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Palladium(II)/Polyoxometalate-Catalyzed Direct Alkenylation of Benzofurans under Atmospheric Dioxygen

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An efficient and selective C2 alkenylation of benzofurans was performed by using $Pd(OAc)_2$ combined with a catalytic amount of 11-molybdovanadophosphoric acid ($H_4PMo_{11}VO_{40}$) under an atmosphere of dioxygen. *N*-Acetylglycine (Ac-Gly-OH) was observed to be an effective additive for the olefination reaction.

The benzofuran motif is present in a wide range of natural and unnatural compounds that exhibit a variety of important biological activities.[1] As such, derivatives of benzofuran have found use as versatile intermediates in organic synthesis, and the study of methods to prepare and functionalize benzofurans continues to be an active area of research.[2]

Transition-metal-catalyzed C–H bond functionalization of benzofurans is a practical synthetic tool,[3] as it eliminates the need for preparing benzofuryl halides,[4] benzofuryl triflates,[5] benzofurylstannanes,[6] benzofurylboronic acids,[7] and benzofurylzinc compounds,[8] which are intermediates in some benzofuran functionalization strategies. The Fujiwara–Moritani reaction,[9] which is the palladium-catalyzed direct oxidative coupling of aromatic substrates with alkenes, is among the most effective and straightforward strategies used to introduce a side chain into benzofurans.[10] This reaction was first performed by using stoichiometric amounts of palladium,[11] but it was also shown to take place with catalytic amounts of palladium.[12] In recent years, a variety of procedures for the C–H alkenylation of aromatic heterocycles have been successfully developed.[13] For example, Kasahara et al.[10a] and Fujiwara et al.[10b,c] reported the $Pd(OAc)_2$-mediated reaction of benzofurans with a variety of olefins. Fujiwara et al. also presented the oxidative coupling of benzofurans with olefins in the presence of catalytic amounts of palladium acetate and benzoquinone with *tert*-butyl hydroperoxide as the oxidant.[10d] Liu et al. developed a direct Pd^{II}-catalyzed olefination of benzofurans with allylic esters and ethers by using Ag_2CO_3 (1 equiv.) as the oxidant.[10e] In addition, Miura et al. reported the Pd-catalyzed C–H alkenylation/decarboxylation of benzofuran-2-carboxylic acid by using $Cu(OAc)_2{\cdot}H_2O$ (2 equiv.) as the oxidant.[10f] However, each of these procedures suffers from the requirement of high Pd loadings or the need for stoichiometric amounts of a terminal oxidant such as copper(II) salts, silver(I) salts, or benzoquinone. The development of a new catalytic system that uses ecologically benign oxidants such as dioxygen would be highly desirable. Recently, it was demonstrated that the high activation energy for the direct oxidation by O_2 could be circumvented by the use of polyoxometalates (POMs).[14] However, this efficient method often requires harsh reaction conditions such as the use of a strong acid solvent[14d–f] and high O_2 pressure.[14a] Herein, we report an efficient $Pd(OAc)_2$/POM-catalyzed C2 alkenylation of benzofurans in DMF by using atmospheric dioxygen as the terminal oxidant.

To investigate the use of POM/O_2 as an oxidant for the $Pd(OAc)_2$-catalyzed alkenylation of benzofurans, we chose benzofuran (**1a**) and styrene (**2a**) as model substrates to optimize the reaction conditions. Selected results from these initial studies are summarized in Table 1. First, a variety of POMs were evaluated. The best yield of **3a** was obtained if the heteropoly acid $H_4PMo_{11}VO_{40}$ was used as the reoxidation catalyst (Table 1, entry 1). The use of other heteropoly acids such as $H_9PMo_6V_6O_{40}$, $H_3PMo_{12}O_{40}$, and $H_5PMo_{10}V_2O_{40}$ resulted in a significant decrease in the yield (Table 1, entries 4–6), whereas $(NH_4)_5H_4PMo_6V_6O_{40}$ and $(NH_4)_4PMo_{11}VO_{40}$ did not catalyze the coupling reaction at all (Table 1, entries 2 and 3). External bases, which are believed to act as proton abstractors, have been observed to be beneficial to palladium-catalyzed C–H cleavage reactions. Thus, the effect of base was examined. Other alkali metal salts were less effective than Na_2CO_3 (Table 1, entries 1 and 7–9). Notably, additives played a crucial role in the reaction. Removing Hacac from the reaction mixture resulted in a lower yield (6%; Table 1, entry 10), dibenzoylmethane showed no benefit over Hacac (Table 1, entry 11), and DMAP and Boc-Leu-OH seemed to inhibit the reaction (Table 1, entries 12 and 13). However, in the presence of Ac-Gly-OH, a type of monoprotected amino acid, the coupling of **1a** with **2a** afforded **3a** in 50% yield under O_2 pressure (1 atm; Table 1, entry 14). Monoprotected amino acids were recently developed as powerful additives in Pd^{II}-catalyzed oxidative C–H cross-coupling reactions by Yu et al.[15] A further increase in yield was obtained by changing the solvent from DMSO to DMF; in this case, the product was formed in 86% yield (Table 1, entry 20). Other solvents such as TFA, *t*AmOH, NMP, and 1,4-dioxane significantly attenuated the reaction or caused it to fail altogether (Table 1, entries 15–19). The reaction of **1a**

