Article

Palladium-Catalyzed, Site-Selective Direct Allylation of Aryl C–H Bonds by Silver-Mediated C–H Activation: A Synthetic and Mechanistic Investigation

Sarah Yunmi Lee, and John F. Hartwig

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 31 Oct 2016

Palladium-Catalyzed, Site-Selective Direct Allylation of Aryl C–H Bonds by Silver-Mediated C–H Activation: A Synthetic and Mechanistic Investigation

Sarah Yunmi Lee and John F. Hartwig*

Department of Chemistry, University of California, Berkeley, CA 94720, United States

ABSTRACT: We describe a method for the site-selective construction of C(aryl)-C(sp^3) bond by the palladium-catalyzed direct allylation of arenes with allylic pivalates in the presence of AgOPiv to afford the linear (*E*)-allylated arene with excellent regioselectivity; this reaction occurs with arenes that have not undergone site- and stereoselective direct allylation previously, such as monofluorobenzenes and non-fluorinated arenes. Mechanistic studies indicate that AgOPiv ligated by a phosphine reacts with the arene to form an arylsilver(I) species, presumably through a concerted metalation-deprotonation (CMD) pathway. The activated aryl moiety is then transferred to an allylpalladium(II) intermediate formed by oxidation addition of the allylic pivalate to the Pd(0) complex. Subsequent reductive elimination furnishes the allyl-aryl coupled product. The aforementioned proposed-intermediates, including an arylsilver complex, have been isolated, structurally characterized, and determined to be chemically and kinetically competent to undergo the proposed elementary steps of the catalytic cycle.

INTRODUCTION

The formation of carbon–carbon bonds by direct functionalization of aryl C–H bonds is a powerful approach for the synthesis and derivatization of aromatic compounds.[1] Common strategies to facilitate the C–H activation of arenes and control the site-selectivity of direct functionalizations of arenes focus on the use of 1) arenes bearing a directing group that can coordinate to the metal catalyst or 2) highly electron-deficient arenes, such as polyfluoroarenes. However, the site-selective functionalizations of the C–H bonds in simple arenes lacking a directing group and lacking a series of strongly activating groups remains challenging.[1c] Although there have been reports on site-selective functionalizations of simple arenes to form C(aryl)–C(sp^2) bonds,[2,3] simple arenes have not been reported to undergo site-selective formation of C(aryl)–C(sp^3) bonds by reactions with C(sp^3)-electrophiles.[4] Yet, such reactions would be valuable because the substrate scope and site selectivity would complement those of electrophilic aromatic substitution (Friedel-Crafts reactions) in which electron-rich arenes are more reactive than electron-poor arenes.[5]

In this vein, the direct allylation of simple arenes would be a useful process because the allyl group in the product could undergo further functionalization. Although the allylation of polyfluoroarenes and the allylation of arenes containing directing groups have been described,[6,7] the allylation of arenes that are less electron poor and that lack directing groups have not been reported. The allylation of arenes with allylic esters could occur by a few apparently well-established steps. The reaction could occur by oxidative addition of the allylic ester to form an allylpalladium carboxylate[8] and cleavage of the C–H bond of an arene by the allylpalladium carboxylate complex in a fashion proposed for reactions of arylpalladium carboxylate complexes; the proposed mechanism for Pd-catalyzed direct arylations of arenes with aryl halides typically includes the cleavage of an aryl C–H bond by a palladium intermediate, such as a phosphine-ligated arylpalladium carboxylate LArPd(OCOR).[1,9]

The higher reactivity of electron-deficient arenes than electron-rich arenes toward C–H bond functionalization is often explained by the involvement of a concerted metalation-deprotonation (CMD) step for cleavage of the C–H bond by metal carboxylates.[9] Thus, the relative reactivity of the arene parallels the relative acidity of the aryl C–H bonds. The requirement that the arene possess multiple strongly activating groups, presumably, results from the need for an acidic C–H bond to enable cleavage of the C–H bond by a palladium(II) species by a CMD pathway.[1d]

Recent studies by Larrosa[10] and Sanford[11] independently on Pd-catalyzed direct functionalizations of aryl C–H bonds in the presence of silver carboxylates reveal that the silver carboxylate can cleave the C–H bonds in arenes bound to $Cr(CO)_3$, polyfluoroarenes, and acidic heteroarenes, such as thiophenes; the resulting arylsilver(I) complex is proposed to transfer its aryl moiety to a palladium intermediate.[12,13] However, isolation of a phosphine-ligated arylsilver(I) species, investigation of its ability to undergo transmetallation of the aryl group to palladium, and evaluation of its competency as a reaction intermediate in the catalytic process have not been described. Moreover, determination of whether the Ag(I) system can cleave the C–H bonds in less activated arenes as well as extensions of this step to reactions that form C–C bonds between sp^2 and sp^3 sites have not been reported.

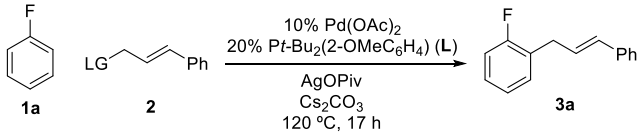
We report the site-selective formation of C(aryl)-C(sp^3) bonds by a palladium-catalyzed direct allylation of monofluorobenzenes and non-fluorinated arenes with allylic pivalates in the presence of a silver(I) additive to generate linear (*E*)-allylated arenes. Detailed mechanistic studies are consistent with a synergistic catalytic cycle involving a (π-allyl)palladium complex formed from the oxidative addition of allylic pivalate to bisphosphine-Pd(0) and an arylsilver species ligated by a phosphine resulting from silver-mediated cleavage of relatively unactivated aryl C–H bonds. Isolation of the allylpalladium and arylsilver species and studies of their reactivity support the proposed cycle.

