverse electron demand Diels–Alder reactions with enamines *in situ* generated from ketone and pyrrolidine followed by 1,2-elimination and a dehydrogenation, affording fluorescent benzophosphacoumarins.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of NMR spectra for all products. 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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(7) CCDC 1037285 (**5aaa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.

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