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Palladium-Catalyzed 1,1- Aryloxygenation of Terminal Olefins

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Abstract

This paper describes the 1,1-aryloxylation of diverse α -olefins using organostannanes and hypervalent iodine oxidants. The reaction provides a convergent approach for generating a C–C and a C–O bond as well as a new stereocenter in a single catalytic transformation.

The coupling of olefins with aryl-metal species in the presence of a terminal oxidant (the oxidative Heck reaction) is an important method for the formation of substituted alkenes.¹ This reaction proceeds via a pathway involving: transmetalation, olefin insertion (to generate intermediate **C**; Scheme 1), β -hydride elimination/olefin dissociation (to release **G**), and finally oxidation of Pd^0 to regenerate the Pd^{II} catalyst.¹ Work from our group² and others^{3,4,5,6} has shown that oxidative Heck intermediate **C** (or the related species **D**) can be intercepted to form 1,2- and 1,1-difunctionalized products such as **F** and **H**, respectively. These arylfunctionalization reactions combine the C–C bond-forming step of the oxidative Heck reaction with the generation of an additional bond and a new stereocenter. As such, they provide an attractive means for the convergent coupling of three components (**A**, **B**, and **E**) in a single transformation.⁷

We have recently utilized this approach for the Pd-catalyzed 1,2- and 1,1-aryloxylation of unactivated olefins using arylstannanes in conjunction with halide-based oxidants.² We sought to expand this methodology to analogous aryloxygenations of diverse alkene substrates.⁸ We report herein the development and scope of a Pd-catalyzed reaction for the 1,1-aryloxygenation of olefins using organostannane transmetallating reagents and hypervalent iodine oxidants.

Iodobenzene diacetate [$\text{PhI}(\text{OAc})_2$] has been widely used to oxidatively functionalize Pd^{II} alkyl intermediates formed in catalytic sp^3 C–H activation,⁹ olefin nucleopalladation^{10,11} and Pd-catalyzed cascade reactions.¹² We reasoned that this reagent could promote a similar transformation in the context of oxidative Heck intermediates **C** and/or **D** (Scheme 1). Thus, the reaction of 2-(hex-3-en-1-yl)isoindoline 1,3-dione (**1**) with PhSnBu_3 was examined in the presence of 2 equiv of $\text{PhI}(\text{OAc})_2$. Gratifyingly, the Pd^{II} catalyst $\text{PdCl}_2(\text{PhCN})_2$ provided 1,1-phenylacetoxylated product **2** in 50% yield in diethyl ether at rt (Table 1, entry 1). None of the corresponding 1,2-aryloxylation isomer was detected; however, a significant quantity (21% yield) of the Heck product **3** was formed under these conditions.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Several strategies were examined to limit formation of **3**. First, we used LiBr as an additive, since this salt has been shown to suppress β -hydride elimination/alkene dissociation pathways in other Pd-catalyzed transformations.¹³ Gratifyingly, the addition of 1 equiv of LiBr to the room temperature reaction in Et₂O increased the yield of **2** (to 59%), while decreasing that of **3** (to 16%) (Table 1, entry 3). A similar improvement was also observed in toluene (entries 2 and 4).

Lowering the temperature of the toluene reaction also decreased formation of Heck product **3**. For example, when the reaction mixture was stirred for 4 h at $-78\text{ }^{\circ}\text{C}$ and then slowly warmed to rt, product **2** was formed in 66% yield along with only 19% of **3** (entry 7). The combination of LiBr and low temperature further minimized the formation of **3** (entry 8); however, the yield of **2** did not improve, due to the generation of significant quantities of the corresponding arylbrominated product.¹⁴

With these optimized conditions in hand (Table 1, entry 7), we next explored the scope of this reaction. A number of electronically different arylstannanes were effective arylating reagents (Table 2). For example, ArSnBu₃ derivatives containing both electron-donating (entries 3, 4) and electron withdrawing (entries 6–8) *para*-substituents provided reasonable to good yields. In comparison, *ortho*-substituted arylstannanes showed modest reactivity. For example, *p*-MeOC₆H₄SnBu₃ afforded 75% yield of 1,1-arylacetoxylation (entry 4), while the analogous *o*-MeO-substituted stannane provided 35% yield of the corresponding product (entry 5).

Iodine(III) reagents of general structure PhI(O₂CR')₂ could be used to introduce diverse carboxylates. These oxidants are readily prepared by reacting commercially available PhI(OAc)₂ with 2 equiv of R'CO₂H in chlorobenzene.¹⁵ As shown in Table 2, acetate, trifluoroacetate, pivalate, and benzoate-containing products could be accessed in moderate to good yields (entries 4, 9, 10, and 11). Furthermore, substituted benzoate derivatives (containing both electron withdrawing and electron donating *para*-substituents) afforded comparable results (entries 12 and 13).

This 1,1-arylacetoxylation reaction was also effective across a wide range of terminal olefin substrates. For example, alkenes containing remote protected alcohol derivatives (Table 3, entries 1–3, 6–7) as well as alkyl bromides (entry 4) and aryl iodides (entry 5) were effective substrates in these transformations. Allylic ethers and acetates (entries 8–9) also afforded 1,1-arylacetoxylation products in good yield. Interestingly, products derived from β -acetoxy elimination (which is typically fast at Pd^{II} in the absence of Ag^I additives)^{16,17,18} were not detected in these latter systems.

All of the substrates in Table 3 reacted with >20: 1 selectivity for the 1,1-regioisomer. These results suggest that the oxidative functionalization of intermediate **C** (Scheme 1) with PhI(OAc)₂ is significantly slower than β -hydride elimination/equilibration to form Pd^{II}-benzyl complex **D**.² We reasoned that analogous 1,2-arylacetoxylation products might be accessible if the initially-formed Pd^{II} alkyl complex **C** was more reactive towards oxidative functionalization. Indeed, when *p*-methoxystyrene was utilized as the alkene substrate with *p*-FC₆H₄SnBu₃, the 1,2-arylacetoxylation product **13** was obtained with >20: 1 selectivity (Scheme 2). In this case the 1,2-product is formed because intermediate **C** is a Pd-benzyl complex, which are known to be highly reactive towards oxidative functionalization.^{2,19}

Vinyl ether substrates were also examined in this context. In these systems, the initially formed α -alkoxy-alkyl Pd intermediate **C-a** (Scheme 3) is expected to be highly electron rich. As such, we anticipated that the relative rate of oxidative functionalization with PhI(OAc)₂ (to form the 1,2-product) might be faster than that of β -hydride elimination. Gratifyingly, the use of ethyl, cyclohexyl and *t*-butyl vinyl ether under our standard reaction

conditions afforded excellent yields of the 1,2-arylacetoxylation products **14–16**, respectively.²⁰ Interestingly, 2,3-dihydrofuran afforded a somewhat different result, providing the 1,4-arylacetoxylation product **17** in 68% yield as a 1.3: 1 mixture of the cis and trans isomers (Scheme 4). This latter reaction is believed to proceed via initial carbopalladation to place the aryl group α to oxygen. A series of β -H elimination/Pd-H reinsertion reactions then generates an alkyl Pd complex at the 4-position, which undergoes rapid oxidative cleavage with $\text{PhI}(\text{OAc})_2$ to afford **17**.

The current reaction provides a straightforward route to products such as **3–17**. However, the requirement for toxic tin reagents (and the generation of toxic Sn-containing by-products) is a clear limitation. A highly attractive alternative would be to use a simple C–H substrate like benzene as the arene precursor. In this case, intermediate **C** could be formed via C–H activation of Ph–H followed by olefin insertion (the first two steps of the Fujiwara-Moritani reaction for benzene olefination).^{1b,6,18c} Gratifyingly, a preliminary screen of conditions showed that $\text{Pd}(\text{acac})_2$ is an effective catalyst for the coupling of allyl acetate with benzene and $\text{PhI}(\text{OAc})_2$. The reaction proceeds efficiently at 60 °C in benzene in the presence of 0.1 equiv of AgOAc to afford the 1,1-phenylacetoxylation product **18** in 51% (Scheme 5). Further studies of the scope and limitations of this transformation are underway.

In summary, this paper describes the 1,1-arylacetoxylation of diverse α -olefins using organostannanes and hypervalent iodine oxidants. The reaction provides a convergent approach for merging these three components, and it generates a C–C and a CO bond as well as a new stereocenter in a single catalytic transformation. Preliminary results also indicate that the aryl tin reagents can be replaced by simple arene derivatives. Ongoing work is focused on fully exploring the scope of alternative arylating reagents and oxidants that can be utilized for this and related alkene functionalization reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Oxidatively Intercepting Heck Intermediates

Scheme 2.
1,2-Arylacetoxylation with *p*-Methoxystyrene

Scheme 3.**1,2-Arylacetoxylation with Vinyl Ether Substrates**

Yields determined by ¹H NMR spectroscopic analysis of crude reaction mixtures; isolated yields were significantly lower due to decomposition of the mixed acetal products on silica gel. See Supporting Information for full details.

Scheme 4.
1,4-Arylacetoxylation of 2,3-Dihydrofuran

Scheme 5.

1,1-Phenylacetoxylation via Benzene C-H Activation

Table 1

Optimization of 1,1-Arylacetoxylation Reaction

entry	solvent	temp (°C)	additive ^a	yield 2 ^{b, c}	yield 3 ^b
1	Et ₂ O	rt	none	50%	21%
2	PhMe ^d	rt	none	22%	34%
3	Et ₂ O	rt	LiBr	59%	16%
4	PhMe ^d	rt	LiBr	35%	29%
5	Et ₂ O	-78 °C to rt	none	51%	13%
6	Et ₂ O	-78 °C to rt	LiBr	25%	7%
7	PhMe ^d	-78 °C to rt	none	66%	19%
8	PhMe ^d	-78 °C to rt	LiBr	62%	12%

^a 1 equiv of additive.

^b Yield of products determined by ¹H NMR spectroscopic analysis of crude reaction mixture. In most reactions, the mass balance was 5–20% of the 1,1-arylchlorinated product. The chloride is presumably derived from the Pd catalyst. When LiBr was present, 5–17% of the 1,1-aryl/brominated product was observed. See Supporting Information for complete optimization table.

^d Degassed toluene was used.

Table 2

Scope of Organostannanes and Iodoarene Dicarboxylates

entry	Aryl	R'	isolated (crude) yield ^a
1	C ₆ H ₅	CH ₃	66% (66%) ^b
2	2-naphthyl	CH ₃	52% (62%)
3	<i>p</i> -MeC ₆ H ₄	CH ₃	59% (68%)
4	<i>p</i> -MeOC ₆ H ₄	CH ₃	75% (78%)
5	<i>o</i> -MeOC ₆ H ₄	CH ₃	35% (51%)
6	<i>p</i> -ClC ₆ H ₄	CH ₃	56% (63%)
7	<i>p</i> -BrC ₆ H ₄	CH ₃	50% (57%)
8	<i>p</i> -FC ₆ H ₄	CH ₃	49% (56%)
9	<i>p</i> -MeOC ₆ H ₄	CF ₃	41% (49%) ^c
10	<i>p</i> -MeOC ₆ H ₄	<i>t</i> -Bu	48% (55%)
11	<i>p</i> -MeOC ₆ H ₄	C ₆ H ₅	60% (72%)
12	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -MeOC ₆ H ₄	53% (52%)
13	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -FC ₆ H ₄	68% (73%)

^a Crude yields of products determined by ¹H NMR spectroscopic analysis of crude reaction mixture. In most reactions, the mass balance was the Heck product **3** (5–20%) and the 1,1-arylchlorinated product (5–15%).

^b At 1 mmol scale, the reaction afforded 68% isolated yield

^c The trifluoroacetate product was observed by ¹H NMR analysis of the crude reaction mixture; however, it hydrolyzed upon chromatographic purification and was isolated as the free alcohol.

Table 3

Substrate Scope for 1,1-Arylacetoxylation

Entry	substrate	product	isolated (crude) yield
1			62% (64%)
2			61% (62%)
3			47% (54%)
4			53% (61%)
5			64% (67%)
6			67% (72%)
7			62% (62%)
8			64% (71%)

Entry	substrate	product	isolated (crude) yield
9			58% (69%)
(12)			

^aCrude yields of products determined by ^1H NMR spectroscopic analysis of crude reaction mixture. In most reactions 5–15% of the corresponding Heck product formation was observed along with <5% of the 1,1-arylchlorinated product.