RESULTS AND DISCUSSION

Reaction Development. Our studies began with the mechanistic hypothesis that the allylation of arenes could occur by a pathway often invoked for the direct arylation of arenes. Allylic esters readily undergo oxidative additions to Pd(0) species, and the carboxylate ligand on palladium resulting from this oxidative addition could trigger the cleavage of a C–H bond of the arene by a CMD pathway.[9] Reductive elimination would form the allylarene.

On the basis of this initial mechanistic hypothesis and prior studies suggesting the viability of this pathway for the allylation of polyfluoroarenes,[7a,c] we sought to identify conditions for the direct allylation of monofluoroarenes. We investigated a series of palladium precursors, ligands, bases and additives for the direct coupling of neat fluorobenzene **1a** with cinnamyl electrophiles. These studies showed that the linear (*E*)-allylated fluorobenzene (**3a**) formed as a single isomer in 82% yield when catalyzed by $Pd(OAc)_2$ and di-*tert*-butyl 2-anisylphosphine (**L**)[14] in the presence of Cs_2CO_3 as a base and AgOPiv as a stoichiometric additive (Table 1, entry 1). The allylation occurred selectively at the position *ortho* to fluorine.

Table 1. Effect of Reaction Parameters on Palladium-Catalyzed Allylations of Fluorobenzene with Cinnamyl Pivalate[a]



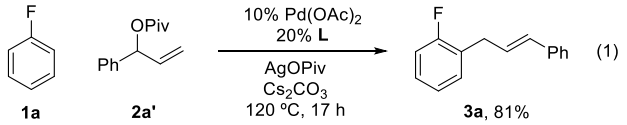
1a **2** **3a**

entry	LG[b]	deviation from standard conditions	yield (%)[c]
1	OPiv	none	82
2	OPiv	**PdL_2**, instead of $Pd(OAc)_2$ and **L**	83
3	OPiv	no $Pd(OAc)_2$	<5
4	OPiv	no **L**	<5
5	OPiv	PPh_3, instead of **L**	<5
6	OPiv	PCy_3, instead of **L**	16
7	OPiv	P*t*-Bu_3, instead of **L**	14
8	OPiv	P*t*-$BuCy_2$, instead of **L**	40
9	OPiv	PAd_2Bu, instead of **L**	17
10	OPiv	PCy_2Ph, instead of **L**	22
11	OPiv	P*t*-Bu_2Ph, instead of **L**	66
12	OPiv	P*t*-$Bu_2(2\text{-}CF_3C_6H_4)$, instead of **L**	21
13	OPiv	P*t*-$Bu_2(2\text{-}NMe_2C_6H_4)$, instead of **L**	<5
14	OPiv	P*t*-$Bu_2(2\text{-}PhC_6H_4)$, instead of **L**	<5
15	OPiv	P*t*-$Bu_2(4\text{-}OMeC_6H_4)$, instead of **L**	60
16	OPiv	P*t*-$Bu_2(4\text{-}CF_3C_6H_4)$, instead of **L**	73
17	OPiv	no AgOPiv	<5
18	OPiv	Ag_2CO_3, instead of AgOPiv	74
19	OPiv	AgOTf, instead of AgOPiv	54
20	Cl	none	62
21	Br	none	47
22	OCO_2Me	none	34
23	OAc	none	76

[a]Reaction conditions: **1a** (0.20 mL), **2** (0.05 mmol, 1.0 equiv), $Pd(OAc)_2$ (10%), **L** (20%), AgOPiv (1.0 equiv), and Cs_2CO_3 (2.4 equiv) at 120 °C for 17 h. [b]LG = leaving group. [c]Determined by GC analysis.

Table 1 shows the influence of a series of reaction parameters on the yield. The reaction catalyzed by $Pd[P(t\text{-}Bu)_2(2\text{-}OMeC_6H_4)]_2$ (**PdL_2**) formed **3a** in a yield that was comparable to that obtained with $Pd(OAc)_2$ and phosphine **L** as catalyst (entry 2); no allylation was observed in the absence of either $Pd(OAc)_2$ or **L** (entries 3 and 4). The allylation catalyzed by complexes of other phosphine ligands, including PPh_3 (entries 5), trialkylphosphines (entries 6–10), and di-*tert*-butylarylphosphines (entries 11–16), occurred in lower yields of **3a** than did the reaction catalyzed by $Pd(OAc)_2$ and **L**. Furthermore, the allylation did not proceed without a silver additive (entry 17). Reactions with Ag(I) salts besides AgOPiv, such as Ag_2CO_3 or AgOTf, led to a lower yield of **3a** (entries 18 and 19) than did those with AgOPiv. The allylation with cinnamyl pivalate generated **3a** in higher yield than did those with cinnamyl electrophiles containing other leaving groups (entries 20–23).

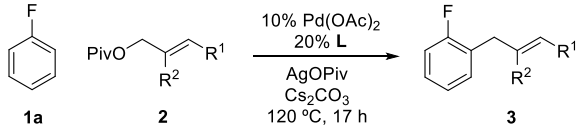
The reaction of fluorobenzene with the branched isomer of cinnamyl pivalate (**2a**) under the standard conditions afforded linear allylarene **3a** in 81% yield as a single product (eq 1). This result suggests that the allylation reaction occurs through a (π-allyl)palladium intermediate.



1a **2a'** **3a**, 81% (1)

Scope of Direct Allylation of Arenes. Under our standard conditions for the allylation of arenes, various allylic pivalates coupled with fluorobenzene **1a** to generate linear (*E*)-allylarenes with excellent site-selectivity (Table 2).[15] A single isomer of the corresponding allylarene was obtained with cinnamyl pivalates containing *para*-, *meta*, or *ortho*-substituents (entries 2–7), or an extended π-system (entry 8). In addition, the allylation with 2-methylallyl chloride proceeded to form **3i** as a single product (entry 9). Finally, the reaction of a trisubstituted allylic pivalate formed a mixture of *E* and *Z* isomers (3:1) of allylarene **3j** (entry 10).

