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Palladium-Catalyzed Selective Heck-Type Diarylation of Allylic Esters with Aryl Halides Involving a β-OAc Elimination Process

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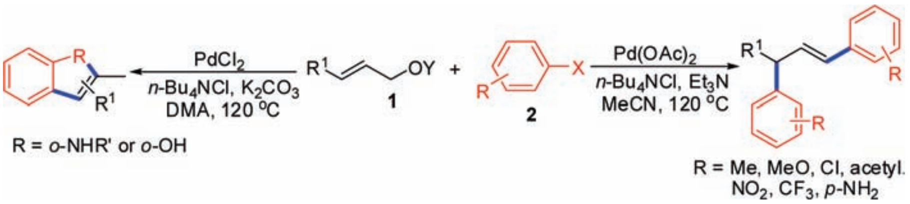
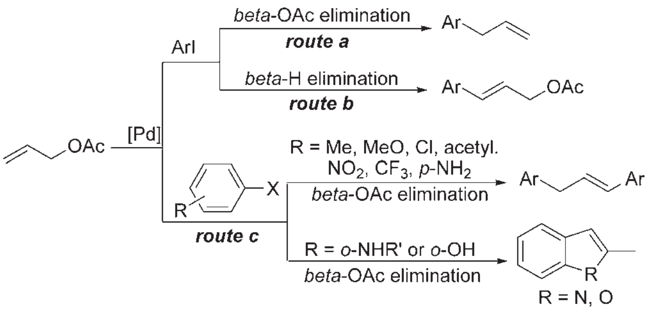
ABSTRACT



Palladium-catalyzed selective Heck-type diarylation of allylic esters with aryl halides has been developed. Allylic esters are reacted with aryl iodides to provide the corresponding 1,3-diaryl propenes through a β-OAc elimination process. It is noteworthy that the methodology can be applied in constructing the indole and benzofuran skeletons.

The Heck reaction is one of the most important methods in organic chemistry, and widely applies in organic synthesis, pharmaceutical, and material industries.[1−6] Despite important advances in the Heck reaction of halides, pseudohalides, or arenes, the selective Heck reactions of allylic esters processes are scarce.[3−6] Until now, there are only two monoarylation routes for the Heck reactions of allylic esters, including (1) β-OAc elimination to terminal alkenes (route a, Scheme 1)[4,5] and (2) β-H elimination to internal allylic esters (route b).[6] For example, Lautens and coworkers have developed an intermolecular Heck reaction of allylic acetates with aryl iodides through a β-OAc elimination process in good yields.[4b−e] They observed some β-H elimination products during their procedures,

Scheme 1. The Heck Reactions of Allyl Acetates



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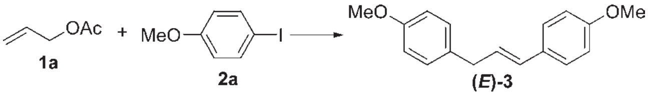
10.1021/ol1031552

but low yields and low selectivity hindered the β-H elimination transformation. Recently, Jiao and co-workers described a selective Heck reaction of aryl halides with allylic esters by β-H elimination avoiding β-OAc elimination.[6] To the best of our knowledge, however, examples of selective diarylation of allylic esters are not explored. Here, we report a selective palladium-catalyzed Heck-type diarylation of allylic esters with aryl iodides protocol for one-step synthesizing 1,3-diaryl propenes involving a β-OAc elimination process (route c).[7,8] It is noteworthy that the methodology can be applied in constructing the indole and benzofuran skeletons.[9,10]

Table 1. Palladium-Catalyzed Diarylation Reaction of Allyl Acetate (**1a**) with 4-Iodoansole (**2a**)[a]



entry	[Pd]	additive	base	solvent	yield (%)[b]
1	Pd(OAc)$_2$		Et$_3$N	MeCN	40
2	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	MeCN	89
3[c]	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N		23
4	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	n-PrCN	81
5	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	DMF	73
6	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	DMA	67
7	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	NMP	61
8	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	toluene	69
9	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	THF	57
10[d]	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	MeCN	57
11	PdCl$_2$	n-Bu$_4$NCl	Et$_3$N	MeCN	75
12	PdCl$_2$(MeCN)$_2$	n-Bu$_4$NCl	Et$_3$N	MeCN	71
13	Pd(PPh$_3$)$_4$	n-Bu$_4$NCl	Et$_3$N	MeCN	17
14[e]	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	MeCN	71
15	Pd(OAc)$_2$	n-Bu$_4$NCl	DABCO	MeCN	62
16	Pd(OAc)$_2$	n-Bu$_4$NCl	K$_2$CO$_3$	MeCN	27
17	Pd(OAc)$_2$	n-Bu$_4$NBr	Et$_3$N	MeCN	61
18	Pd(OAc)$_2$	n-Bu$_4$NF	Et$_3$N	MeCN	82
19	Pd(OAc)$_2$	n-Bu$_4$NOAc	Et$_3$N	MeCN	32
20[f]	Pd(OAc)$_2$	n-Bu$_4$NCl	Et$_3$N	MeCN	90

