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Oxidatively Intercepting Heck Intermediates: Pd-Catalyzed 1,2- and 1,1-Arylhalogenation of Alkenes

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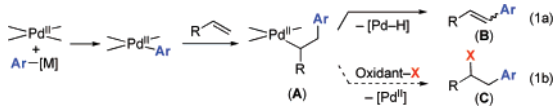
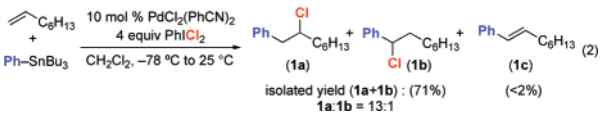
Palladium-catalyzed cascade reactions are widely used for the assembly of complex organic molecules.[1] These transformations frequently involve σ-alkyl Pd^{II} intermediates that are formed by Heck-type olefin insertion into a Pd−aryl bond (**A** in eq 1).[1] Such intermediates are typically intercepted by olefin/alkyne insertion[2] or CO insertion[2] to afford valuable functionalized products. In contrast, selective and high yielding approaches to the direct oxidative functionalization of Heck intermediates remain rare.[3] Such reactions would be particularly valuable, as they would allow direct conversion of the Pd−C bond of **A** into diverse C−X bonds (X = Cl, Br, I, F, O, N, and/or C, eq 1b).

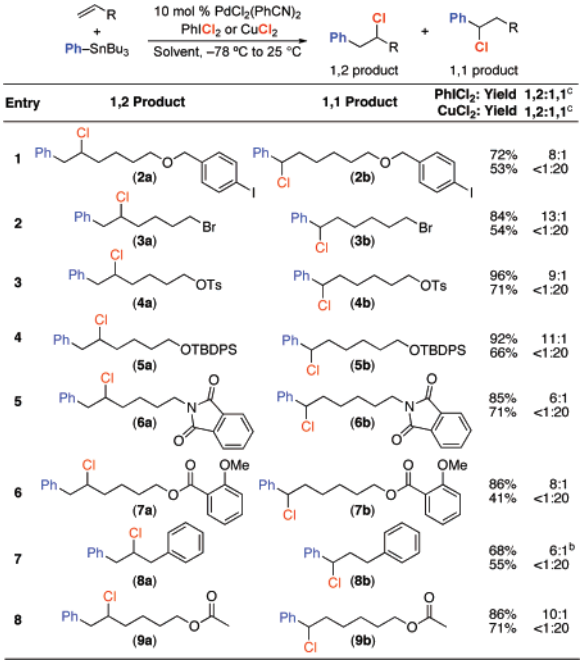


An early report by Heck described the oxidative halogenation of intermediates of general structure **A** to form 1,2-arylhalogenated compounds (**C**, X = Cl).[3a] However, competing formation of alkene products (via β-hydride elimination followed by olefin dissociation, eq 1a) severely limited the scope, yields, and overall synthetic utility of these transformations. Recently, we and others have demonstrated that Pd−alkyl species generated through C−H activation,[4] olefin aminopalladation,[5] or enyne cyclization[6] can be oxidatively intercepted using iodine(III) reagents. Importantly, with appropriate selection of oxidant and reaction conditions, these transformations proceed with little to no formation of β-hydride elimination products.[4−6] On the basis of this work, we reasoned that highly reactive iodine(III) oxidants such as $PhICl_2$ might be effective at out-competing β-hydride elimination from Heck intermediates. *We describe herein the successful application of this strategy to the Pd-catalyzed 1,2-arylchlorination of* α*-olefins. In addition, we report that isomeric 1,1-arylchlorinated products can be obtained in high yields simply by tuning the electrophilic chlorinating reagent.* This report discusses the scope, mechanism, and origin of the intriguing reversal of selectivity in these reactions.