Table 2. Scope of the Allylation of Fluorobenzene with Allylic Pivalates[a]



1a **2** **3**

entry		R^1	R^2	yield (%)[b]
1	**2a**	Ph	H	**3a,** 82
2	**2b**	4-MeC_6H_4	H	**3b,** 76
3	**2c**	4-$CF_3C_6H_4$	H	**3c,** 58
4	**2d**	4-ClC_6H_4	H	**3d,** 62
5	**2e**	4-$(CO_2Me)C_6H_4$	H	**3e,** 54
6[c]	**2f**	2-$(OMe)C_6H_4$	H	**3f,** 87
7	**2g**	3-$(OMe)C_6H_4$	H	**3g,** 84
8	**2h**	2-naphthyl	H	**3h,** 78
9[d,e]	**2i**	H	Me	**3i,** 74
10[f]	**2j**	Ph	Me	**3j,** 75

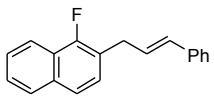
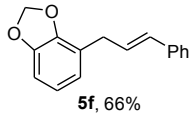
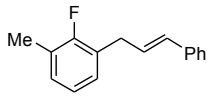
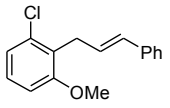
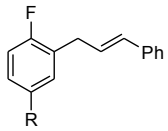
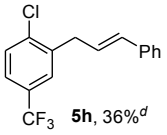
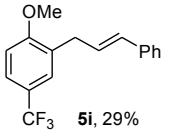
[a]Reaction conditions: **1a** (1.40 mL), **2** (0.35 mmol, 1.0 equiv), $Pd(OAc)_2$ (10%), **L** (20%), AgOPiv (1.0 equiv), and Cs_2CO_3 (2.4 equiv) at 120 °C for 17 h. [b]Yield of purified product. [c]**2f** contained 11% of (*Z*)-isomer. [d]Determined by GC analysis. [e]2-Methylallyl chloride was used instead of 2-methylallyl pivalate. [f]**3j** was obtained as a 3:1 mixture of *E* and *Z* isomers.

The direct allylations of various arenes with cinnamyl pivalate **2a** also occurred under the standard conditions (Table 3). *Ortho*-substituted monofluorobenzenes such as 1-fluoronaphthalene and 1-fluoro-2-methylbenzene, as well as 1-fluoro-4-methylbenzene, were suitable substrates for the allylation, affording the corresponding allylarenes as single products (entries 1–3). However, *para*-methoxy fluorobenzene

gave two constitutional isomers (entry 4). The observation of the product allylated at the position *ortho* to OMe as a minor isomer is also consistent with the CMD pathway; CMD process with anisole has been reported to proceed at the *ortho* position.[2f,9] Finally, the allylation of *para*-trifluoromethyl fluorobenzene underwent C–C bond formation to yield a single isomer of allylarene **5e** (entry 5).

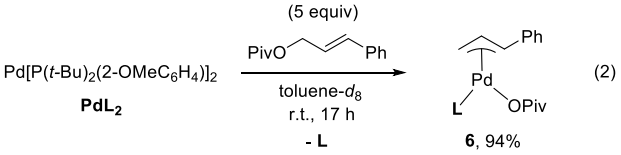
In addition to the allylations of monofluoroarenes, the allylations of non-fluorinated arenes with **2a** occurred (Table 3, entries 6–9). The allylation of 1,3-benzodioxole proceeded selectively at the *ortho* position to form **5f** (entry 6). The allylation of chlorinated arenes also occurred, furnishing allylarenes **5g** and **5h** as the major products (entries 7 and 8).[16] Furthermore, the reaction of 1-methoxy-4-(trifluoromethyl)benzene produced allylation product **5i**, albeit in low yield (entry 9).

Table 3. Scope of the Allylation of Arenes with Cinnamyl Pivalate[a]

entry	major product[b]	entry	major product[b]
1	 **5a**, 64%	6	 **5f**, 66%
2	 **5b**, 48%	7[c]	 **5g**, 79% (major:minor[e] = 6:1)
3 4 5	 **5c**, R = Me: 74% **5d**, R = OMe: 83% (*o*-F:*o*-OMe = 3:1) **5e**, R = CF_3: 87%[d]	8[c]	 **5h**, 36%[d]
9	 **5i**, 29% (*o*-OMe:*o*-CF_3 = 16:1)		

[a]Reaction conditions: arene (1.40 mL), **2a** (0.35 mmol, 1.0 equiv), $Pd(OAc)_2$ (10%), **L** (20%), AgOPiv (1.0 equiv), Cs_2CO_3 (2.4 equiv) at 120 ºC for 17 h. [b]Yield of purified product. [c]Ag_2CO_3 was used instead of AgOPiv. [d]Determined by ^{1}H NMR spectroscopy. [e]Cinnamylated at the position *ortho* to Cl and *para* to OMe.

Mechanistic Studies. *(π-Allyl)palladium intermediate*. A proposed mechanism for the palladium-catalyzed direct functionalization of arenes with organic electrophiles generally begins with the oxidative addition of the organic electrophile to Pd(0).[7a,c,8] Indeed, treatment of $Pd[P(t\text{-}Bu)_2(2\text{-}OMeC_6H_4)]_2$ (**PdL_2**) with 5 equivalents of cinnamyl pivalate **2a** at room temperature generated (π-cinnamyl)palladium pivalate **6** (eq 2). The structure of this complex was confirmed by X-ray crystallography. The solid-state structure contains a π-cinnamyl ligand and an η^1-pivalate ligand in addition to the phosphine (Figure 1). No interaction of the palladium center with the *ortho*-methoxy group on the ligand was observed.