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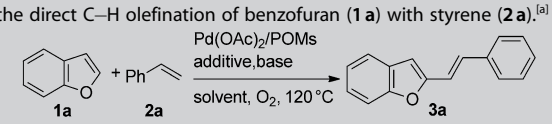
Table 1. Screening of the direct C–H olefination of benzofuran (**1a**) with styrene (**2a**).[a]



Entry	POM	Base	Solvent	Additive	*P* [atm O_2][b]	Yield[c] [%]
1	$H_4PMo_{11}VO_{40}$	Na_2CO_3	DMSO	Hacac	5	23
2	$(NH_4)_5H_4PMo_6V_6O_{40}$	Na_2CO_3	DMSO	Hacac	5	0
3	$(NH_4)_4PMo_{11}VO_{40}$	Na_2CO_3	DMSO	Hacac	5	0
4	$H_9PMo_6V_6O_{40}$	Na_2CO_3	DMSO	Hacac	5	trace
5	H_3PMo_{12}	Na_2CO_3	DMSO	Hacac	5	5
6	$H_5PMo_{10}V_2O_{40}$	Na_2CO_3	DMSO	Hacac	5	3
7	$H_4PMo_{11}VO_{40}$	NaOAc	DMSO	Hacac	5	15
8	$H_4PMo_{11}VO_{40}$	$KHCO_3$	DMSO	Hacac	5	7
9	$H_4PMo_{11}VO_{40}$	Cs_2CO_3	DMSO	Hacac	5	trace
10	$H_4PMo_{11}VO_{40}$	Na_2CO_3	DMSO	–	5	6
11	$H_4PMo_{11}VO_{40}$	Na_2CO_3	DMSO	DBM	5	26
12	$H_4PMo_{11}VO_{40}$	Na_2CO_3	DMSO	DMAP	5	10
13	$H_4PMo_{11}VO_{40}$	Na_2CO_3	DMSO	Boc-Leu-OH	1	5
14	$H_4PMo_{11}VO_{40}$	Na_2CO_3	DMSO	Ac-Gly-OH	1	50
15	$H_4PMo_{11}VO_{40}$	Na_2CO_3	TFA	Ac-Gly-OH	1	3
16	$H_4PMo_{11}VO_{40}$	Na_2CO_3	EtCOOH	Ac-Gly-OH	1	0
17	$H_4PMo_{11}VO_{40}$	Na_2CO_3	*t*AmOH	Ac-Gly-OH	1	7
18	$H_4PMo_{11}VO_{40}$	Na_2CO_3	NMP	Ac-Gly-OH	1	0
19	$H_4PMo_{11}VO_{40}$	Na_2CO_3	1,4-dioxane	Ac-Gly-OH	1	0
20	$H_4PMo_{11}VO_{40}$	Na_2CO_3	DMF	Ac-Gly-OH	1	86
21	$H_4PMo_{11}VO_{40}$		DMF	Ac-Gly-OH	1	65

[a] Conditions: **1a** (1.0 mmol), **2a** (0.2 mmol), Pd catalyst (10 mol%), POM·H_2O (≈10 mol%), base (1 equiv.), additive (15 mol%), solvent (1 mL), O_2, 120 °C, 24 h. Hacac = acetylacetone, NMP = *N*-methyl-2-pyrrolidone, *t*AmOH = *tert*-amyl alcohol, TFA = trifluoroacetic acid, DMAP = 4-dimethylaminopyridine, DBM = dibenzoylmethane, Boc = *tert*-butoxycarbonyl. [b] 1 atm = 101.3 kPa. [c] Yield according to GC analysis on the basis of the amount of **2a** used.