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), [Pd] (10 mol %), additive (1.5 equiv), base (8 equiv), and solvent (2 mL) at 120 °C under air atmosphere for 12 h. [b] Isolated yield. [c] Et$_3$N (2 mL). [d] Pd(OAc)$_2$ (5 mol %) for 26 h. [e] Et$_3$N (4 equiv). [f] Under N$_2$ atmosphere.

As shown in Table 1, the reaction of allyl acetate **1a** with 4-iodoansole **2a** was carried out to determine the optimal reaction conditions. Initially, treatment of substrate **1a** with iodide **2a**, Pd(OAc)$_2$ (10 mol %), and Et$_3$N (8 equiv) in MeCN at 120 °C for 12 h afforded the desired (E)-4,4′-(prop-1-ene-1,3-diyl)bis(methoxybenzene) (**3**) in 40% yield together with some monoarylation β-OAc or β-H elimination products (entry 1). It is noteworthy that the configuration of the carbon−carbon double bond in product **3** is determined according to the authoritative ^{1}H NMR spectra. To our delight, n-Bu$_4$NCl could improve the reaction, enhancing the yield of **3** sharply to 89% (entry 2).[11] Prompted by these results, a series of solvents, such as Et$_3$N, n-PrCN, DMF, DMA (N,N-dimethylacetamide), NMP (N,N-dimethylpyridin-4-amine), toluene, and THF, were investigated, and they were less effective than MeCN (entries 3−9). The yield was reduced to 23% when Et$_3$N was used as the base and medium (entry 3). It was found that n-PrCN, the higher boiling point solvent, also decreased the activity of the reaction slightly (entry 4). Notably, the yield of **3** was lowered to 57% at 5 mol % of Pd(OAc)$_2$ even prolonging the reaction time (entry 10). Although three other Pd catalysts, PdCl$_2$, PdCl$_2$(MeCN)$_2$, and Pd(PPh$_3$)$_4$, had activity for the reaction, they were less effective than Pd(OAc)$_2$ (entries 11−13). In light of the above results, the effect of bases was evaluated (entries 14−16). The yield of **3** was reduced when 4 equiv of Et$_3$N was added (entry 14). We found that both DABCO and KOAc displayed less efficiency for the diarylation reaction (entries 15 and 16). Among the additives examination, it turned out that the reaction gave the best results in the presence of n-Bu$_4$NCl (entries 2 and 17−19). It is noteworthy that the identical results are observed under either air or nitrogen atmosphere (entries 2 and 20).

Consequently, the scope of both ally lactates and aryl halides was explored for the diarylation reaction under the standard conditions (Table 2). In the presence of Pd(OAc)$_2$, n-Bu$_4$NCl, and Et$_3$N, a variety of aryl halides **2b**−**k** were first examined by reacting with allyl acetate (**1a**) (entries 1−10). The results indicated that both electron-rich and electron-deficient aryl iodides were suitable for the diarylation reaction, but aryl bromides had no activity. For example, aryliodide **2b**, bearing a 2-MeO group on the aryl ring, was treated with acetate **1a**, Pd(OAc)$_2$, n-Bu$_4$NCl, and E$_3$N smoothly to afford the desired product **4** in 80% yield (entry 1). Gratifyingly, substrate **2g** with a p-NH$_2$ group was successfully diarylated with acetate **1a** leading

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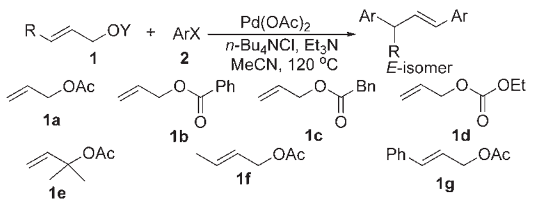
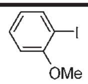
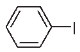
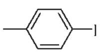
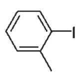
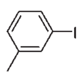
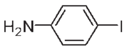
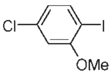
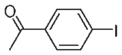
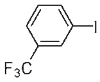
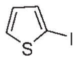
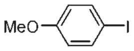
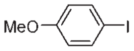
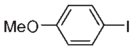
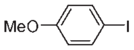
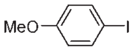
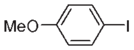
Table 2. Palladium-Catalyzed Diarylation Reactions of Allylic Esters (**1**) with Aryl Halides (**2**)[a]