(2)

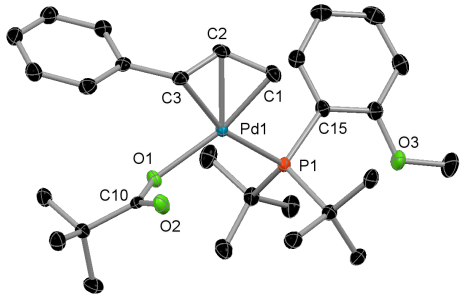
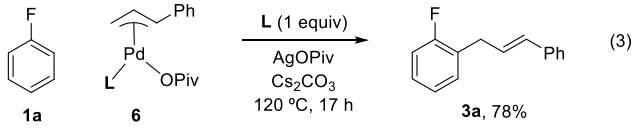


Figure 1. ORTEP diagram of complex **6** (O1–Pd1 2.117(14) Å; P1–Pd1 2.332(6) Å; C1–Pd1 2.094(2) Å; C2–Pd1 2.145(2) Å; C3–Pd1 2.259(2) Å) (C3–C2–C1 118.8(2)°; C15-P1-Pd1 109.0(7)°; C10-O1-Pd1 112.1(13)°) (ellipsoids are shown at 50% probability, and hydrogen atoms are omitted for clarity).

The competency of complex **6** to be an intermediate in the catalytic process was investigated. The stoichiometric reaction of complex **6** with fluorobenzene in the presence of AgOPiv at 120 ºC formed allylarene **3a** in 78 % yield after 17 h (eq 3). This yield is similar to the 82% yield of the catalytic reaction (Table 1, entry 1). No allylarene **3a**, as determined by gas chromatography, was formed when AgOPiv was omitted from the stoichiometric reaction of complex **6** with **1a** (eq 3). This lack of formation of allylarene is consistent with the lack of product formed in the catalytic reaction without silver(I) additive (Table 1, entry 17). Monitoring of the reaction of eq 3 by ^{31}P NMR spectroscopy showed that complex **6** was fully converted within 10 min to a new palladium species and at this time, allylarene **3a** was formed in only 36% yield. As discussed later in this paper, the palladium species formed by this reaction is the resting state of the catalyst (**12**) in the direct allylation process.[17]

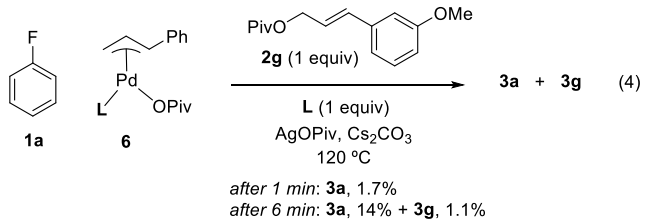


(3)

The difference in conversion of allylpalladium **6** and formation of allylarene **3a** suggests that the allylarene **3a** formed by heating **6** with fluorobenzene (**1a**) might not form directly from **6**. Instead, it could be generated by production of the free cinnamyl pivalate (**2a**) and the active catalyst, and the active catalyst could mediate a process to form allylarene **3a** from arene **1a** and allylic pivalate **2a** without the intermediacy of allylpalladium complex **6**. Therefore, this stoichiometric reaction was not sufficient to confirm the intermediacy of complex **6** in the allylation process.

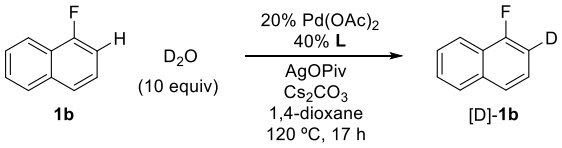
To distinguish between the potential role of allylpalladium **6** as an intermediate or a source of an allylic ester, we monitored the initial formation of allylation products during the stoichiometric reaction of complex **6** with **1a** in the presence of 1 equivalent of allylic pivalate **2g** (eq 4). If the allylic pivalate reacted with the arene directly, then the major allylarene prod-

uct at early times would be derived from the allyl group on **6**. However, if complex **6** is a precatalyst and the allylarene does not form from **6**, then the major allylarene product at early times would be derived from the free allylic pivalate. After 1 min, 1.7% of allylarene **3a** formed and no allylarene **3g** detectable by gas chromatography was formed. After ~6 min 14% of allylarene **3a** and 1.1% of allylarene **3g** had formed (Figure S1 in the Supporting Information). This result implies that complex **6** does lie on the reaction pathway and that **3a** is generated by the reaction of complex **6** with fluorobenzene **1a**, rather than the reaction of **1a** with cinnamyl pivalate **2a** in a process catalyzed by a palladium complex generated from **6**.



Role of Ag(I) salts in direct allylation of arenes. The role of Ag(I) salts in the direct allylation process was unusual. Because the addition of Ag(I) salts to our Pd-catalyzed allylation enabled the process to occur with arenes that were unreactive in the absence of the silver carboxylate (Table 1, entries 1 and 17), we hypothesized that this additive might be involved in the step that cleaves the aryl C–H bond.[10-13]

Table 4. H/D exchange experiments of 1-fluoronaphthalene[a]



entry	variation from the condition above	%D[b]
1	none	44
2	no AgOPiv	-
3	no **L**	<5
4	no $Pd(OAc)_2$	**67**

[a]Reaction conditions: **1b** (0.10 mmol, 1.0 equiv), D_2O (10 equiv), $Pd(OAc)_2$ (20%), **L** (40%), AgOPiv (1.0 equiv), Cs_2CO_3 (2.4 equiv) in 1,4-dioxane (0.10 mL) at 120 °C for 17 h. [b]Determined by ^1H and ^{19}F NMR spectroscopy.

To test this hypothesis, we studied H/D exchange reactions of 1-fluoronaphthalene **1b** with 10 equivalents of D_2O (Table 4; see supporting information for details). In the presence of the combination of $Pd(OAc)_2$, **L** and AgOPiv, 44% deuterium incorporation occurred selectively at the position *ortho* to the fluorine substituent of **1b** at 120 °C after 17 h (entry 1). No deuteration was observed when the reaction was conducted without added AgOPiv (entry 2), and only a trace amount of deuterated [D]-**1b** was observed without the added phosphine **L** (entry 3). In addition, the H/D exchange reaction in the presence of AgOPiv and **L** in the absence of $Pd(OAc)_2$ resulted in 67% of deuterium incorporation at the site *ortho* to the fluorine of **1b** (entry 4). These results suggest that the combination of phosphine **L** and AgOPiv, rather than the palladium species, are responsible for C–H activation of the arene.