with **2a** also afforded the desire product in 65% yield in the absence of Na_2CO_3. This fact indicates that Ac-Gly-OH may serve as the internal base for proton abstraction (Table 1, entry 21).[16]

Table 2 shows the effect of the loading of $Pd(OAc)_2$ and $H_4PMo_{11}VO_{40}$ on the formation of **3a**. If the amounts of $Pd(OAc)_2$ and $H_4PMo_{11}VO_{40}$ were reduced to 5 and 3 mol%, respectively, the yield of **3a** was still high (85%; Table 2, entry 2). A further decrease in the loading of $Pd(OAc)_2$ or $H_4PMo_{11}VO_{40}$ resulted in lower yields of **3a** (Table 2, entries 3 and 4). Removal of $H_4PMo_{11}VO_{40}$ from the catalytic system resulted in a sluggish reaction (Table 2, entry 6). Clearly, no reaction was induced in the absence of the $Pd(OAc)_2$ catalyst (Table 2, entry 5). If

Table 2. Effect of the loading of $Pd(OAc)_2$/$H_4PMo_{11}VO_{40}$.[a]

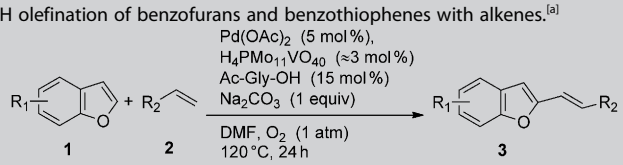
Entry	$Pd(OAc)_2$ [mol%]	$H_4PMo_{11}VO_{40}$ [mol%]	Yield [%][b]
1	10	10	86
2	5	3	85 (76)
3	5	1	47
4	3	3	30
5	0	3	0
6	5	0	25

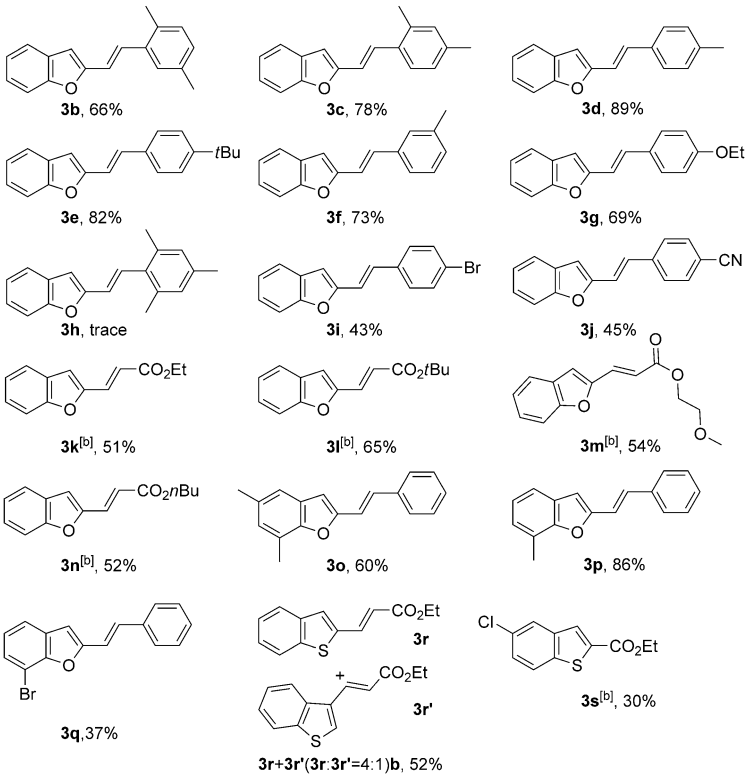
[a] Conditions: **1a** (1.0 mmol), **2a** (0.2 mmol), Pd catalyst, $H_4PMo_{11}VO_{40}$, base (1 equiv.), Ac-Gly-OH (15 mol%), DMF (1 mL), O_2, 120 °C, 24 h. [b] Yield according to GC analysis on the basis of the amount of **2a** used. Number in parentheses is the yield of the isolated product.

taken together, these results indicated the following as the optimal reaction conditions: $Pd(OAc)_2$ (5 mol%), $H_4PMo_{11}VO_{40}$ (≈3 mol%), Na_2CO_3 (1 equiv.), Ac-Gly-OH (15 mol%) in DMF under an atmosphere of O_2 (1 atm) at 120 °C. This method is highly site selective at the 2-position. Additionally, the reaction proceeded with complete stereoselectivity and generated (*E*)-**3a** exclusively.

