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Palladium-Catalyzed Oxidative Arylhalogenation of Alkenes: Synthetic Scope and Mechanistic Insights

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Abstract

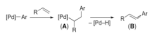
This article describes the development of a Pd-catalyzed reaction for the arylhalogenation (halogen = Cl or Br) of diverse α-olefins by oxidatively intercepting Mizoroki-Heck intermediates. These transformations afford synthetically useful 1,2- and 1,1-arylhalogenated products in good yields with good to excellent selectivities that can be modulated by changing the nature of the halogenating reagent and/or the reaction conditions. The selectivity of these reactions can be rationally tuned by: (i) controlling the relative rates of oxidative functionalization versus β-hydride elimination from equilibrating Pd^{II}-alkyl species and (ii) stabilization of organometallic Pd^{II} intermediates through the formation of π-benzyl adducts. These arylhalogenations exhibit modest to excellent levels of stereospecificity, and the key carbon-halogen bond-forming step proceeds with predominant retention of stereochemistry at carbon.

Keywords

Alkene; Arylhalogenation; Palladium; Catalysis; Heck; Mechanism; π-benzyl

Introduction

The Mizoroki-Heck reaction involves the Pd-catalyzed coupling of an alkene with an aryl halide or aryl metal species.1 This transformation is widely used in organic synthesis for the construction of carbon–carbon bonds,2 and significant effort has been devoted to both catalyst development1⁻3 and mechanistic investigations.1⁻4 As shown in eq. 1, the general mechanism of the Heck reaction involves formation of a σ-aryl Pd species followed by olefin insertion to generate σ-alkyl Pd intermediate **A** and then β-hydride elimination/olefin dissociation to release product **B**.



(1)

Methods for intercepting Mizoroki-Heck intermediate **A** via other fundamental organometallic reactions would provide attractive routes for the 1,2-arylfunctionalization of α-olefins (eq. 2). Such transformations would complement the traditional Mizoroki-Heck reaction by providing access to products containing one additional bond and one additional stereocenter as compared to **B**. Some success has been realized in this area by trapping

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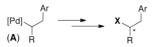
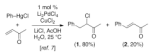
intermediate **A** via alkene, alkyne, or CO insertion.5,6 However, the scope, generality, and range of products accessible from these reactions remains limited, in large part because the relative rate of β-hydride elimination to form **B** is often competitive in these processes.



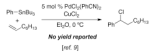
(2)

On the basis of our interest in high oxidation state palladium chemistry, we thought that oxidation of **A** would provide an attractive alternative route for intercepting this intermediate. Indeed, very early studies by Heck demonstrated the feasibility of this transformation. For example, in 1968, he reported the Pd-catalyzed reaction of methylvinylketone with PhHgCl and $CuCl_2$ to afford 1,2-arylchlorination product **1** in 80% yield (eq. 3).7 However, the overall synthetic utility of this transformation was limited by a modest substrate scope, competing β-hydride elimination/olefin dissociation (to form **2**), and the requirement for aryl mercury reagents.



(3)

Sporadic subsequent reports have also suggested that Heck intermediate **A** can be intercepted under oxidative conditions to generate 1,1-difunctionalized products.8 For example, Tamaru and coworkers demonstrated the palladium-catalyzed 1,1-phenylchlorination of 1-octene with $PhSnBu_3$ in the presence of $CuCl_2$ (eq. 4).9,10 However, the yield of this transformation was not reported, and 1-octene was the only substrate examined.11 More recently, a similar Pd-catalyzed 1,1-phenylchlorination product **4** was unexpectedly observed in the reaction between **3**, $PhSnBu_3$, and $CuCl_2$ (eq. 5).12 Again, this was an isolated example, and the reaction was not explored further.



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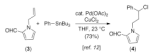
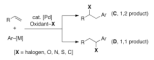


(5)

These prior studies suggested that it might be possible to develop oxidative transformations for the predictable and selective conversion of α-olefins into 1,2 or 1,1-arylfunctionalized products of general structures **C** and **D** (eq. 6). Recent work from our group and others has shown that σ-alkyl Pd intermediates related to **A** can be intercepted with a wide variety of oxidants to install diverse functional groups, including C–Cl, C–Br, C–I, C–F, C–N, C–O, and C–C bonds. This has been demonstrated in the context of Pd-catalyzed ligand-directed C–H functionalization,13 where sp^3 C–H activation has been followed by oxidative halogenation,14 amination,15 oxygenation,16 and arylation.17 In addition, a variety of sequences involving amino-, oxy- or halopalladation of olefins to generate σ-alkyl Pd intermediates followed by oxidative halogenation,18,19 amination,20 oxygenation,21 and arylation22 have been developed to afford diverse organic products.



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We report herein the implementation of this strategy in the development of general oxidative Mizoroki-Heck reactions for the 1,2- and 1,1-arylhalogenation of alkenes.23 The full scope of both 1,2-and 1,1-arylchlorination and bromination reactions is described. Additionally, investigations of the mechanism and the stereospecificity of these transformations are discussed in detail.

Results

Reaction Design

In order to develop general and robust conditions for alkene arylfunctionalization, we needed a working mechanistic hypothesis for the formation of each of the products. As shown in Scheme 1, the Heck product **B** is known to be generated from σ-alkyl Pd intermediate **A** via β-hydride elimination/olefin dissociation. The 1,2-arylfunctionalization product **C** could be formed by direct oxidative functionalization of **A**. Finally, the isomeric 1,1-product **D** could derive from **A** via a sequence involving β-hydride elimination, olefin insertion with opposite regiochemistry, and finally oxidative functionalization of the resulting Pd-benzyl complex (**E**) (Scheme 1). This mechanistic proposal suggests that the ratio of products **B, C**, and **D** should be tunable by modifying the relative rates of four fundamental organometallic transformations: oxidative functionalization, β-hydride elimination, olefin dissociation, and olefin insertion.

1,2-Arylchlorination Reactions

We reasoned that use of the highly reactive electrophilic chlorinating reagent $PhICl_2$ should increase the rate of oxidative functionalization of **A** relative to that of β-hydride elimination, thereby promoting formation of 1,2-product **C**. Thus, we first studied the Pd-catalyzed reaction between alkene **5**, $PhICl_2$, and $PhSnBu_3$24 in a variety of common solvents. Unexpectedly, the 1,1-product (**6b**) was the major isomer observed at room temperature in all solvents examined (Table 1, entries 1–5). The most promising initial lead was in CH_2Cl_2, which showed formation of significant quantities of **6a** (1 : 1.3 ratio of **6a : 6b**, 46% overall yield, entry 5). Lowering the temperature to −78 °C and increasing the reaction concentration to 0.064 M in CH_2Cl_2 led to a significant enhancement in both selectivity for and yield of **6a** (entry 8). The yield was improved further by increasing the amount of $PhSnBu_3$ from 1.3 to 2.6 equiv (entry 9). Ultimately, optimal conditions were found to be: 10 mol % of $PdCl_2(PhCN)_2$, 2 equiv of $PhICl_2$, 2.6 equiv of $PhSnBu_3$ in CH_2Cl_2 (0.064 M) starting at −78 °C with gradual warming over 5 h to 25 °C. This afforded a quantitative yield of **6** as a 10 : 1 mixture of isomer **6a : 6b** (entry 9).

These conditions proved general for the 1,2-arylchlorination of numerous α-olefins (Table 2). The reactions were tolerant of a wide variety of common functional groups, including esters, aromatic and alkyl halides, benzylic hydrogens, amides, and silyl ethers. Additionally, both electron rich and electron deficient arylstannanes were effective coupling partners. The products were obtained in good to excellent yields and with good selectivity for the 1,2-isomer. In general, the mass balance in these reactions consisted of small amounts of the 2,1-phenylchlorination, dichlorination, and/or β-hydride elimination products.

