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Palladium-Catalyzed 1,1-Aryloxygenation of Terminal Olefins

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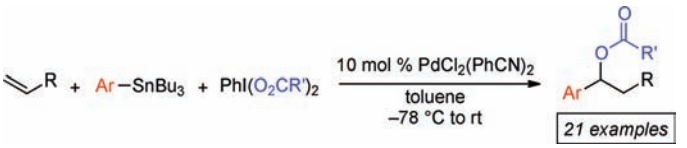
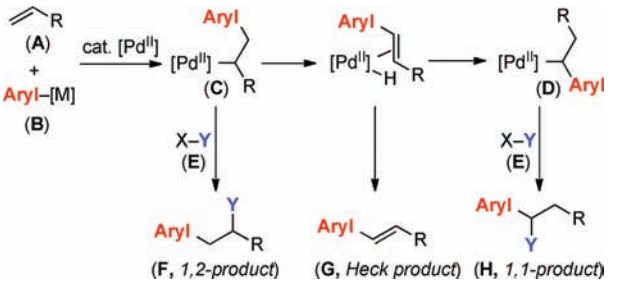
ABSTRACT



This paper describes the 1,1-arylacetoxylation 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 group[2] and others[3−6] 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]

Scheme 1. Oxidatively Intecepting Heck Intermediates



We have recently utilized this approach for the Pd-catalyzed 1,2- and 1,1-arylhalogenation of unactivated olefins using arylstannanes in conjunction with halide-based oxidants.[2] We sought to expand this methodology

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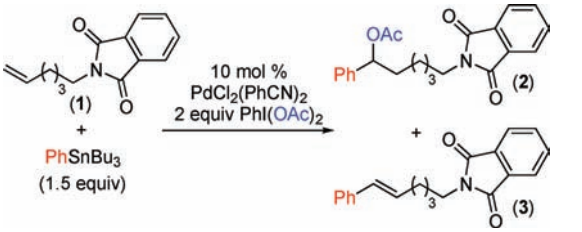
to analogous aryloxygenations of diverse alkene substrates.[8] We report herein the development and scope of a Pd-catalyzed reaction for the 1,1-aryloxygenation of olefins using organostannane transmetallating reagents and hypervalent iodine oxidants.

Iodobenzene diacetate [$PhI(OAc)_2$] 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 $PhI(OAc)_2$. Gratifyingly, the Pd^{II} catalyst $PdCl_2(PhCN)_2$ provided 1,1-phenylacetoxylated product **2** in 50% yield in diethyl ether at rt (Table 1, entry 1). None of the corresponding 1,2-arylacetoxylated isomer was detected; however, a significant quantity (21% yield) of the Heck product **3** was formed under these conditions.

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 Et_2O 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 °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]

Table 1. Optimization of 1,1-Arylacetoxylation Reaction



entry	solvent	temp (°C)	additive[a]	yield **2**[b]	yield **3**[b]
1	Et_2O	rt	none	50%	21%
2	PhMe[c]	rt	none	22%	34%
3	Et_2O	rt	LiBr	59%	16%
4	PhMe[c]	rt	LiBr	35%	29%
5	Et_2O	−78 °C to rt	none	51%	13%
6	Et_2O	−78 °C to rt	LiBr	25%	7%
7	PhMe[c]	−78 °C to rt	none	66%	19%
8	PhMe[c]	−78 °C to rt	LiBr	62%	12%

[a] One equivalent 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-arylbrominated product was observed. See Supporting Information for complete optimization table. [c] Degassed toluene was used.

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, $ArSnBu_3$ 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*-$MeOC_6H_4SnBu_3$ 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 $PhI(O_2CR')_2$ could be used to introduce diverse carboxylates. These oxidants are readily prepared by reacting commercially available $PhI(OAc)_2$ with 2 equiv of $R'CO_2H$ 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

(8) A related strategy for the aryloxygenation of α,β-unsaturated olefins is reported in ref 6.