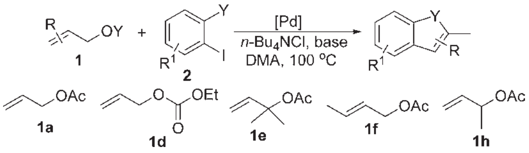


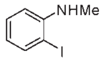
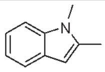
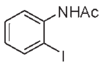
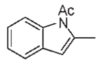
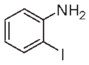
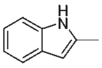
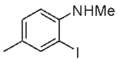
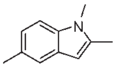
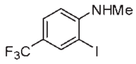
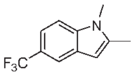
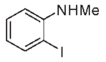
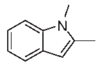
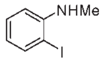
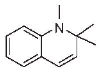
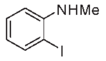
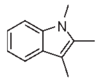
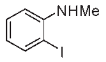
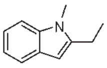
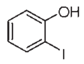
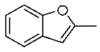
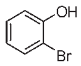
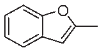
entry	1	aryl halide 2	time (h)	yield (%)[b]
1	**1a**	 **2b**	15	80, **4**
2	**1a**	 **2c**	14	72, **5**
3	**1a**	 **2d**	14	92, **6**
4	**1a**	 **2e**	12	73, **7**
5	**1a**	 **2f**	12	83, **8**
6	**1a**	 **2g**	12	50, **9**
7	**1a**	 **2h**	12	77, **10**
8	**1a**	 **2i**	12	57, **11**
9	**1a**	 **2j**	16	71, **12**
10	**1a**	 **2k**	24	45, **13**
11	**1b**	 **2a**	14	58, **3**
12	**1c**	 **2a**	12	62, **3**
13	**1d**	 **2a**	12	58, **3**
14[c]	**1e**	 **2a**	12	trace, **14**
15	**1f**	 **2a**	12	mixture, **16**
16	**1g**	 **2a**	12	30, **17**

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol), Pd(OAc)$_2$ (10 mol %), n-Bu$_4$NCl (1.5 equiv), Et$_3$N (8 equiv), and MeCN (2 mL) at 120 °C under air. [b] Isolated yield. [c] Another monoarylation product **15**, (E)-4-(4-methoxyphenyl)-2-methylbut-3-en-2-ol, was obtained in 98% yield.

to the target product **9** in 50% yield (entry 6). It was found that some active functional groups, Cl, CH_3CO, and CF_3 groups, were tolerated well under the standard conditions (entries 7−9). Notably, the reaction of heteroaryl iodide **2k** with acetate **1a** was also successful in moderate yield (entry 10). The results showed that the standard conditions were compatible with terminal alkenes **1b−e** (entries 11−14), but were less effective for internal alkenes **1f** and **1g** (entries 15 and 16). For example, the reaction of allyl ethyl carbonate (**1d**) with 4-iodoansole (**2a**), Pd(OAc)$_2$, n-Bu$_4$NCl, and Et$_3$N was carried out smoothly to afford the desired (E)-4,4′-(prop-1-ene-1,3-diyl)bis(methoxybenzene) (**3**) in 53% yield (entry 13). To our surprise, the bulky acetate **1e** underwent the β-H elimination and deacetylation to furnish the monoarylation product **15**,[6d] not the β-OAc elimination to the diarylation product **14** (entry 14). However, internal alkenes, (E)-but-2-enyl acetate (**1f**) or cinnamyl acetate (**1g**), provided a mixture of products including the β-OAc elimination monoarylated or diarylated products, β-H elimination products, and others (entries 15 and 16). It was interesting to observe that the reaction between cinnamyl acetate (**1g**) with iodide **2a** could furnish the target product **17** in 30% yield (entry 16).

Table 3. Applications in the Synthesis of Indoles and Benzofurans[a]



entry	1	aryl halide 2	time (h)	product/yield (%)[b]
1	**1a**	 **2l**	12	 **18**/88
2	**1a**	 **2m**	20	 **19**/41
3	**1a**	 **2n**	20	 **20**/29
4	**1a**	 **2o**	12	 **21**/83
5	**1a**	 **2p**	12	 **22**/71
6	**1d**	 **2l**	20	 **18**/21
7	**1e**	 **2l**	12	 **23**/46
8	**1f**	 **2l**	20	 **24**/44
9	**1h**	 **2l**	20	 **25**/51
10	**1a**	 **2q**	12	 **26**/71
11	**1a**	 **2r**	12	 **26**/52

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), PdCl$_2$ (10 mol %), n-Bu$_4$NCl (1.5 equiv), K$_2$CO$_3$ (2 equiv), and DMA (2 mL) at 100 °C under air atmosphere. [b] Isolated yield.