To gain information on the C–H activation process by the Ag complex, we prepared the phosphine-ligated silver carboxylate by treatment of AgOPiv with 1 equivalent of P*t*-Bu_2(2-$OMeC_6H_4$) (**L**) in C_6D_6 at room temperature. The complex formed within 10 min, as determined by ^1H and ^{31}P NMR spectroscopy.[18] This complex exists as two unequally populated rotamers in C_6D_6 at room temperature with the ratio of 1:1.7 (**7a**:**7b**), due to the restricted rotation around the C(aryl)-P bond of **L**. X-ray crystallographic analysis of the **L**-ligated AgOPiv (**7**) revealed that this complex also crystallizes as two rotamers. Both rotamers are monomeric with a κ^2-pivalate ligand (Figure 2).

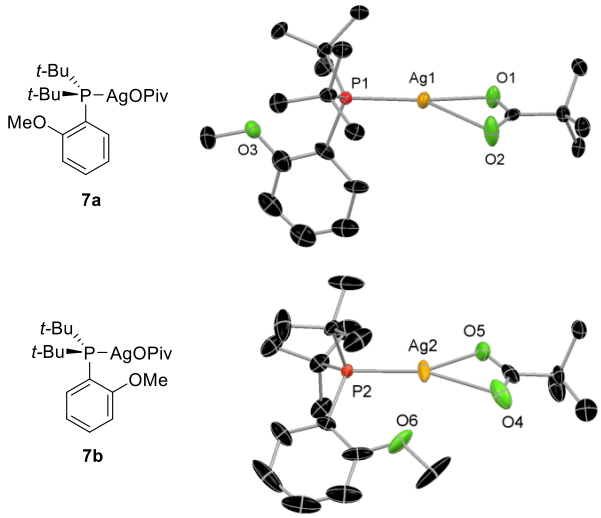
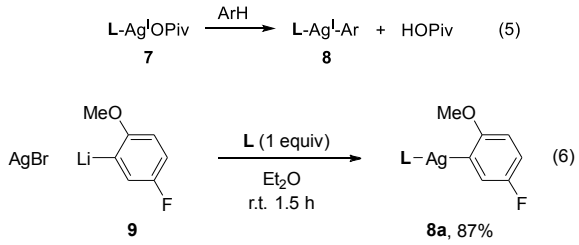


Figure 2. ORTEP diagram of **L**-ligated silver pivalate (**7**) (P1–Ag1 2.349(12) Å; O1–Ag1 2.135(3) Å; O2–Ag1 2.714(4) Å; P2–Ag2 2.346(1) Å; O5–Ag2 2.305(4) Å; O4–Ag2 2.447(5) Å) (O1–Ag1–P1 171.4(10)°; O2–Ag1–P1 136.5(9)°; O1–Ag1–O2 52.0(1)°; O5–Ag2–P2 148.4(1)°; O4–Ag2–P2 156.0(1)°; O5–Ag2–O4 55.0(1)°) (ellipsoids are shown at 50% probability, and hydrogen atoms are omitted for clarity).

Monitoring of the catalytic reaction under the standard conditions by ^{31}P NMR spectroscopy showed that the **L**-ligated Ag complex **7** was present throughout the process. Moreover, the initial rate of the catalytic allylation process was higher for reactions conducted with higher concentrations of phosphine **L** (Figure S3). In addition, the kinetic isotope effect (KIE) of the direct allylation of fluorobenzene **1a** and fluorobenzene-d_5 with cinnamyl pivalate in separate reaction vessels was 2.3.[19] Collectively, these observations are consistent with the proposal that cleavage of the aryl C–H bond occurs by the **L**-ligated AgOPiv **7** and that this C–H bond cleavage step strongly affects the overall rate of the reaction.

We hypothesized that the reaction of the **L**-ligated AgOPiv (**7**) with arene would form arylsilver(I) intermediate **8** (eq 5), which could transfer an activated aryl moiety to a palladium intermediate. Because arylsilver species are rare and no phosphine-ligated arylsilver complexes have been prepared previously,[20] we sought additional information on the structure, stability, and reactivity of this proposed intermediate. The arylsilver complex **8a** was prepared from the reaction of AgBr and aryllithium **9** in the presence of **L** (eq 6).[21] Arylsilver **8a** is stable at 4 °C under a nitrogen atmosphere, in the dark, for at least one month.



Although we were not able to obtain crystals of complex **8a** suitable for X-ray diffraction, we characterized an analog of **8a** containing P(2-anisyl)$_3$ as the ligand by X-ray diffraction (Figure 3). The ORTEP diagram of this complex is shown in Figure 3 and consists of a monomeric structure with a linear disposition of the phosphine and aryl groups around the silver. The Ag–C(aryl) distance of this complex (2.12 Å) is shorter than that in mesitylsilver (2.20 Å), an arylsilver(I) complex which lacks a phosphine ligand and is tertrameric.[22]