With the optimized reaction conditions established, the substrate scope of this reaction was investigated (Table 3). First, various styrenes were employed to couple with **1a**, and the electronic effects of the substituents on the phenyl rings were very significant. Styrenes with electron-donating groups were good substrates for the coupling reaction and afforded the corresponding products in good to excellent yields (see **3b**–**g**). For example, 4-methylstyrene reacted with **1a** to give alkenylation product **3d** in 89% yield. The coupling reaction of styrenes with electron-withdrawing groups also occurred, but lower yields of the desired products (see **3i** and **3j**) were obtained. Unfortunately, 2,4,6-trimethylstyrene was not a suitable substrate for this reaction, probably because of steric hindrance (see **3h**). This catalytic system was also applied to acrylates of various alcohols such as ethyl acrylate, *tert*-butyl acrylate, 2-methoxyethyl acrylate, and *n*-butyl acrylate, and the corresponding benzofuran products (see **3k**–**n**) were obtained in moderate yields. To explore the scope of the reaction further, we subjected benzofurans and benzothiophenes to the standard reaction conditions. The reaction of 7-methylbenzofuran with **2a** gave desired product **3p** in 86% yield. Similarly, 5,7-dimethylbenzofuran reacted with **2a** to give **3o** in 60% yield. However, upon employing 7-bromobenzofuran, a lower yield (37%) of coupling product **3q** was obtained. The reaction of benzothiophene with styrene gave a 2:1 mixture of 2-styryl-/3-styrylbenzothiophene along with small amounts of dibenzothiophene from homocoupling. Unfortunately, we failed to isolate the styrylbenzothiophene products from the reaction mixture. Benzothiophene also underwent the alkenylation reaction with ethyl acrylate to give a 4:1 mixture of C2- and C3-substituted benzothiophenes **3r** and **3r′** in 52% combined yield, whereas 5-chlorobenzothiophene reacted with ethyl acrylate to give C2-alkenylation product **3s** selectively in 30% yield. These results suggest that electronic effects also play a major role in the observed reactivity.

Table 3. Direct C–H olefination of benzofurans and benzothiophenes with alkenes.[a]





[a] Conditions: **1** (1.0 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), $H_4PMo_{11}VO_{40}$ (≈3 mol%), Na_2CO_3 (1 equiv.), Ac-Gly-OH (15 mol%), DMF (1 mL), O_2 (1 atm), 120 °C, 24 h. [b] Reaction conditions: $Pd(OAc)_2$ (10 mol%), $H_4PMo_{11}VO_{40}$ (≈0.5 mol%), Ac-Gly-OH (30 mol%), without Na_2CO_3.

As evidenced from Table 3, the alkenylation tolerates various functional groups such as ethoxy, cyano, chloro, bromo, and ester. Notably, Cl and Br substituents were compatible with the catalytic reaction, which could provide opportunities for further functionalization.

In summary, an efficient and selective C2 alkenylation of benzofurans was performed by using $Pd(OAc)_2$ combined with a catalytic amount of $H_4PMo_{11}VO_{40}$ under mild conditions with the use of molecular oxygen as the terminal oxidant. Although further improvements are desired with regard to the substrate scope and reaction efficiency, the present study provided a practical method toward the synthesis of benzofuran derivatives.

Experimental Section

Representative Procedure for the oxidative coupling of benzofuran (1a) with styrene (2a)

Formation of (*E*)-2-styrylbenzofuran **3a**: Benzofuran (**1a**; 107 μL, 1.0 mmol), styrene (23 μL, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), $H_3PMo_{11}VO_{40}$ (14 mg, ≈0.006 mmol), Ac-Gly-OH (3.5 mg, 0.03 mmol), Na_2CO_3 (21.2 mg, 0.2 mmol), and DMF (1 mL) were placed in a 50 mL Schlenk-type sealed tube (with a Teflon high-pressure valve and a side arm). The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon, ×3).The mixture was heated in an oil bath at 120 °C with stirring for 24 h. After the reaction vessel was cooled to room temperature, the crude reaction mixture was diluted with CH_2Cl_2 to 5 mL and $C_{16}H_{34}$ (0.2 mmol) was added as an internal standard for GC analysis. After GC and GC–MS analyses of the reaction mixture, volatiles were removed under reduced pressure, and the residue was subjected to silica gel column chromatography (eluting with petroleum ether) to afford **3a** as a white solid in 76% yield. GC analysis of the reaction mixture disclosed the formation of **3a** in 85% yield.

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