Our initial studies focused on the Pd-catalyzed reaction of 1-octene and $PhSnBu_3$ (eq 2). We were delighted to find that under optimal conditions (10 mol % of $PdCl_2(PhCN)_2$, 4 equiv of $PhICl_2$, and 2.6 equiv of $PhSnBu_3$ in CH_2Cl_2 at −78 °C) this reaction provided the desired 1,2-phenylchlorinated product **1a** in 72% yield (as determined by ^1H NMR spectroscopy). Remarkably, only traces (<2%) of alkene product **1c** were observed in the crude reaction mixture. Instead, the major side product was the corresponding 1,1-isomer **1b** (obtained in 6% yield by ^1H NMR). As shown in Table 1, this reaction could be applied to a wide variety of α-olefin substrates. In all cases, the 1,2-phenylchlorinated compounds were obtained with good to excellent selectivity, and <10% of products derived from β-hydride elimination/alkene dissociation were observed. Furthermore, these reactions were compatible with many common organic functional groups, including amides, silyl ethers, esters, and benzylic hydrogens, as well as alkyl and aromatic halides.

Table 1. Substrate Scope for Phenylchlorination Reactions[a]



Entry	1,2 Product	1,1 Product	$PhICl_2$: Yield 1,2:1,1[c] / $CuCl_2$: Yield 1,2:1,1[c]
1	(2a)	(2b)	72% 8:1 / 53% <1:20
2	(3a)	(3b)	84% 13:1 / 54% <1:20
3	(4a)	(4b)	96% 9:1 / 71% <1:20
4	(5a)	(5b)	92% 11:1 / 66% <1:20
5	(6a)	(6b)	85% 6:1 / 71% <1:20
6	(7a)	(7b)	86% 8:1 / 41% <1:20
7	(8a)	(8b)	68% 6:1[b] / 55% <1:20
8	(9a)	(9b)	86% 10:1 / 71% <1:20

[a] Conditions: 10 mol % of $PdCl_2(PhCN)_2$, 2−4 equiv of $PhICl_2$, 2.6 equiv of $PhSnBu_3$, CH_2Cl_2, −78 to 25 °C or 10 mol % of $PdCl_2(PhCN)_2$, 4 equiv of $CuCl_2$, 1.3 equiv of $PhSnBu_3$, Et_2O, −78 to 25 °C. [b] Reaction at 0 °C in CH_3NO_2/Et_2O (1:1). [c] Isolated yields and selectivities.

As discussed above, 1,1-arylchlorinated isomers were observed as minor side products in the reactions with $PhICl_2$. However, intriguingly, when $PhICl_2$ was substituted with less reactive electrophilic chlorinating reagents such as *N*-chlorosuccinimide or $CuCl_2$,[7a] the reaction of 1-octene and $PhSnBu_3$ afforded *only* the 1,1-phenylchlorinated product **1b**, albeit in low (4 and 13%) yields.[7] Subsequent optimization revealed that, with $CuCl_2$ as the oxidant, simply changing the solvent from CH_2Cl_2 to Et_2O resulted in exclusive formation of **1b** in 50% isolated yield.[8] Furthermore, this Pd-catalyzed 1,1-phenylchlorination with $CuCl_2$ was also general and highly selective across a wide range of functionally diverse α-olefins (Table 1). Importantly, only minimal (<10%) amounts of alkenes derived from β-hydride elimination/olefin dissociation were observed. *These results show that two different, synthetically useful products can be accessed selectively simply by changing the oxidant in these reactions.*

We propose the mechanistic manifold outlined in eq 3 to account for the formation of 1,2- and 1,1-arylchlorinated products **C** and

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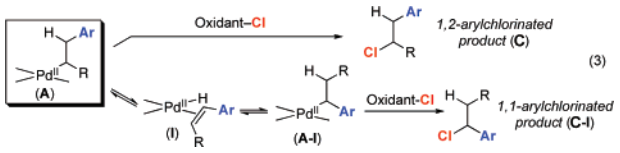
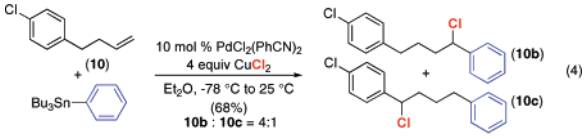
C-I in these transformations. With highly reactive $PhICl_2$ as the electrophilic chlorinating reagent, the oxidative halogenation of Heck intermediate **A** is believed to be significantly faster than competing β-hydride elimination, providing isomer **C** as the predominant product. We hypothesize that the small quantity of isomer **C-I** observed in these reactions is formed from Pd−alkyl intermediate **A-I** via β-hydride elimination from **A**, reinsertion to generate **A-I**, and finally oxidative functionalization of **A-I** with $PhICl_2$.[9]



(3)

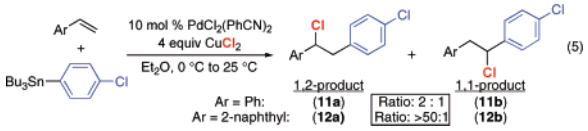
In contrast, we propose that with less electrophilic oxidants (e.g., $CuCl_2$)[7a] the rate of β-hydride elimination is significantly faster than that of oxidative functionalization, allowing rapid equilibration between **A** and **A-I**. In this scenario, the observed selectivity for the 1,1-product (**C-I**) would derive from selective chlorination of Pd−benzyl intermediate **A-I** versus Pd−alkyl intermediate **A**.[10] Initial support for this proposal was obtained by studies of the Pd-catalyzed reaction between $CuCl_2$ and 1-octene-(1,1-d_2). The isolated product **1b-*d*$_2$** contained a single D at the 1-position and a single D at the 2-position, as predicted based on a β-deuteride elimination/reinsertion/oxidative cleavage pathway such as that in eq 3 (see Supporting Information for full details).

To further probe this hypothesis, we examined the Pd-catalyzed phenylchlorination of 4-(4-chlorophenyl)-1-butene (**10**) with $CuCl_2$ under our standard conditions. As shown in eq 4, this reaction afforded two isomeric phenylchlorinated products—1,1-functionalized **10b** and 1,4-functionalized **10c**—in a 4:1 ratio. The formation of **10c** (which requires the Pd to migrate two carbons down the alkyl chain) provides strong evidence in support of equilibrating β-hydride elimination/reinsertion steps prior to oxidative cleavage. In addition, the sole formation of **10b** and **10c** (as opposed to isomers resulting from chlorination at other positions along the alkyl chain) further supports the proposed preference for benzylic functionalization with $CuCl_2$.



(4)

We hypothesized that the selectivity for benzylic chlorination in the $CuCl_2$ reactions might arise from equilibration of σ-benzyl Pd intermediate **A-I** with the corresponding π-benzyl Pd species (**A-I**π).[11] A π-benzyl interaction could lead to increased amounts of the 1,1-product by shifting the equilibrium between σ-alkyl complex **A** and **A-I**/**A-I**π to the right and/or by increasing the rate of oxidative chlorination of **A-I**/**A-I**π versus **A**.[11] To investigate this further, the Pd-catalyzed reactions of styrene and of 2-vinylnaphthalene with *p*-Cl−$PhSnBu_3$ and $CuCl_2$ were compared under identical conditions (eq 5). In both cases, initial alkene insertion would directly generate a Pd−benzyl or Pd−naphthyl intermediate; therefore, significant quantities of 1,2-arylchlorinated products **11a** and **12a** were expected (and observed) in both transformations. However, while the ratio of 1,2-/1,1-products with styrene was 2:1, the corresponding reaction with vinylnaphthalene provided a >50:1 ratio of **12a**/**12b**. Literature reports have shown that π-naphthyl complexes are both more thermodynamically stable and more kinetically reactive than the corresponding π-benzyl species.[11c] As such, this large difference between vinylnaphthalene and styrene provides support for π-aryl stabilization as a key factor in the selectivity of these $CuCl_2$-mediated arylchlorinations.



(5)

In summary, we have developed two Pd-catalyzed reactions for the arylchlorination of α-olefins by oxidatively intercepting Heck intermediates. Depending on the nature of the oxidant and the reaction conditions, both 1,1- and 1,2-arylchlorinated products can be obtained in good yield and selectivity. Furthermore, the selectivity of these reactions can be rationally tuned by controlling the relative rates of oxidative functionalization versus β-hydride elimination from equilibrating Pd^{II}−alkyl species and by π-benzyl stabilization of Pd intermediates. Future work will apply insights from these studies to a broad scope of oxidants and transmetalating reagents. In addition, studies are underway to gain further insights into the mechanism of these transformations.

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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.

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