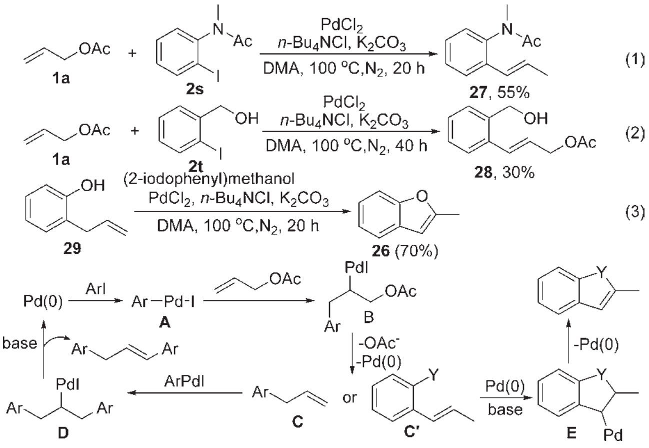
To our delight, the present methodology could be applied in indole and benzofuran preparation (Table 3).[9,10] However, the above standard conditions were not efficient for the reaction of allyl acetate (**1a**) with 2-iodo-N-methylaniline (**2l**) (38% yield, Table S1 in the Supporting Information). Screening revealed that the best results of

2-dimethyl-1*H*-indole (**18**) synthesis were obtained using the $PdCl_2/K_2CO_3$/DMA system (entry 1). In light of the above results, a variety of 2-iodoanilines **2m**−**p** and 2-halophenols **2q**,**r** were examined to construct indoles and benzofurans (entries 2−11). While *N*-(2-iodophenyl)acetamide (**2m**) and 2-iodoaniline (**2n**) displayed low activities for the reaction with substrate **1a**, $PdCl_2$, *n*-Bu_4NCl and K_2CO_3 (entries 2 and 3), *N*-methyl substrates **2o** and **2p**, bearing a Me or CF_3 group on the aryl ring, were consistent with the optimized conditions leading to good yields (entries 4 and 5). The other allyl acetates **1d**, **1e**, **1f**, and **1h** were also successful for constructing nitrogen-containing heterocyles in moderate yields (entries 6−9). Notably, a six-membered ring product **23**, 1,2,2-trimethyl-1,2-dihydroquinoline, was obtained from the reaction between 2-methylbut-3-en-2-yl acetate (**1e**) and 2-iodo-*N*-methylaniline (**2*l***) (entry 7). To our delight, both 2-iodophenol (**2q**) and 2-bromophenol (**2r**) are also suitable substrates, providing the desired benzofuran **26** in satisfactory yields (entries 10 and 11).

Three controlled experiments were carried out to understand the mechanism (Scheme 2). Treatment of acetate **1a** with substrate **2s** afforded an internal alkene **27** in 55% yield under the standard conditions, and no cyclized product was observed by GC-MS analysis (eq 1). (2-Iodophenyl)methanol (**2t**) only gave the β-H elimination product **28** by reacting with acetate **1a**, $PdCl_2$, *n*-Bu_4NCl, and K_2CO_3 (eq 2). Substrate **29** was also cyclized to furnish the desired benzofuran **26** in 70% yield (eq 3).

Therefore, a possible mechanism was proposed on the basis of the present results and the reported mechanism (Scheme 2).[2−6] Insertion of Pd(0) into ArI yields ArP(II)I, followed by addition of ArP(II)I to the C=C bond of allyl acetate affords intermediate **B**. Reductive β-OAc elimination of intermediate **B** gives intermediate **C** or **C′**: (1) the Heck reaction of intermediate **C** takes place leading to 1,3-diaryl propenes and (2) intramolecular nucleophilic cyclization of intermediate **C′** provides indoles and benzofurans. We deduce that two roles of *n*-Bu_4NCl are played in the reaction including: (1) the use as the phase-transfer catalyst to improve the reaction[11] and (2) stability of intermediate **B** to inhibit the β-hydride elimination.

Scheme 2. Controlled Experiments and Possible Mechanism



In summary, a palladium-catalyzed tandem Heck protocol has been described for selectively synthesizing 1,3-diaryl propenes in moderate to good yields. Importantly, this protocol could be applied in indole and benzofuran preparation. Work to extend the reaction in organic synthesis is currently underway.

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Supporting Information Available. Analytical data and spectra (^1H and ^{13}C NMR) for all the products and typical procedure. This material is available free of charge via the Internet at http://pubs.acs.org.