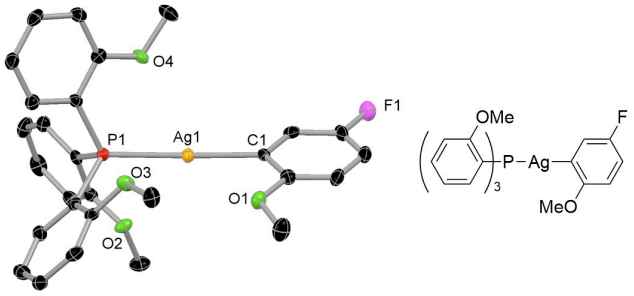
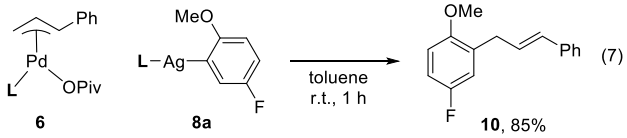
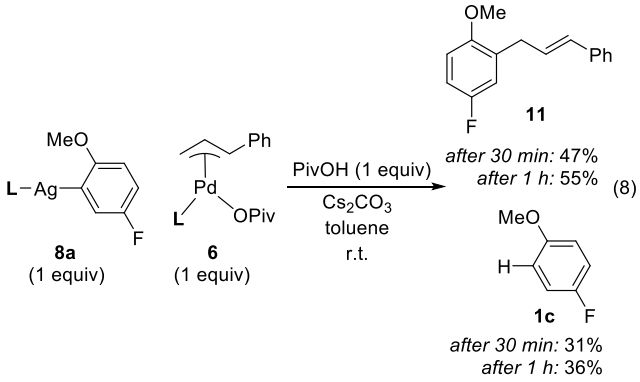


Figure 3. ORTEP diagram of the P(2-anisyl)$_3$-ligated silver-aryl complex (P1–Ag1 2.378(9) Å; C1–Ag1 2.123(3) Å) (P1–Ag1–C1 178.5(1)°) (ellipsoids are shown at 50% probability, and hydrogen atoms are omitted for clarity).

The reaction of Ag complex **8a** with cinnamylpalladium **6** formed allylarene **10** in 85% yield within 1 h at room temperature. **PdL$_2$** was the palladium-containing product, as determined by ^{31}P NMR spectroscopy (eq 7); the formation of **PdL$_2$** indicates that phosphine **L** binds tighter to the palladium(0) center than it binds to the silver(I) center. The high yield of allylarene from reaction of **8a** with **6** implies that the transmetallation of the aryl group from silver to palladium and the following reductive elimination are chemically and kinetically competent to be part of the catalytic cycle.



For cleavage of the arene C–H bond by **L**-AgOPiv **7** to contribute substantially to the rate of the direct allylation process, the reaction of AgAr **8a** with palladium complex **6** should occur with a rate that is similar to or greater than the reaction of AgAr **8a** with PivOH (a reverse of the arene C–H activation). To reveal these relative rates, we treated arylsilver **8a** with a 1:1 ratio of allylpalladium **6** and PivOH in the presence of 2.4 equivalents of Cs_2CO_3. This reaction formed allylarene 10 in 47% yield and arene 1c in 31% yield after 30 min, and 55% yield and arene 1c in 36% yield after 1 h (eq 8).[23] This result indicates that the rate of the reaction of **8a** with **6** is similar to that of the reaction of **8a** with pivalic acid or $CsHCO_3$ and that the silver intermediate would partition almost equally between transmetallation to form the allylarene and regeneration of the silver carboxylate. This partial reversibility of the C–H bond cleavage step accounts for the modest KIE of 2.3.



Proposed synergistic catalytic cycle. The mechanism in Figure 4 for the allylation of arenes with palladium(0), phosphine ligand and AgOPiv is consistent with all of our data. In this mechanism, **L**-AgOPiv **7** reacts with the arene to form arylsilver intermediate **8** in an endoergic step, presumably by a pivalate-assisted CMD mechanism. In parallel, oxidative addition of the allylic ester to the Pd(0) complex bound by **L** (**PdL$_2$**) forms the allylpalladium complex **6**. The aryl group is transferred from silver to **6**. The resulting allylpalladium aryl complex **11** undergoes reductive elimination to form the allylarene product and **PdL$_2$**.

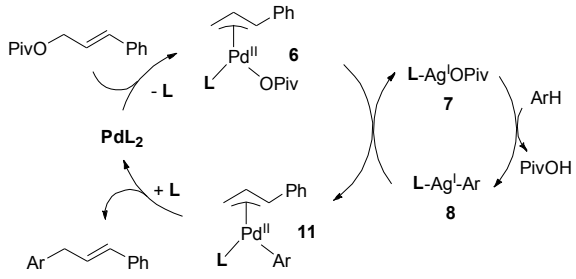
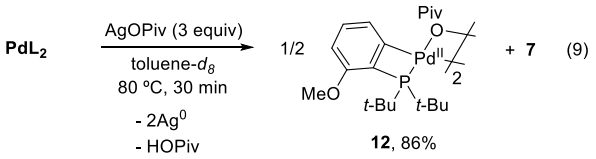
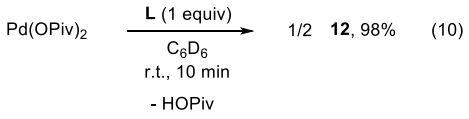


Figure 4. Outline of a possible mechanism for Pd-catalyzed and Ag-mediated direct allylation of arenes with allylic pivalates.

Resting state of the catalyst. Although our C–H allylation is not an oxidative process, we examined the possibility that the Ag(I) salt serves as an oxidant in the catalytic system.[1] Treatment of bisphosphine-Pd(0) (**PdL$_2$**) with 3 equivalents of AgOPiv afforded **L**-AgOPiv **7** and a new palladium(II) complex, which resonated in the upfield region of the ^{31}P NMR spectrum at –23.1 (eq 9). Single-crystal X-ray diffraction showed that this new complex is the pivalate-bridged dimeric palladacycle **12**, resulting from the intramolecular activation of the *ortho* C–H bond of the phosphine **L** (Figure 5).[24] Complex **12** also forms from the reaction of Pd(OPiv)$_2$ and 1 equivalent of **L** at room temperature within 10 min in C_6D_6 (eq 10).