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1,1 Arylchlorination Reactions

We next sought conditions that would selectively provide 1,1-arylchlorinated products. The solvent screen in Table 1 showed that the reaction of **5** with $PhICl_2$ significantly favored formation of the 1,1-product **6b** in ethereal solvents. We reasoned that the use of a less reactive chlorinating reagent would further slow competing 1,2 functionalization and thus provide higher selectivity for **6b**. Gratifyingly, the use of NCS or $CuCl_2$ under otherwise identical conditions resulted in >20 : 1 selectivity for **6b** in a variety of solvents (Table 3). While the yields were modest at room temperature (ranging from 10–58%), they could be significantly improved by conducting the reactions at −78 °C. Under optimal conditions (10 mol % of $PdCl_2(PhCN)_2$, 4 equiv of $CuCl_2$, 1.3 equiv of $PhSnBu_3$ in Et_2O (0.032 M) starting at −78 °C with gradual warming over 5 h to 25 °C), **6b** was obtained in 82% yield and >20 : 1 selectivity as determined by ^{1}H NMR spectroscopy (entry 8).

The substrate scope of 1,1-arylchlorination with $CuCl_2$ was similar to that of the $PhICl_2$ reactions. Aryl stannanes and α-olefins containing diverse functional groups were effective coupling partners, and the 1,1-isomer was consistently obtained in >20 : 1 selectivity (Table 4). In all cases, <10% of alkene products derived from β-hydride elimination/alkene dissociation were observed by ^{1}H NMR spectroscopic analysis of the crude mixtures.25

1,2 and 1,1 Arylbromination Reactions

We next pursued analogous palladium-catalyzed arylbromination reactions using $CuBr_2$ and NBS as electrophilic brominating reagents ($PhIBr_2$ is not readily available).26,27 As shown in Table 5, NBS was poorly effective for this transformation. In contrast, $CuBr_2$ efficiently promoted the formation of both 1,1-arylbromination product **28b** and 1,2-arylbromination product **28a**. The isomer ratio in these $CuBr_2$-mediated reactions could be tuned by simply changing the solvent. For example, 1,1-product **28b** was formed in high (82%) yield and with >20 : 1 selectivity in Et_2O (entry 6). However, moving from Et_2O to THF under similar conditions resulted in a reversal of selectivity to afford **28a** as the major product **(28a : 28b** = 3 : 1), albeit in modest (49%) yield (Table 5, entry 8). This is in notable contrast to the trend observed for arylchlorination, where the use of $CuCl_2$ in THF favored 1,1-products. Subsequent optimization revealed that increasing the concentration to 0.128 M resulted in 80% yield of a 10 : 1 mixture of **28a : 28b** (entry 10). Under these conditions, the mass balance consisted of 29 (20% yield), which is the product of 1,2-addition of Ph and ring opened THF to the alkene.28

As shown in Table 6 and Table 7, the optimal conditions for formation of the 1,1- and 1,2-arylbrominated products were general for numerous α-olefins. These transformations exhibited a scope and functional group tolerance similar to the arylchlorination reactions. Notably, THF-addition products analogous to **29** were formed as significant by-products (5–20% yield as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures) in the 1,2-arylbrominations.29

Mechanistic Investigations: General Goals

We next turned our efforts to investigating the mechanism of these transformations. In particular, we sought to: (i) interrogate the proposed reaction pathways for formation of the 1,2- and the 1,1-products, (ii) understand the role of oxidant and solvent in imparting 1,2- versus 1,1 selectivity, (iii) gain mechanistic insights into the high selectivity for benzylic functionalization with $CuCl_2$ and $CuBr_2$ in Et_2O, and (iv) probe the stereochemical course of the key carbon-halogen bond-forming step of these transformations. The results of these mechanistic studies are detailed below, and their implications are discussed later in the manuscript.

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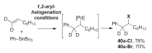
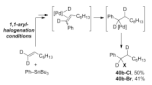
Deuterium Labeling

Deuterium labeled 1-octene-(1,1-d_2) was utilized as a substrate for both the 1,2- and 1,1-phenylhalogenations. Reaction with $PhICl_2$ or with $CuBr_2$/THF afforded **40a–Cl/Br** as the sole 1,2-phenylhalogenated products (eq. 7). Less than 5% deuterium incorporation was observed at any other site along the alkyl chain.



(7)

The reaction of 1-octene-(1,1-d_2) was also examined with $CuCl_2$ and $CuBr_2/Et_2O$. In both cases, **40b–Cl/Br** was the only 1,1-phenylhalogenated product formed (eq. 8). Again, less than 5% of other isomers were observed, indicating clean migration of the deuterium from the 1- to the 2-position.8



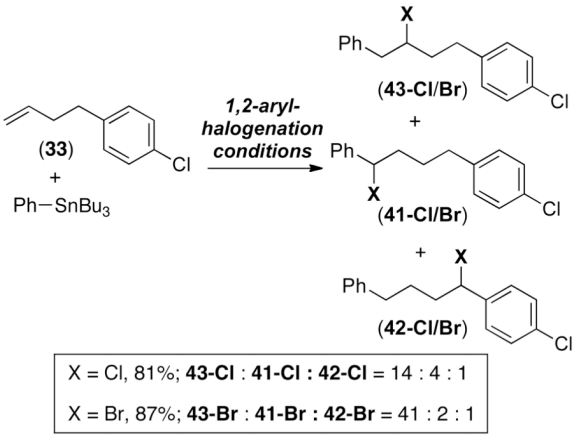
(8)

4-(4-Chlorophenyl)-1-butene

The reactivity of 4-(4-chlorophenyl)-1-butene (**33**) was examined under both 1,2- and 1,1-arylhalogenation conditions. With $CuCl_2$ and $CuBr_2/Et_2O$, mixtures of two isomeric products were formed (eq. 9). In both cases, the major isomer was the expected 1,1-product **41-Cl/Br**. However, a minor amount of a second benzylic halogenation product **42-Cl/Br** was also observed. The ratio of **41-Cl : 42-Cl** was 4 : 1 in the chlorination reaction and the ratio of **41-Br : 42-Br** was 7 : 1 under the bromination conditions as determined by ^1H NMR spectroscopic analysis of the crude reaction mixtures.

(9)

The use of $PhICl_2$ or $CuBr_2$/THF as the oxidant produced 1,2-arylhalogenated products **43-Cl/Br** in 62/81% crude yield (eq. 10). The analogous 1,1-products were also formed (17/4% crude yield) along with traces (2/2%) of the 1,4-arylfunctionalized compounds **42-Cl/Br** (eq. 10). Notably, isomers derived from chlorination/bromination at other sites in the middle of the alkyl chain were not detected in these transformations.



(10)

Styrene Substrates

The Pd-catalyzed reaction of 4-fluorostyrene with $PhSnBu_3$ under 1,2-arylhalogenation conditions afforded the expected 1,2-isomer (**44-Cl/Br**) with >20 : 1 selectivity (Table 8, entries 1 and 3). Intriguingly, the 1,2-product **44-Cl/Br** was also favored in this transformation with $CuCl_2$ or $CuBr_2/Et_2O$ as the oxidant (selectivity = 1.4 : 1 in the chlorination and 9 : 1 in the bromination reaction) (Table 8, entries 2 and 4). This experiment was repeated with styrene as the alkene substrate and (p-FC_6H_4)$SnBu_3$, and, again, 1,2-arylhalogenated products predominated in all four cases (Table 8, entries 5–8).

Vinylnaphthalene Substrate

The Pd-catalyzed reaction between vinylnaphthalene and (p-FC_6H_4)$SnBu_3$ was also explored, and the 1,2-arylhalogenation product **46-Cl/Br** was the major isomer observed under all four sets of conditions (Table 9).30 The regioselectivity with $CuCl_2$ and $CuBr_2/Et_2O$ increased significantly in comparison to that observed in the corresponding reactions of styrene. For example, upon changing from styrene to vinylnaphthalene, the 1,2 : 1,1 selectivity changed from 2.2 : 1 to >50 : 1 for chlorination with $CuCl_2$ and from 24 : 1 to >50 : 1 for bromination with $CuBr_2/Et_2O$.

Solvent Effects in Arylbromination

To explore the role of solvent in the 1,1- versus 1,2-arylbrominations with $CuBr_2$/THF, the reactions were examined in 2-methyltetrahydrofuran (Me-THF) and 2,5-dimethyltetrahydrofuran (Me_2-THF). As shown in Table 10, changing the solvent resulted in a dramatic decrease in selectivity for the 1,2-product. With Me-THF, a 1.5 : 1 ratio of **28a : 28b** was obtained, with similar results (**28a : 28b** = 1.8 : 1) in Me_2-THF.

These reactions were also examined in a series of aprotic solvents with dielectric constants (ε) ranging from 7.58 to 2.25. As shown in Table 11, there is a rough correlation between product ratio and ε, with more of 1,2-product **28a** generally formed in higher dielectric solvents.

Stereochemistry

Finally, we examined the stereochemical outcome of these transformations with alkenes *cis*-**48** and *trans*-**48**. With *cis*-**48**, all of the reactions produced arylfunctionalization product **49-Cl/Br** as the major diastereomer with modest to excellent levels of selectivity (Table 12,

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entries 1–3).31 Compound **49-Cl/Br** is the result of net *syn* addition of Ph and X across the alkene.31,32 With *trans* **48**, the stereoselectivity was significantly diminished, particularly with $PhICl_2$ (Table 12, entries 4–6).32 However, in all cases, the major product was diastereomer **50-Cl/Br**, which is again the product of *syn* Ph/X addition.

Discussion

1,2-Arylhalogenation Reactions

All of the mechanistic experiments presented above are consistent with the mechanism proposed in Scheme 1. In this scenario, 1,2-arylhalogenation products are generated via oxidative halogenation of Mizoroki-Heck intermediate **A**. The deuterium labeling studies in eq. 7 are in line with this proposal, as they show clean formation of **40-Cl/Br** without accompanying migration of the deuterium label.

The 1,2-arylbrominations are particularly intriguing because simply moving from THF to Et_2O reverses product selectivity. We were thus very interested to understand the role of solvent in these transformations. As shown in Table 10, changing the solvent from THF to Me-THF or Me_2-THF resulted in a steep drop in selectivity for the 1,2-product **28a**. Me-THF and Me_2-THF are expected to have very similar polarity but significantly poorer coordinating capabilities than THF.33 Thus, this result suggests that THF coordination (either to Pd34 or Cu35) may play a key role in switching the selectivity in this system. The results in Table 11 suggest that solvent polarity may also be an important factor for selectivity, with more polar solvents favoring the 1,2 product. Polar coordinating solvents are likely to enhance the solubility of $CuBr_2$, which should increase the rate of oxidative bromination relative to that of β-hydride elimination, thereby providing improved selectivity for 1,2-product **28a**.

1,1-Arylhalogenation Reactions

These mechanistic studies provide evidence that the 1,1-products are derived from the β-hydride elimination/reinsertion/oxidation mechanism shown in Scheme 1 and in Scheme 2, path 1. The migration of deuterium from the 1 to the 2 position to generate **40b-Cl/Br** (eq. 8) is fully consistent with this mechanism. In addition, the formation of 1,4-addition product **42-Cl/Br** from the reactions of 4-(4-chlorophenyl)-1-butene with CuX_2/ether (eq. 9) provides strong evidence for equilibrating β-hydride elimination/reinsertion steps prior to oxidative cleavage.

A possible alternative pathway involving a standard Mizoroki-Heck mechanism followed by hydrohalogenation of the resulting alkene (Scheme 2, path 2) can be ruled out based on the data in Table 8. In path 2, the reaction of styrene/(*p*-FC_6H_4)$SnBu_3$ should produce the same alkene product as that of 4-fluorostyrene/$PhSnBu_3$. Accordingly, the mechanism in path 2 should afford identical mixtures of **44** to **45** for both reactions. However, as shown in Table 8, the ratio of **44 : 45** changed depending on the alkene/stannane used (entries 2 versus 6 and 4 versus 8).

Selective 1,1-arylfunctionalization with CuX_2/ether appears to derive from a preference for oxidative functionalization of Pd^{II}–benzyl intermediates (like **E**) versus Pd^{II}–alkyl intermediates (like **A**) (Scheme 2). This preference is reflected in the sole formation of **42** and **41** (as opposed to isomers resulting from halogenation at other sites along the alkyl chain) in reactions of 4-(4-chlorophenyl)-1-butene with CuX_2/ether (eq. 9). Additionally, the observation that 1,2-products predominate in the functionalization of styrene derivatives with CuX_2/ether (Table 8) is consistent with fast oxidative functionalization of an initially formed Pd^{II}-benzyl species in these systems.

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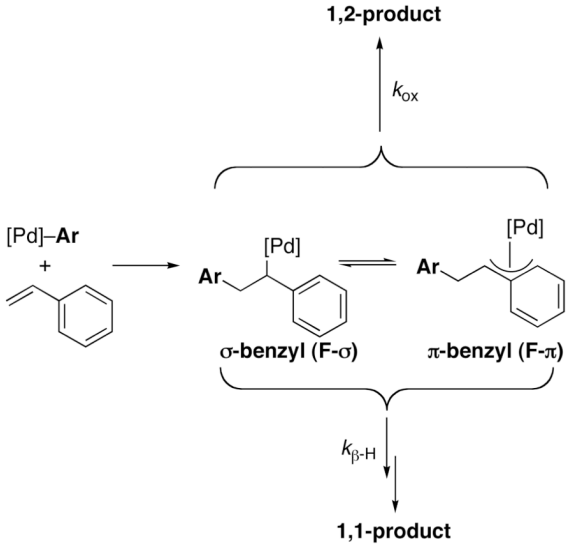
We hypothesize that the selectivity for Pd-benzyl functionalization under equilibrating conditions derives from a stabilizing π-benzyl interaction (**F**-π, eq. 11). This proposal is supported by the experiments in Table 8 and Table 9, which compare CuX_2/ether reactions of styrene to those of vinylnaphthalene. With both $CuCl_2$ and $CuBr_2$, the selectivity for 1,2-functionalization increases significantly upon moving from styrene to vinylnaphthalene (from 2.2 : 1 to >50 : 1 with $CuCl_2$, and from 24 : 1 to >50 : 1 with $CuBr_2$). In both cases, initial alkene insertion should generate a Pd^{II}-benzyl intermediate **F**-σ/π (eq. 11) or Pd^{II}-naphthyl intermediate **G**-σ/π (eq. 12). Thus, the increase in 1,2-product with vinylnaphthalene suggests that $k_{Ox}/k_{\beta\text{-H}}$ (where k_{Ox} = rate constant for direct oxidative functionalization and $k_{\beta\text{-H}}$ = rate constant for β-hydride elimination) is significantly larger for intermediate **G** than for **F**. Importantly, this is consistent with literature precedent, which has shown that π-naphthyl complexes are more kinetically reactive towards nucleophilic functionalization than their π-benzyl counterparts.36



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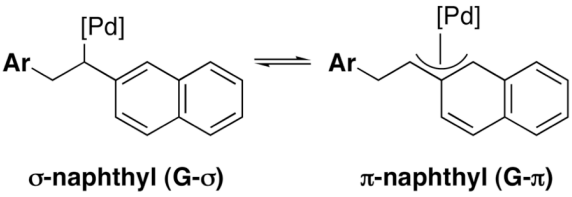

(12)

Stereochemistry

The stereochemical course of oxidatively-induced sp^3-carbon–halogen bond-formation is of interest from a fundamental mechanistic perspective. Additionally, the future development of asymmetric arylfunctionalization reactions hinges upon the ability to achieve clean retention or inversion of stereochemistry at carbon during C–X coupling. Without high stereochemical fidelity in this step, the new stereocenter will be eroded over the course of the reaction.

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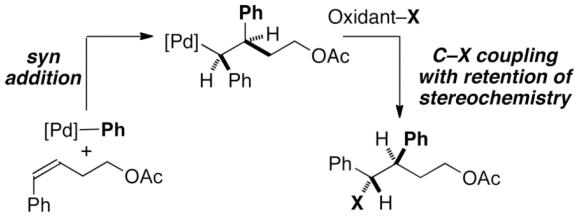
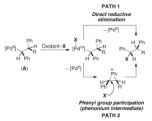
As summarized in Table 12, the arylfunctionalization of *cis*-**48** and *trans*-**48** favors products of *syn* addition. The insertion of alkenes into Pd–Ph bonds is well-known to occur with high *syn*-selectivity.37 Thus, this result indicates that C–X bond-formation occurs primarily with retention of configuration at carbon (eq. 13).



(13)

Carbon–halogen formation most likely occurs via initial 1 or 2 e^{-}oxidation of Pd^{II}–alkyl species **A** with $PhICl_2$ or CuX_2 to form a Pd^{IV} or Pd^{III} intermediate.38,39,40 The observed retention of configuration is consistent with direct C–X bond-forming reductive elimination from this high oxidation state Pd center (eq. 14, path 1)41 or with a phenyl group assistance mechanism involving double inversion (eq, 14, path 2).41b Both of these pathways have been proposed in the literature for related transformations.41



(14)

While *syn* addition predominated in every case, modest levels of stereospecificity were observed in some reactions, particularly with *trans*-**48** and $PhICl_2$ (Table 12, entry 4). There are several potential explanations for these observations. First, selectivity would be eroded if oxidative functionalization occurred with competing retention and inversion of configuration at carbon. Literature studies of related oxidatively-induced carbon-heteroatom coupling reactions at Pd suggest that both retention41 and inversion42 are possible. Further, small modifications of the reaction conditions can sometimes lead to large changes in the stereochemical outcome.43 However, such competing pathways would most likely affect reactions of *cis*-**48** and *trans*-**48** to similar degrees and thereby provide similar levels of stereochemical erosion with both the *cis* and *trans* substrates. Thus, this explanation does not readily account for the dramatically different results for *cis*-**48**/$PhICl_2$ (12 : 1 isomer ratio) versus *trans*-**48**/$PhICl_2$ (1 : 1.6 isomer ratio).

A second possible explanation for formation of mixtures of diastereomers would be competing isomerization of the alkene starting material under the reaction conditions. This scenario would lead to an “apparent” erosion of stereospecificity even if C–X coupling proceeded with clean retention. Olefin isomerization is likely to be particularly problematic with *trans*-**48**, since it undergoes arylfunctionalization at a slower rate than *cis*-**48**.44 Thus, the observation of lower diastereoselectivities in reactions of *trans*-**48** is consistent with a contribution from this pathway. In addition, ^{1}H NMR spectroscopic analysis of the reaction between *trans*-**48**/$PhSnBu_3$, and $PhICl_2$ at 50% conversion revealed the presence of detectable quantities (2%) of *cis*-**48**. Furthermore, reaction of *cis*-**48** at 23 °C with 2 equiv of $PhICl_2$ and 2 equiv of $PhSnBu_3$ resulted in 18% yield and an 8 : 1 ratio of **49-Cl : 50-Cl**) along with 17% recovery of *trans*-**48**. These results clearly indicate that alkene

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isomerization can occur to a significant extent under the $PhICl_2/CH_2Cl_2$ reaction conditions. While this side reaction undoubtedly needs to be addressed, the observation of good levels of stereospecificity with the *cis* substrates provides impetus for moving forward in the development of asymmetric versions of these transformations.

Summary

In summary, we have developed Pd-catalyzed reactions for the arylchlorination and arylbromination of α-olefins by oxidatively intercepting Mizoroki-Heck intermediate **A** (Scheme 1). 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^{II} intermediates. This work provides a mechanistic basis for the future development of synthetically useful aryloxygenation, arylamination, arylhalogenation, and diarylation reactions using a variety of oxidants and transmetalating reagents. Additionally, the insights gained from these studies will be valuable for the design of enantioselective versions of these transformations. Work in all of these areas is ongoing in our laboratory and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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27. NIS, CuI, and I_2 did not produce appreciable yields of 1,2- or 1,1-aryliodinated products under any conditions examined.
28. The catalyst $Pd(Cl)_2(MeCN)_2$ afforded slightly better yields than $Pd(Cl)_2(PhCN)_2$ for arylbromination.
29. The 1,2 and 1,1-arylbromination products typically underwent some decomposition during isolation/chromatographic purification (as reflected in the discrepancy between the isolated yield and the yield determined from analysis of the crude reaction mixtures).
30. For analogous reactions between substituted stannanes and vinylnaphthalene/styrene, see Table S5.
31. The stereochemistry of **49-Cl/Br** and **50-Cl/Br** was determined by ^1H NMR spectroscopy (based on chemical shift and coupling constant analysis) by analogy to several related products that were characterized by X-ray crystallography. See Supporting Information for complete details.
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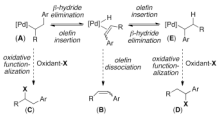
44. See Supporting Information (Table S3) for details.



Scheme 1.
Working Mechanistic Hypothesis for Formation of **B-D**

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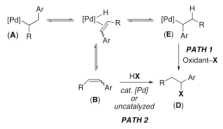

Scheme 2.

Two Possible Mechanisms for Formation of 1,1-Products

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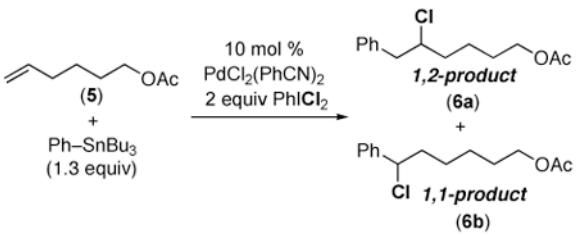
Table 1

Optimization of the 1,2-Arylchlorination Reaction



Entry	Solvent	Temperature	Concentration	Yield[a]	6a : 6b[a]
1	Dioxane	25 °C	0.032 M	77%	1 : 6.7
2	THF	25 °C	0.032 M	53%	1 : 9.6
3	Et_2O	25 °C	0.032 M	64%	1 : 9.7
4	C_6H_6	25 °C	0.032 M	55%	1 : 8.9
5	CH_2Cl_2	25 °C	0.032 M	46%	1 : 1.3
6	CH_2Cl_2	0 °C to 25 °C	0.032 M	55%	1.9 : 1
7	CH_2Cl_2	−78 °C to 25 °C	0.032 M	56%	8 : 1
8	CH_2Cl_2	−78 °C to 25 °C	0.064 M	82%	10 : 1
9[b]	CH_2Cl_2	−78 °C to 25 °C	0.064 M	100%	10 : 1

[a]Yield and ratio of isomers determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

[b]2.6 equiv of PhSnBu3.

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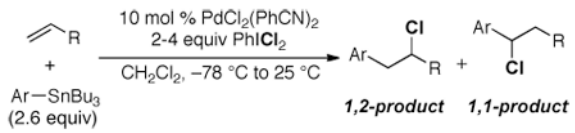
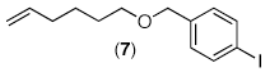
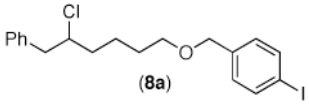
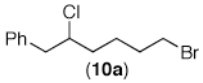
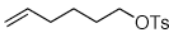
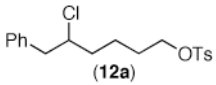
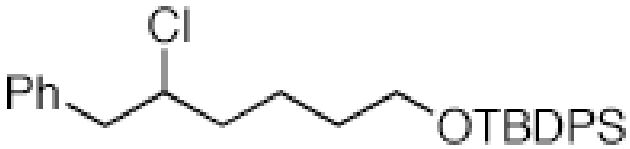
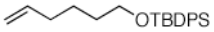
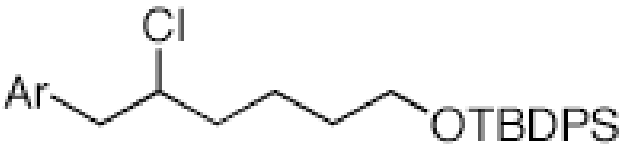
Table 2

Substrate Scope for 1,2-Arylchlorination



Entry	Alkene	Stannane	Major Product	Yield[a]	1,2 : 1,1
1	 (7)	$PhSnBu_3$	 (8a)	72%	8 : 1
2	(9)	$PhSnBu_3$	 (10a)	84%	13 : 1
3	 (11)	$PhSnBu_3$	 (12a)	96%	9 : 1
4	(13)	$PhSnBu_3$	 (14a)	92%	11 : 1
5	 (13)	$p\text{-}FC_6H_4SnBu_3$	 Ar = p-FC_6H_4 (15a)	84%	11 : 1