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(14) The use of degassed toluene also enhanced the yield of **2**. For example, when the reaction in Table 1, entry 7 was run in nondegassed toluene, **2** was formed in 42% yield along with 29% of **3**.

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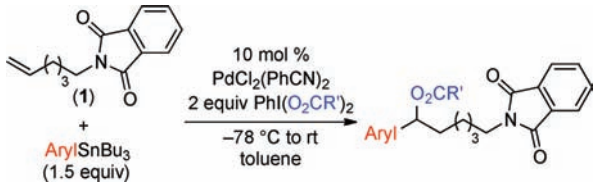
Table 2. Scope of Organostannanes and Iodoarene Dicarboxylates



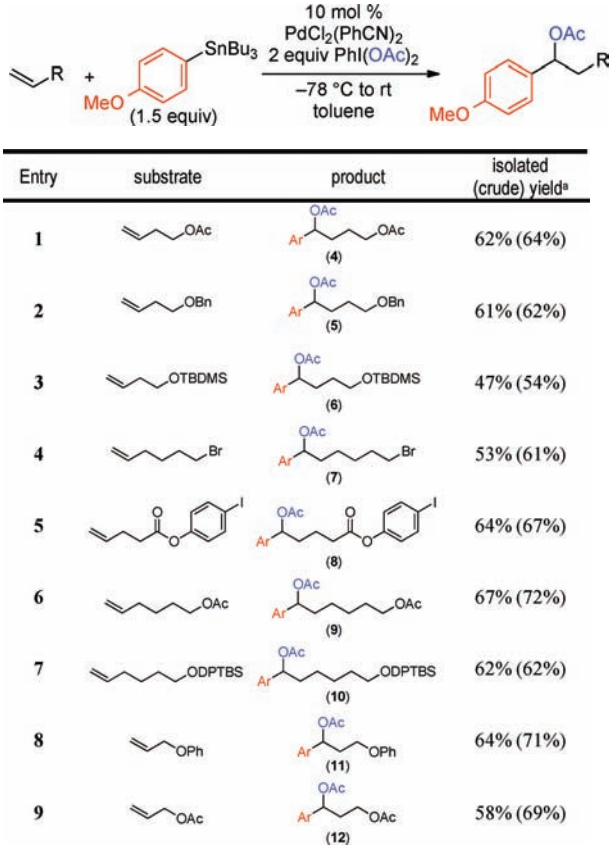
entry	aryl	R′	isolated (crude) yield[a]
1	C_6H_5	CH_3	66% (66%)[b]
2	2-napthyl	CH_3	52% (62%)
3	*p*-MeC_6H_4	CH_3	59% (68%)
4	*p*-$MeOC_6H_4$	CH_3	75% (78%)
5	*o*-$MeOC_6H_4$	CH_3	35% (51%)
6	*p*-ClC_6H_4	CH_3	56% (63%)
7	*p*-BrC_6H_4	CH_3	50% (57%)
8	*p*-FC_6H_4	CH_3	49% (56%)
9	*p*-$MeOC_6H_4$	CF_3	41% (49%)[c]
10	*p*-$MeOC_6H_4$	*t*-Bu	48% (55%)
11	*p*-$MeOC_6H_4$	C_6H_5	60% (72%)
12	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	53% (52%)
13	*p*-$MeOC_6H_4$	*p*-FC_6H_4	68% (73%)

[a] Crude yields of products determined by ^{1}H 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] Reaction conducted on 0.22 mmol scale. The isolated yield was 68% at 1 mmol scale. [c] The trifluoroacetate product was observed by ^{1}H NMR analysis of the crude reaction mixture; however, it hydrolyzed upon chromatographic purification and was isolated as the free alcohol.

substrates in these transformations. Allylic ethers and acetates (entries 8−9) also afforded 1,1-arylacetoxylated 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)[16−18] 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-arylacetoxylated products might be accessible if the initially formed Pd^{II} alkyl complex **C** was more reactive toward oxidative functionalization. Indeed, when *p*-methoxystyrene was utilized as the alkene substrate with *p*-$FC_6H_4SnBu_3$, the 1,2-arylacetoxylation product **13** was obtained with >20:1 selectivity (Scheme 2). In this case, the 1,2-product is

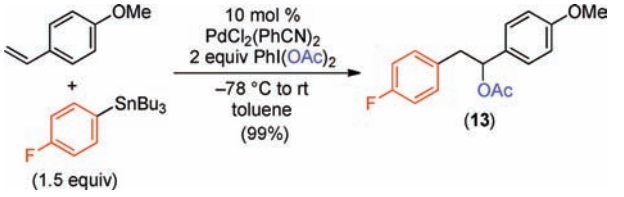
Table 3. Substrate Scope for 1,1-Arylacetoxylation



[a] Crude yields of products determined by ^{1}H 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.

formed because intermediate **C** is a Pd-benzyl complex, which are known to be highly reactive toward oxidative functionalization.[2,19]

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



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

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(17) Pan, D.; Jiao, N. *Synlett* **2010**, 1577.
(18) For examples of selective β-H elimination in Heck-type reactions using allyl acetate substrates see: (a) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729. (b) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980. (c) Pan, D.; Yu, M.; Chen, W.; Jiao, N. *Chem. Asian J.* **2010**, *5*, 1090. For examples of selective β-OAc elimination in Heck-type reactions using allyl acetate substrates see:(d) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745. (e) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276.

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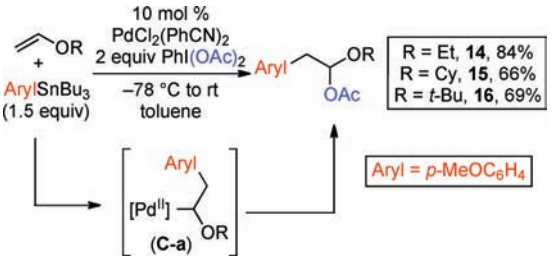
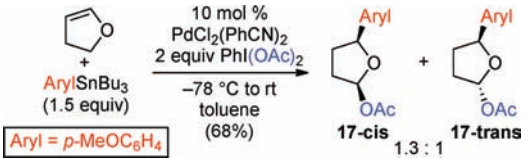
Scheme 3. 1,2-Arylacetoxylation with Vinyl Ether Substrates[a]



[a] Yields determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures; isolated yields were significantly lower due to decomposition of the mixed acetal products on silica gel.

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-arylacetoxylated products **14**−**16**, respectively.[20] Interestingly, 2,3-dihydrofuran afforded a somewhat different result, providing the arylacetoxylated 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 5-position, which undergoes rapid oxidative cleavage with $PhI(OAc)_2$ to afford **17**.

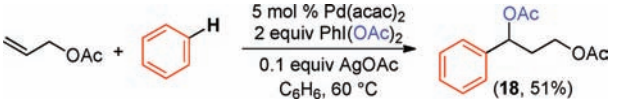
Scheme 4. Arylacetoxylation of 2,3-Dihydrofuran



See Supporting Information for full details.

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 byproducts) 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 $Pd(acac)_2$ is an effective catalyst for the coupling of allyl acetate with benzene and $PhI(OAc)_2$. 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% yield (Scheme 5). Further studies of the scope and limitations of this transformation are underway.

Scheme 5. 1,1-Phenylacetoxylation via Benzene C−H Activation



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 C−O 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.

Acknowledgment. We thank Dr. Dipannita Kalyani for preliminary studies of this transformation. This work was supported by NIH NIGMS (R01-GM073836).

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.

(20) For an alternative approach to the 1,2-aryloxygenation of olefins, see: (a) Heinrich, M. R.; Wetzel, A.; Kirschstein, M. *Org. Lett.* **2007**, *9*, 3833. (b) Lazzaroni, S.; Protti, S.; Fagnoni, M.; Albini, A. *Org. Lett.* **2009**, *11*, 349.