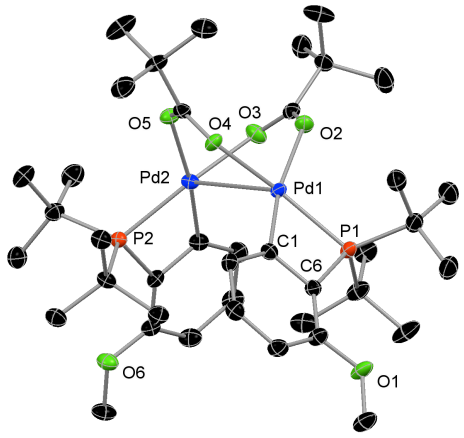
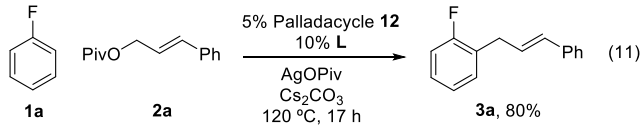


Figure 5. ORTEP diagram of dimeric palladacycle **12** (Pd1–Pd2 3.248(6) Å; C1–Pd1 1.984(3) Å; P1–Pd1 2.237(9) Å; O2–Pd1 2.130(2) Å; O4–Pd1 2.105(2) Å) (P1–Pd1–C1 69.3(9)°; Pd1–C1–C6 108.2(2)°; C1–C6–P1 97.1(2)°; C6–P1–Pd1 85.4(1)°; O4–Pd1–O2 90.8(8)°) (ellipsoids are shown at 50% probability, and hydrogen atoms are omitted for clarity).

Palladacycle **12** is the resting state of the palladium catalyst during the allylation process. This complex and the **L**-ligated silver complex **7** were the major phosphine-ligated complexes in the system, as determined by monitoring the catalytic reaction of fluorobenzene with cinnamyl pivalate by ^{31}P NMR spectroscopy (Figure S5). We have also determined that palladacycle **12** catalyzes the allylation of **1a** with **2a** to form allylarene **3a** (eq 11). The yield (80%) of this process is similar to that of the reaction catalyzed by the combination of $Pd(OAc)_2$ and **L** or by **PdL₂** (Table 1, entries 1 and 2). Moreover, the initial rate and induction period (~8 min) for the reaction catalyzed by palladacycle **12** (eq 11) are similar to those of the reactions catalyzed by the combination of $Pd(OAc)_2$ and **L** or by **PdL₂** (Table 1, entries 1 and 2) (Figure S2). This result indicates that palladacycle **12** does not lie on the reaction pathway but that it generates the active Pd species, presumably a Pd(0) species bound by the phosphine, in the catalytic cycle of the allylation and is not formed irreversibly as an inactive catalyst.[23,25] The mechanism by which **12** forms a Pd(0) species is not clear.



CONCLUSIONS

We have discovered a method for the highly site-selective formation of C(aryl)–C(sp^3) bonds by the Pd-catalyzed and Ag-mediated allylation of aryl C–H bonds with allylic pivalates to furnish linear (*E*)-allylarenes in good yields. This process occurs with arenes that have not been described to undergo site-selective direct allylations previously, including those containing fluoro, chloro, trifluoromethyl, or methoxy groups. The observed site-selectivity suggests that the C–H bond cleavage proceeds through a concerted metalation-deprotonation pathway at the most acidic C–H bond.

The available mechanistic data are consistent with a synergistic catalytic process wherein the cleavage of an aryl C–H bond occurs by a phosphine-ligated AgOPiv complex; the resulting arylsilver species then transfers an aryl group to the (π-allyl)palladium pivalate species formed by oxidative-addition of an allylic pivalate to Pd(0). Subsequent C–C bond-forming reductive elimination affords the allylation product and regenerates the Pd(0) species. The proposed palladium and silver intermediates have been synthesized, unambiguously characterized by X-ray crystallography, and shown to be chemically and kinetically competent to be intermediates by the suggested elementary steps of the catalytic cycle. The implications of these findings to other palladium-catalyzed reactions that occur with silver additives and that have been computed to occur by clusters containing Ag and Pd as well as the applications of Ag(I)-mediated C–H activation to new C–H functionalization processes are underway.

ASSOCIATED CONTENT

Supporting Information
Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

jhartwig@berkeley.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the Director, Office of Science, of the U.S. Department of Energy under contract No. DE-AC02-05CH11231 and the National Institutes of Health (postdoctoral fellowship to S.Y.L.: F32-GM113404). We thank Dr. Antonio DiPasquale for X-ray crystallographic analysis (NIH Shared Instrumentation Grant S10-RR027172) and Thomas J. O'Connor (supported by UC Berkeley Amgen Scholars program and CENTC program) for assistance on the initial investigation. S.Y.L. thanks Taegyo Lee for insightful discussions and David M. Peacock for assistance on NMR experiments and for the gift of di-*tert*-butylarylphosphines used for initial studies.

REFERENCES

(1) For reviews on C–H functionalizations, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Yu, J.-Q., Shi, Z., Eds. *Topics in Current Chemistry: C−H Activation*, 1st ed.; Springer: Berlin/Heidelberg, 2010. (c) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (d) He, M.; Soulé, J.-F.; Doucet, H. *ChemCatChem* **2014**, *6*, 1824. (e) Liu,

C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138.

(2) For selected examples on direct arylations of arenes, see: (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Science* **2012**, *337*, 1644. (c) Ricci, P.; Krämer, K.; Cambeiro, X. C.; Larrosa, I. *J. Am. Chem. Soc.* **2013**, *135*, 13258. (d) Wagner, A. M.; Hickman, A. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 15710. (e) Durak, L. J.; Lewis, J. C. Organometallics **2014**, *33*, 620. (f) Ricci, P.; Krämer, K.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 18082.

(3) For selected references on alkenylation and alkynylation of arenes, see: (a) Vora, H. U.; Silvestri, A. P.; Engelin, C. J.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 2683. (b) de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512.

(4) (a) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596. (b) Ying, C.-H.; Duan, W.-L. *Org. Chem. Front.* **2014**, *1*, 546.