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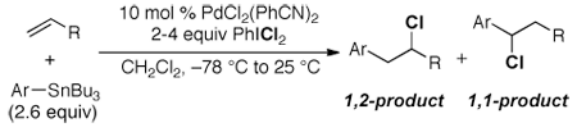
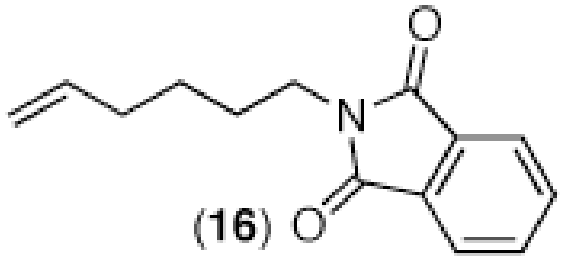
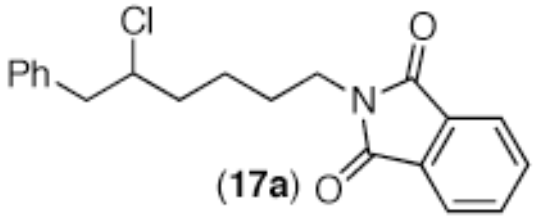
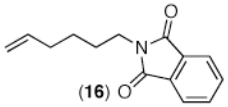
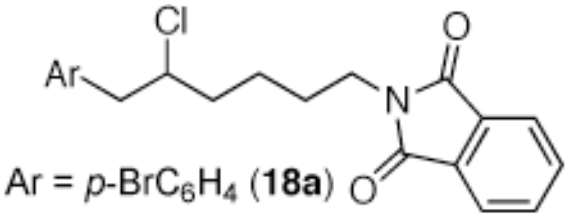
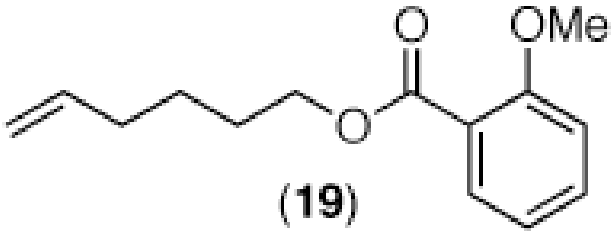
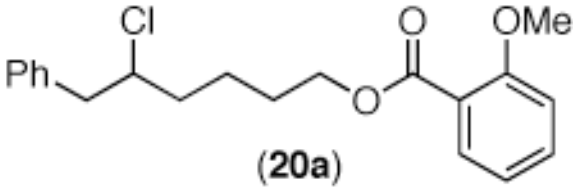


Entry	Alkene	Stannane	Major Product	Yield[a]	1,2 : 1,1
6		$PhSnBu_3$		85%	6: 1
7		p-$BrC_6H_4SnBu_3$		96%	7 : 1
8		$PhSnBu_3$		86%	8 : 1

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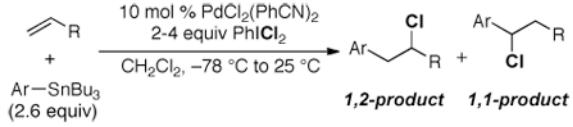
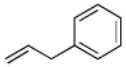
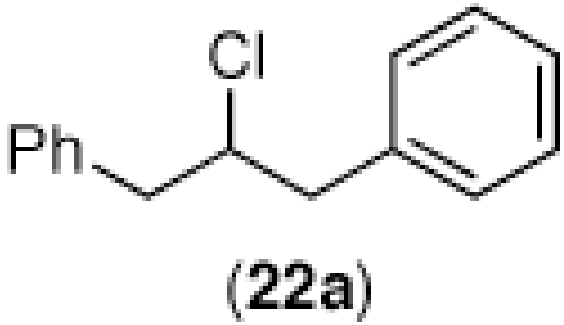
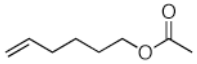
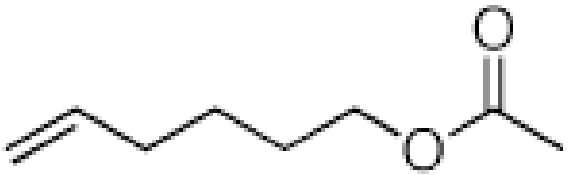
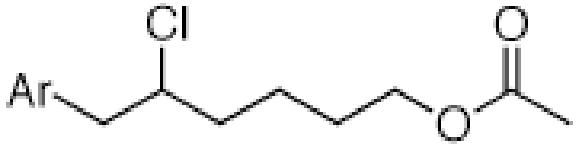


Entry	Alkene	Stannane	Major Product	Yield[a]	1,2 : 1,1
9	 (21)	$PhSnBu_3$	 (22a)	68%	6 : 1
10	 (5)	$PhSnBu_3$	(6a)	86%	10 : 1
11	 (5)	$p\text{-}CH_3C_6H_4SnBu_3$	 Ar = $p\text{-}CH_3C_6H_4$ (23a)	74%	5 : 1

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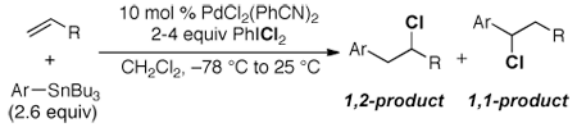
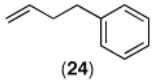
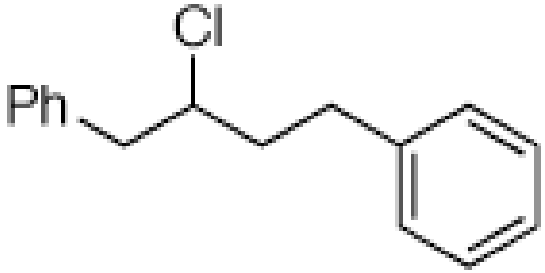


Entry	Alkene	Stannane	Major Product	Yield[a]	1,2 : 1,1
12	 (**24**)	$PhSnBu_3$	 (**25a**)	80%	14: 1

[a]Isolated yields and selectivities. Notably, in some cases, the isolated material contained minor impurities (typically 2,1-phenylchlorination or dichlorination products). See Supporting Information for details.

[b]The 1,1 and 1,2-isomers were generally not separable by column chromatography, but could be isolated in pure form using HPLC.

[c]The variation in 1,2 : 1,1 selectivity as a function of substrate may be due to differing interactions of polar functional groups within the substrate with the palladium catalyst.

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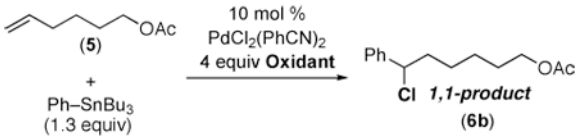
Table 3

Optimization of 1,1-Arylchlorination Reaction



Entry	Solvent	Temperature	Yield $CuCl_2$[a]	Yield NCS[a]
1	Dioxane	25 °C	13%	34%
2	C_6H_6	25 °C	28%	48%
3	AcOH	25 °C	10%	46%
4	CH_2C1_2	25 °C	32%	36%
5	THF	25 °C	58%	39%
6	THF	−78 °C to 25 °C	75%	nd[b]
7	Et_2O	25 °C	29%	36%
8	Et_2O	−78 °C to 25 °C	82%	44%

[a] Yield and ratio of isomers determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

[b] nd = not determined

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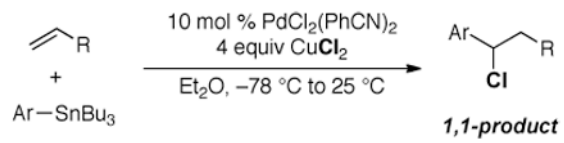
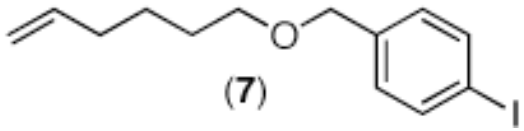
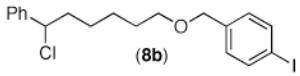
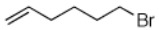
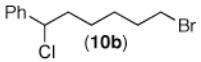
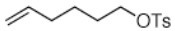
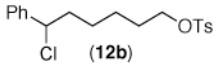
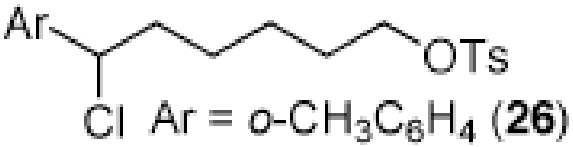
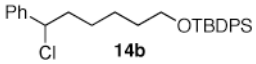
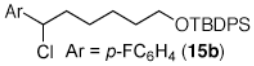
Table 4

Substrate Scope for 1,1-Arylchlorination25



Entry	Alkene	Stannane	Major Product	Yield[a]	1,2 : 1,1
1	 (7)	$PhSnBu_3$	 (8b)	75% (53%)	1 : >20
2	 (9)	$PhSnBu_3$	 (10b)	83% (54%)	1 : >20
3	 (11)	$PhSnBu_3$	 (12b)	84% (71%)	1 : >20
4	(11)	$o\text{-}CH_3C_6H_4SnBu_3$	 Ar = $o\text{-}CH_3C_6H_4$ (26)	87% (67%)	1 : >20
5	(13)	$PhSnBu_3$	 14b	86% (66%)	1 : >20
6	(13)	$p\text{-}FC_6H_4SnBu_3$	 Ar = $p\text{-}FC_6H_4$ (15b)	76% (59%)	1 : >20

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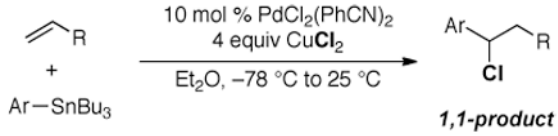
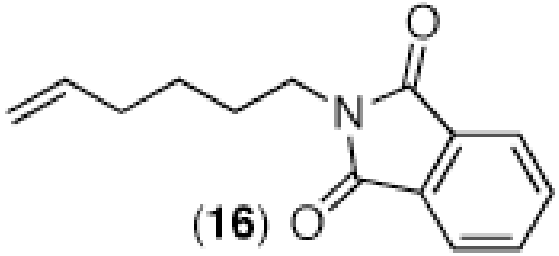
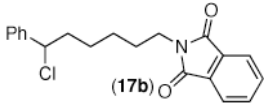
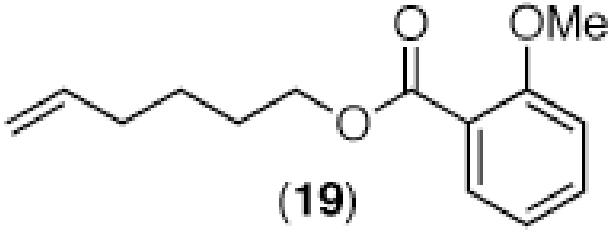
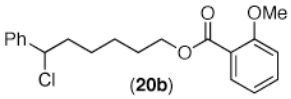
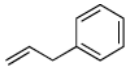
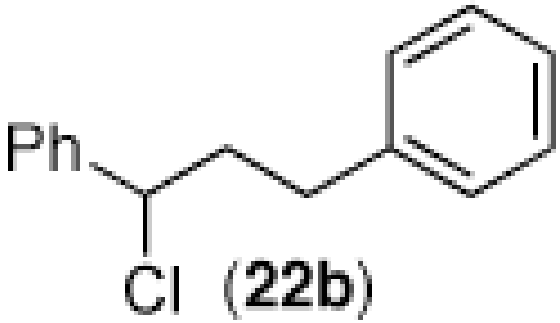


Entry	Alkene	Stannane	Major Product	Yield[a]	1,2 : 1,1
7	 (16)	$PhSnBu_3$	 (17b)	73% (71%)	1 : >20
8	 (19)	$PhSnBu_3$	 (20b)	51% (41%)	1 : >20
9	 (21)	$PhSnBu_3$	 (22b)	74% (55%)	1 : >20

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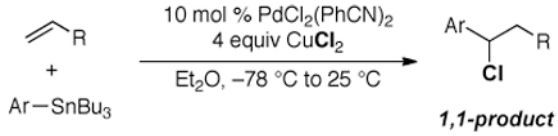
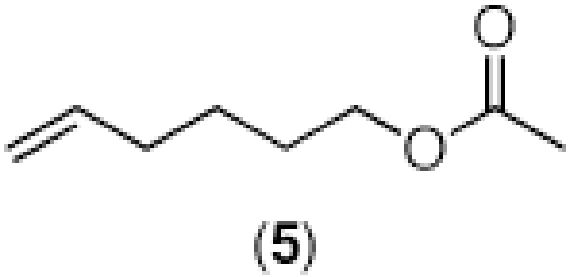
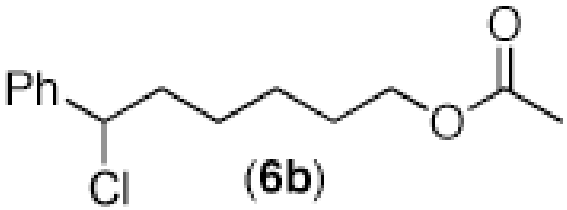
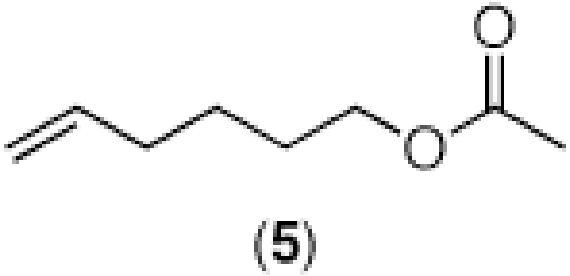
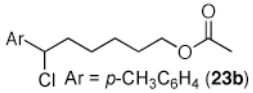
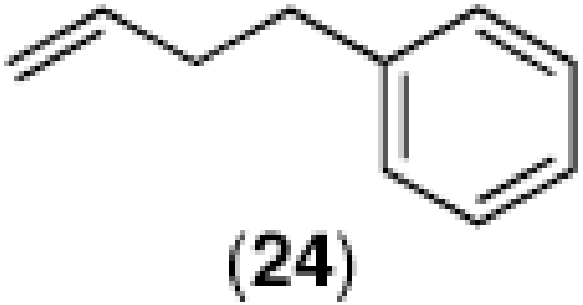
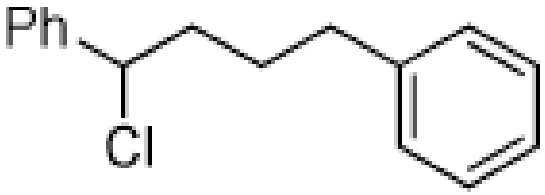


Entry	Alkene	Stannane	Major Product	Yield[a]	1,2 : 1,1
10	 (5)	$PhSnBu_3$	 (6b)	73% (71%)	1 : >20
11	 (5)	$p\text{-}CH_3C_6H_4SnBu_3$	 Ar = $p\text{-}CH_3C_6H_4$ (23b)	78% (72%)	1 : >20
12	 (24)	$PhSnBu_3$	 (25b)	94% (82%)	1 : >20

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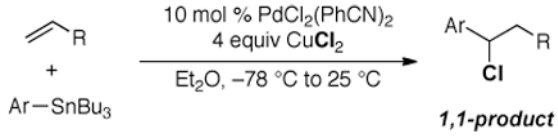
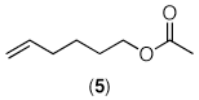
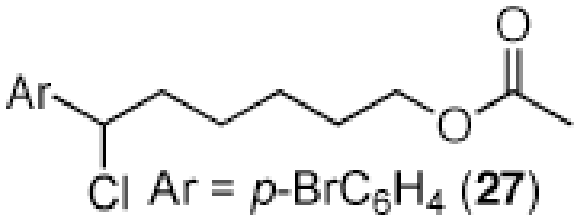


Entry	Alkene	Stannane	Major Product	Yield[a]	1,2 : 1,1
13	 (5)	*p*-$BrC_6H_4SnBu_3$	 Ar = *p*-BrC_6H_4 (**27**)	82% (54%)	1 : >20

[a]Yield determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. Isolated yields are in parentheses.

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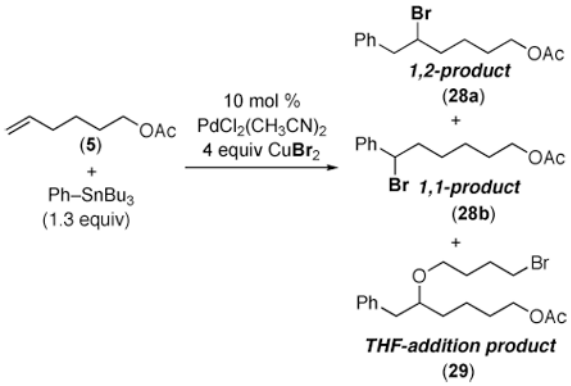
Table 5

Optimization of Arylbromination Reaction



Entry	Solvent	Temperature	Concentration	Yield $CuBr_2$[a]	28a : 28b[a]	Yield NBS[a]	28a : 28b[a]
1	Dioxane	25 °C	0.032 M	29%	1 : >20	19%	1 : >20
2	C_6H_6	25 °C	0.032 M	24%	1 : 13	8%	1 : >20
3	AcOH	25 °C	0.032 M	16%	1 : >20	0%	nd[b]
4	CH_2Cl_2	25 °C	0.032 M	27%	1 : >20	6%	1 : >20
5	Et_2O	25 °C	0.032 M	46%	1 : >20	8%	1 : >20
6	Et_2O	−78 °C to 25 °C	0.032 M	82%	1 : >20	nd[b]	nd[b]
7	THF	25 °C	0.032 M	25%	1 : >20	11%	1 : >20
8[c]	THF	−78 °C to 25 °C	0.032 M	49% (17%)	3 : 1	nd[b]	nd[b]
9[c]	THF	−78 °C to 25 °C	0.064 M	50% (5%)	10 : 1	nd[b]	nd[b]
10[c]	THF	−78 °C to 25 °C	0.128 M	80% (20%)	10 : 1	nd[b]	nd[b]

[a]Yield and ratio of isomers determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. The yield of **29** is shown in parentheses where applicable.

[b]nd = not determined.

[c]1.9 equiv of PhSnBu3.

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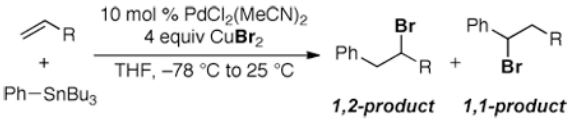
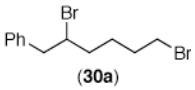
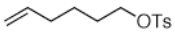
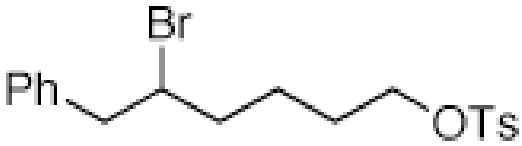
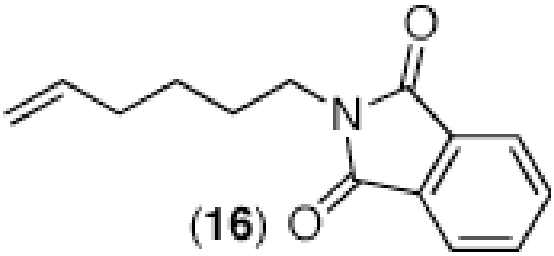
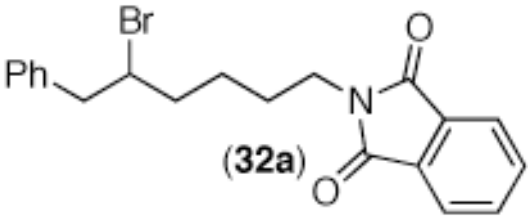
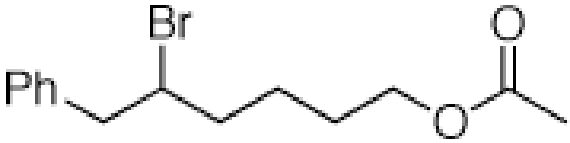
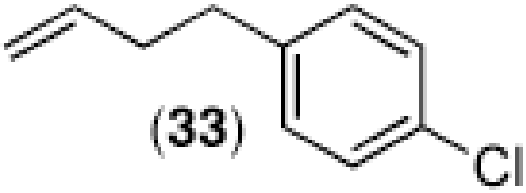
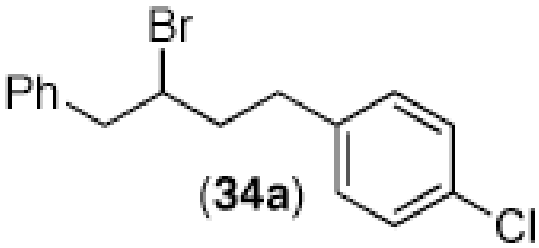
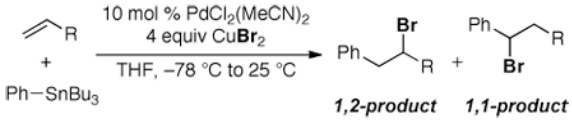
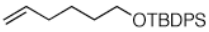
Table 6

Substrate Scope for 1,2-Arylbromination29



Entry	Alkene	Major Product[b]	Yield[a]
1	(9)	 (30a)	73% (54%)
2	 (11)	 (31a)	86% (64%)
3	 (16)	 (32a)	72% (56%)
4	(5)	 (28a)	84% (60%)
5	 (33)	 (34a)	87% (63%)



Entry	Alkene	Major Product[b]	Yield[a]
6	 (**13**)	(**35a**)	87% (63%)
7	(**36**)	(**37a**)	65% (52%)

[a]Yield and ratio of isomers determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. Isolated yields and selectivities are in parentheses.

[b]Between 5 and 20% of THF-addition products analogous to **29** was observed by crude ^{1}H NMR spectroscopic analysis with all substrates.

[c]Isolated ratio reflects 1,2 product to a mixture of 1,1 and 1,4 products.

[d]The 1,1 and 1,2-isomers were generally not separable by column chromatography, but could be isolated in pure form using HPLC.

[e]The variation in 1,2 : 1,1 selectivity as a function of substrate may be due to differing interactions of polar functional groups within the substrate with the palladium catalyst.

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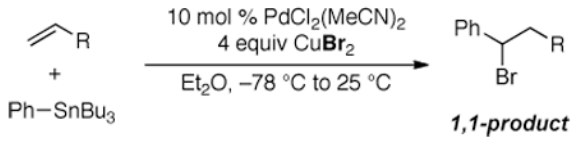
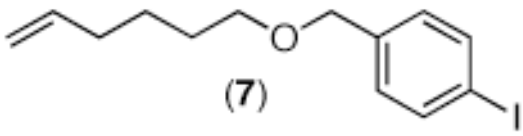
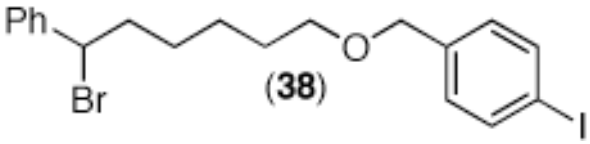
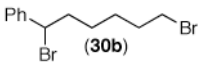
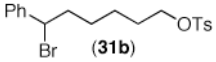
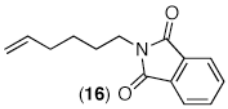
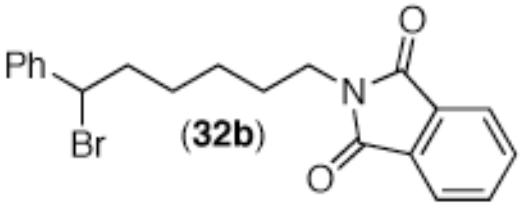
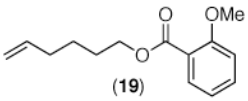
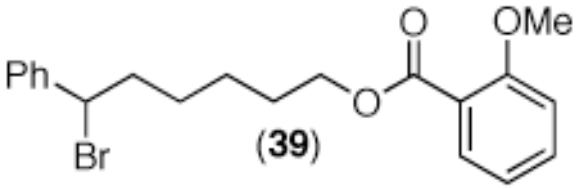
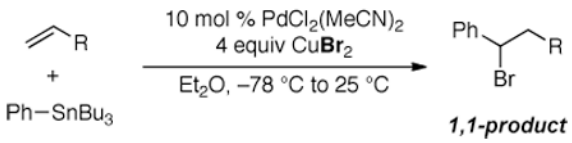
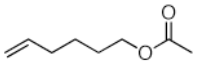
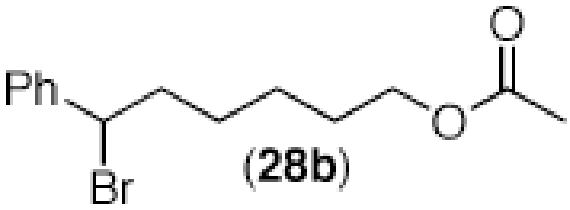
Table 7

Substrate Scope for 1,1-Arylbromination29



Entry	Alkene	Major Product	Yield[a]
1	 (7)	 (38)	66% (56%
2	(9)	 (30b)	85% (70%
3	(11)	 (31b)	70% (67%
4	(13)	(35b)	88% (60%
5	 (16)	 (32b)	79% (69%
6	 (19)	 (39)	50% (41%)



Entry	Alkene	Major Product	Yield[a]
7	 (5)	 (28b)	80% (68%
8	(36)	(37b)	64% (45%

[a]Yield and selectivity determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. Isolated yields are in parentheses.

[b]Approximately 10% of the Heck byproduct was observed by crude NMR.

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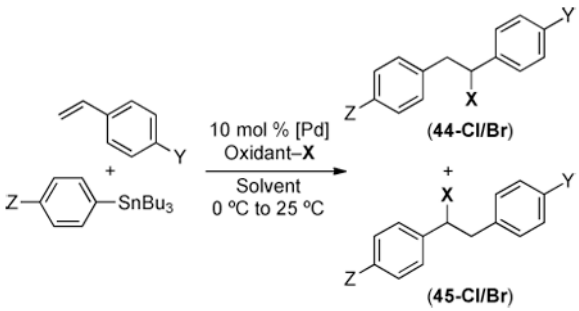
Table 8

Reactions of Styrene Substrates



Entry	Oxidant/Solvent	X	Y	Z	Yield	Ratio 1,2 : 1,1
1	$PhICl_2/CH_2Cl_2$	Cl	F	H	50%[a]	>20 : 1[a]
2	$CuCl_2/Et_2O$	Cl	F	H	48%[b]	1.4 : 1[b]
3[c]	$CuBr_2$/THF	Br	F	H	45%[b]	>20 : 1[b]
4[d]	$CuBr_2/Et_2O$	Br	F	H	69%[b]	9 : 1[b]
5	$PhICl_2/CH_2Cl_2$	Cl	H	F	79%[a]	> 20 : 1[a]
6	$CuCl_2/Et_2O$	Cl	H	F	50%[b]	2.2 : 1[b]
7[c]	$CuBr_2$/THF	Br	H	F	30%[b]	> 20 : 1[b]
8[d]	$CuBr_2/Et_2O$	Br	H	F	50%[b]	24 : 1[b]

[a]Yield and selectivity determined based on isolated material.

[b]Yield and selectivity determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

[c]Reaction conditions were optimized to −78 °C to 25 °C with 2 equiv of organostannane to increase the yield – there was no difference in selectivity compared to the reaction at 0 °C.

[d]$Pd(acac)_2$ used as [Pd].

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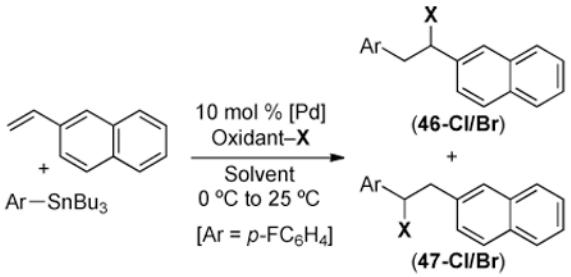
Table 9

Reactions of Vinylnaphthalene



Entry	Oxidant/Solvent	X	Yield[a]	Ratio 1,2 : 1,1[a]
1	$PhICl_2/CH_2Cl_2$	Cl	60%[b]	> 50 :1
2	$CuCl_2/Et_2O$	Cl	76%	> 50 : 1
3[c]	$CuBr_2$/THF	Br	12%[d]	> 50 : 1
4[c]	$CuBr_2/Et_2O$	Br	48%[d]	> 50 : 1

[a]Yield and selectivity determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

[b]Mass balance in 1,2-chlorination is accounted for by formation of 25% of the 1,2-dichloro product.

[c]$Pd(acac)_2$ used as [Pd].

[d]Mass balance in arylbromination reactions is predominantly accounted for by incomplete conversion (15% conversion of vinylnaphthalene in entry 3 and 70% conversion of vinylnaphthylene in entry 4).

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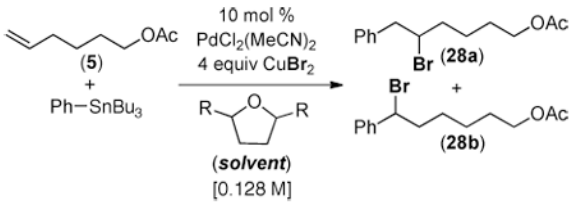
Table 10

Effect of Substituted THF-Derivatives on 1,2- versus 1,1-Phenylbromination with $CuBr_2$



Entry	Solvent	Yield[a]	Ratio 1,2 : 1,1[a]
1	THF	80%	15 : 1
2	MeTHF[b]	37%	1.5 : 1
3	Me_2-THF[c]	57%	1.8 : 1

[a]Yield and selectivity determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

[b]Me-THF = 2-methyltetrahydrofuran.

[c]Me_2-THF = 2,5-dimethyltetrahydrofuran.

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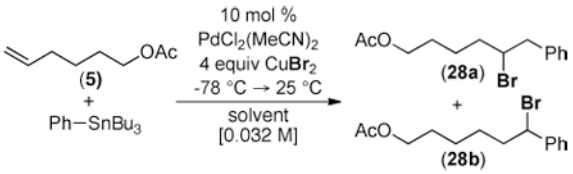
Table 11

Effect of Aprotic Solvents on 1,2 versus 1,1 Arylbromination with $CuBr_2$[a]



Entry	Solvent	ε	Yield[b]	Ratio 1,2 : 1,1[b]
1	THF	7.58	49%[c]	3.4 : 1
2	1,2 Dimethoxyethane	7.2	14%	> 20:1
3	EtOAc	6.02	63%	1 : 8
4	$CHCl_3$	4.81	45%	1: > 20
5	Et_2O	4.33	82%	1 : 24
6	Anisole	4.33	23%[d]	1: > 20
7	$^iPr_2O$	3.9	76%	1 : 5.9
8	MTBE	2.6	56%	1: > 20
9	Dioxane	2.25	30%	1 : 20

[a]These reactions were performed at 0.032 M to maximize solubility and improve reproducibility across this broad range of solvents.

[b]Determined by ^1H NMR spectroscopy.

[c]1.9 equiv $PhSnBu_3$ used.

[d]0 °C → 25 °C.

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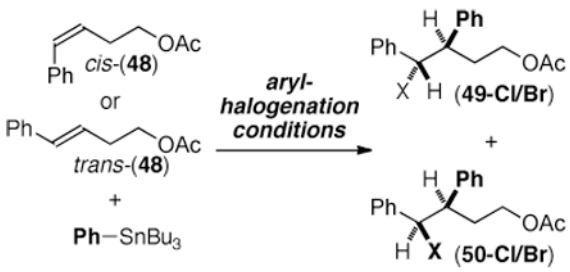
Table 12

Arylhalogenation of *cis*-**48** and *trans*-**48**[a]



Entry	Substrate	Oxidant	Solvent	Yield[b,c]	Ratio 49 : 50[b]
1	*cis*-**48**	$PhICl_2$	CH_2Cl_2	40%	12 : 1
2	*cis*-**48**	$CuCl_2$	Et_2O	51%	>30 : 1
3	*cis*-**48**	$CuBr_2$	Et_2O	41%	5 : 1
4	*trans*-**48**	$PhICl_2$	CH_2Cl_2	21%	1 : 1.6
5	*trans*-**48**	$CuCl_2$	Et_2O	45%	1 : 8
6	*trans*-**48**	$CuBr_2$	Et_2O	9%	1 : 8

[a]Conditions: 2 equiv $PhSnBu_3$, 10 mol % $PdCl_2(PhCN)_2$, 0.032 M, −78 → 23 °C, 36 h.

[b]Yield and selectivity determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

[c]The mass balance in these reactions is accounted for by recovered starting material as well as the corresponding Mizoroki-Heck product. See Supporting Information for full details.