(5) G. A. Olah, *Friedel–Crafts and Related Reactions*, *Vol. 2*, Wiley-Interscience, New York, **1964**.

(6) For selected recent examples on direct allylation of arenes bearing a directing group, see: (a) Wang, H.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5386. (b) Ye, B.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 636. (c) Liu, W.; Richter, S. C.; Zhang, Y.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 7747. (d) Yamaguchi, T.; Kommagalla, Y.; Aihara, Y.; Chatani, N. *Chem. Commun.* **2016**, *52*, 10129. (e) Choi, M.; Park, J.; Sharma, S.; Jo, H.; Han, S.; Jeon, M.; Mishra, N. K.; Han, S. H.; Lee, J. S.; Kim, I. S. *J. Org. Chem.* **2016**, *81*, 4771.

(7) For examples on direct allylation of polyfluoroarenes, see: (a) Fan, S.; Chen, F.; Zhang, X. *Angew. Chem., Int. Ed.* **2011**, *50,* 5918. (b) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2990. (c) Yu, Y,-B.; Fan, S.; Zhang, X. *Chem. Eur. J.* **2012**, *18*, 14643. (d) Jiang. H.; Yang, W.; Chen, H.; Li, J.; Wu, W. *Chem. Commun.* **2014**, *50*, 7202. (e) Xie, W.; Chang, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 1736; for an example of electron-deficient azoles, see: (f) Makida, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4122.

(8) (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; Wiley-Interscience: New York, 1987; pp 322-333. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i. Ed.; Wiley Interscience: New York, 2002.

(9) For reviews and leading references, see: (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658. (d) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754−8756. (e) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (f) Guihaumé, J.; Clot, E.; Eisenstein, O.; Perutz, R. N. *Dalton Trans.* **2010**, *39*, 10510.

(10) Whitaker, D.; Burés, J.; Larrosa, I. *J. Am. Chem. Soc.* **2016**, *138*, 8384.

(11) Lotz, M. D.; Camasso, N. M.; Canty, A. J.; Sanford, M. S. *Organometallics* **2016**, DOI: 10.1021/acs.organomet.6b00437.

(12) For examples on arene C–H activation by silver carbonate, see: (a) He, C.; Min, Q.; Zhang, X. *Organometallics* **2012**, *31*, 1335 (b). Li, H.; Liu, J.; Sun, C. L.; Li, B. J.; Shi, Z. J. *Org. Lett.* **2011**, *13*, 276.

(13) For examples on Pd-Ag bi- or mulitmetallic intermediates in arene C–H cleavage, see: (a) Anand, M.; Sunoj, R. B.; Schaefer, H. F. *J. Am. Chem. Soc.* **2014**, *136*, 5535. (b) Yang, Y.; Cheng, G.; Liu, P.; Leow, D.; Sun, T.; Chen, P.; Zhang, X.; Yu, J.; Wu, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344. (c) Anand, M.; Sunoj, R. B.; Schaefer, H. F. *ACS Catalysis* **2016**, *6*, 696.

(14) (a) Empsall, H. David; Shaw, Bernard L.; Turtle, Brian L. *J. Chem. Soc., Dalton Trans.* **1976**, 1500. (b) Bornand, M.; Torker, S.; Chen, P. *Organometallics* **2007**, *26*, 3585.

(15) (a) Allylic electrophiles containing heterocycles such as furan or thiophene were not compatible with our allylation process. (b) The reactions with allylic electrophiles that bear *β*-hydrogens upon forming an allylpalladium intermediate (e.g., (*E*)-but-2-en-1-yl pivalate) resulted in producing *β*-hydride elimination products.

(16) Biaryls resulting from the direct arylation of arenes with aryl chlorides were obtained as side products.

(17) Complex **6** with 1 equivalent of **L** at 120 °C in fluorobenzene forms a 4:1 mixture of **6** and $\mathbf{PdL_2}$ after 10 min. In the presence of AgOPiv, $\mathbf{PdL_2}$ is oxidized to generate dimeric palladacycle **12** (eq 9).

(18) For examples on silver carboxylates ligated by a phosphine, see: (a) Ng, S. W.; Othman, a. H. *Acta Crystallogr. Sect. C Cryst. Struct. Commun.* **1997**, *53*, 1396. (b) Paramonov, S. E.; Kuzmina, N. P.; Troyanov, S. I. *Polyhedron* **2003**, *22*, 837. (c) Partyka, D. V; Deligonul, N. *Inorg. Chem.* **2009**, *48*, 9463.

(19) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51,* 3066.

(20) Schmidbaur, H.; Bayler, A.; Synthesis and uses of organosilver compounds, in *The Chemistry of Organic Derivatives of Gold and Silver*, Patai. S.; Rappoport, Z., eds., Wiley, Chichester, UK, **1999**, pp. 211-226.

(21) Leusink, A. J.; Koten, G. V.; Noltes, J. G. *J. Organomet. Chem.* **1973**, *56*, 379.

(22) (a) Gambarotta, S.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Chem. Soc., Chem. Commun.* **1983**, 1087. (b) Meyer, E. M.; Gambarotta, S.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *Organometallics* **1989**, *8*, 1067.

(23) When the reaction was conducted in the absence of Cs_2CO_3, 20 % of allylarene **10** and 66 % of arene **1c** were formed after 1 h.

(24) For references on the related palladacycle resulting from the intramolecular C–H activation of P(*t*-Bu)$_3$, see: (a) Geisseler, H.; Gross, P.; Guckes, B. German Patent GWXXBX 19647584, 1998; CAN 129:28078. (b) Henderson, W. H.; Alvarez, J. M.; Eichman, C. C.; Stambuli J. P. *Organometallics* **2011**, *30*, 5038.

(25) Stambuli's study on the related palladacycle with P(*t*-Bu)$_3$ established that this complex could form PdP(*t*-Bu)$_3$]$_2$ upon thermal decomposition (ref 24b).

Table of Contents Graphic: