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Heck Alkynylation (Copper-Free Sonogashira Coupling) of Aryl and Heteroaryl Chlorides, Using Pd Complexes of *t*-Bu_2(*p*-$NMe_2C_6H_4$)P: Understanding the Structure–Activity Relationships and Copper Effects

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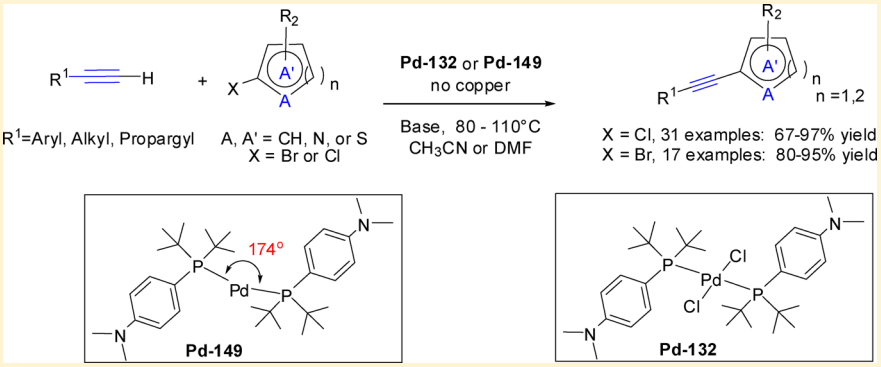
Supporting Information



ABSTRACT: $L_2Pd(0)$ and $L_2Pd(II)$ complexes, where L= *t*-Bu_2(*p*-$NMe_2C_6H_4$)P, have been identified as efficient catalyst systems for the Heck alkynylation of a variety of aryl bromides (17 examples) and aryl/heteroaryl chlorides (31 examples) with a range of aryl- and alkyl-acetylenes in excellent yields, under relatively low Pd loadings. The single-crystal X-ray structure determination of the presumably active catalytic species, $L_2Pd(0)$, was carried out in this study to better understand the superior activity of the current catalyst system from a structure–activity relationship point of view. The P–Pd–P bond angle indicates that the complex is bent (174.7°) in comparison to the perfectly linear (180.0°) structure of the analogous Pd(*t*-$Bu_3P)_2$. Preliminary mechanistic studies on the negative copper effect and substrate effect of aryl acetylenes were conducted to better understand the cross-coupling pathway of Heck alkynylation.

INTRODUCTION

Sonogashira coupling has recently become the third most popular organic transformation[1] in the area of Pd-catalyzed C–C bond-forming reactions.[2] This was based on the number of publications and patents reported,[2a,b] since the original publications of the Pd-catalyzed coupling of acetylene with aryl halides in 1975 by three independent groups: Sonogashira,[3] Cassar,[4] and Heck.[5] While Cassar and Heck employed Cu-free conditions at relatively higher temperatures using aryl bromide substrates, Sonogashira developed a room temperature protocol to couple aryl iodides in the presence of a CuI cocatalyst (Scheme 1). The original Sonogashira procedure has been subsequently modified from time to time to further expand its scope from a practical point of view.[1,6]The industrial application of Sonogashira protocol is demonstrated very effectively for the production of a widely used antimyotic drug, Terbinafin (Lamisil, Sandoz).[7] However, the classical Sonogashira reaction suffers many drawbacks, such as the use of environmentally less friendly amine bases; copper cocatalysts, which can accelerate the dimerization of the acetylene via Glaser coupling. In addition, there are substrate limitations to aryl iodides and aryl bromides. Removal of Cu from the coupled product further complicates the workup and purification, especially in the pharmaceutical processes.[8] Various attempts have been made to either eliminate copper salts or replace them with less-toxic transmetalating agents.[9] Along with the development of copper-free reaction conditions, investigations to couple challenging aryl chlorides or even less reactive tosylates have emerged as a new trend during the past decade.[10]

These improvements have mainly benefited from the utilization of novel bulky electron-rich phosphine ligands (Figure 1). For example, in 2003, Plenio and co-workers were one of the earlier groups to demonstrate the coupling of aryl chlorides with selected alkynes using $Ad_2P(n\text{-}Bu)$ ligand in the presence of a catalyst precursor, Na_2PdCl_4, and CuI cocatalyst.[11] Although activated aryl chlorides (electron withdrawing) gave very good yields (90–95%), electron neutral and electron-donating chlorides gave lower yields (54–85%). For

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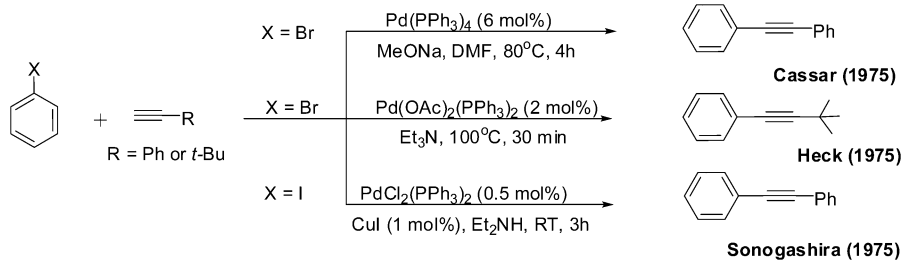
Scheme 1. Original Conditions for Coupling of Aryl Iodides and Bromides with Phenyl and Butyl Acetylenes Using Ph_3P-Based Pd Catalysts



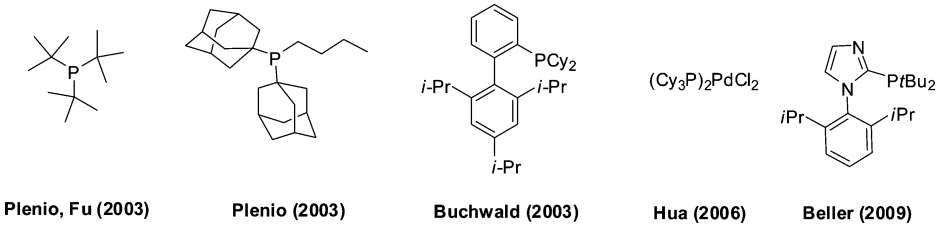


Figure 1. Ligands/catalysts used for Sonogashira coupling of aryl chlorides.

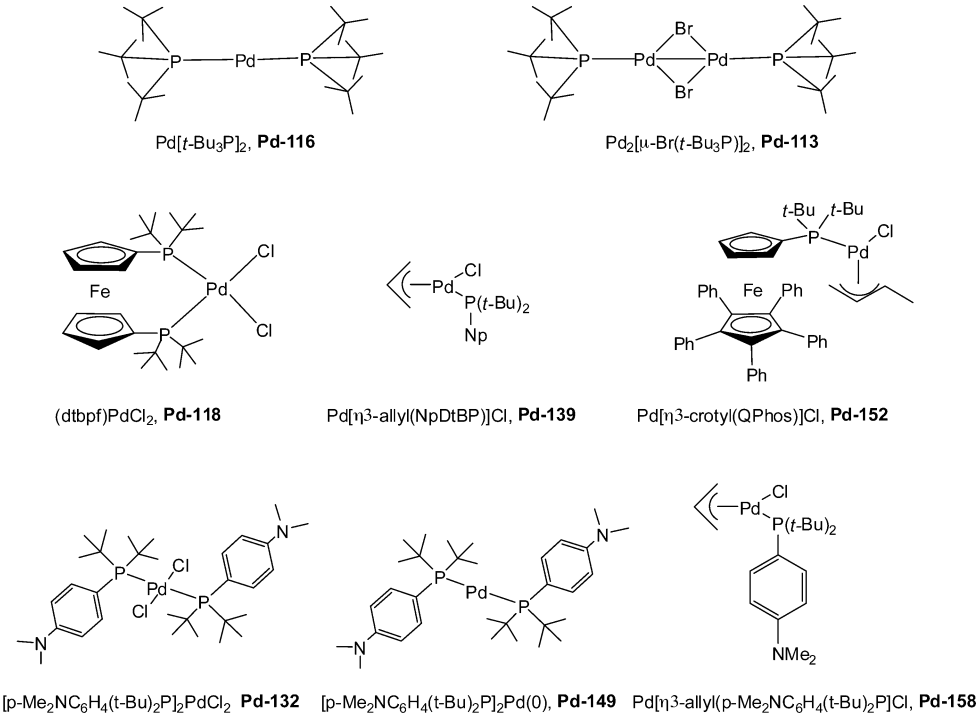


Figure 2. Examples of new generation precatalysts developed in-house for commercial applications, involving challenging cross coupling.

the latter systems, t-Bu_3P gave slightly better yields (77−84%). During the same year, the Buchwald group reported a Cu-free Sonogashira coupling protocol for aryl chlorides using X-Phos in conjunction with $PdCl_2(MeCN)_2$.[12] As of today, this work stands out as an important publication in this area. Three years later, Hua et al. used a commercially available precatalyst, $(Cy_3P)_2PdCl_2$, to couple a few examples of relatively less challenging aryl chlorides with alkyl-substituted alkynes at 150 °C in the absence of Cu.[13] In 2009, Beller also reported a Cu-free coupling of activated aryl chlorides (with the exception of p-chloroanisole) with limited examples of heteroaryl chlorides (3-chlorothiophene and 4-chlorobenzopyridine) using a "Buchwald type" heteroaryl−aryl-based monophospine ligand.[14] The Sonogashira coupling of aryl halides was also conducted in water: in 2003, Plenio[15] and Nájera[16] independently demonstrated the use of aryl halide coupling in the presence of water by taking advantage of the water solubility of the ligands. Recently, the Buchwald group[17] coupled aryl chlorides by using sulfonated S-Phos, while Lipshtuz[18] carried out a room temperature coupling of aryl bromides using phase-transfer surfactants (PTS) technology in conjunction with X-Phos/$PdCl_2(MeCN)_2$. Buchwald et al. have also explored Heck alkynylations with examples of aryl- and heteroaryl chlorides under both batch and continuous flow conditions.[10l]

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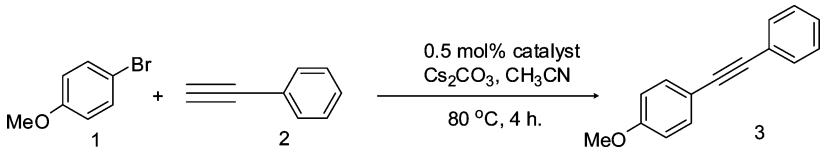
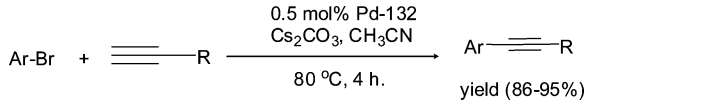
Table 1. Catalyst Screening for Heck Alkynylation of Aryl Bromides[a]

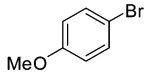
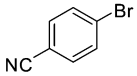
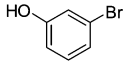
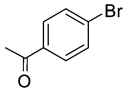
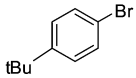


entry	catalyst	code	% yield[b]
1	$PdCl_2(t\text{-}Bu_2(p\text{-}NMe_2C_6H_4)P)/CuI$[d]	**Pd-132**	56
2	$PdCl_2(t\text{-}Bu_2(p\text{-}NMe_2C_6H_4)P)$	**Pd-132**	99 (95)[c]
3	$PdCl_2(t\text{-}Bu_2PhP)_2$	**Pd-122**	96
4	$PdCl_2$(dtbpf)	**Pd-118**	91
5	$Pd(t\text{-}Bu_3P)_2$	**Pd-116**	73
6	$[Pd(t\text{-}Bu_3P)Br]_2$	**Pd-113**	61
7	$Pd(PPh_3)_4$	**Pd-101**	15
8	$PdCl_2(PCy_3)_2$	**Pd-114**	2

[a]Conditions: 1.5 mmol of aryl bromide, 1.2 equiv of phenylacetylene, 2 equiv of Cs_2CO_3, 2.0 mL of CH_3CN, 0.5 mol % of catalyst. [b]GC yield. [c]Isolated yield in parentheses. [d]0.1 mol % CuI.

Table 2. Cu-Free Sonogashira Coupling of Aryl Bromides[b]



entry	Ar-Br	R	% yield[a]	entry	Ar-Br	R	% yield[a]
1		Ph	93	10		Ph	89
2		-C_6H_{13}	90	11		-C_6H_{13}	86
3			87	12			91
4		Ph	95	13		Ph	93
5		Ph	91	14		Ph	90
6		Ph	86	15		Ph	92
7		Ph	88	16		Ph	93
8		Ph	92	17		Ph	93
9		Ph	93				

[a]Isolated yield. [b]Conditions: 1.5 mmol of aryl bromide, 1.2 equiv of alkyne, 2 equiv of Cs_2CO_3, 2.0 mL of CH_3CN, 0.5 mol % of catalyst.

Although the catalytic systems mentioned above are fairly effective in covering a series of aryl chloride substrates, there is still room for further development of this area. Clearly there is a need to develop more reliable, robust, practical catalyst systems and conditions to expand the scope of this class of reaction by addressing problematic substrates such as unactivated aryl chlorides and heteroaromatic chlorides containing more than one heteroatom. In addition, aromatic acetylenes are also

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challenging coupling partners. Therefore, in this study, our main intention is to expand the scope of Heck alkynylations to various aryl and heteroaryl chlorides with challenging acetylenes using commercially available precatalysts.

In our ongoing efforts to discover/develop new and efficient practical cross-coupling catalysts, in recent years, we have implemented several catalytic systems for solving some of the unmet challenges.[19] Among those catalyst systems, preformed palladium phosphine complexes that we have developed have been effectively used for a wide variety of challenging cross-coupling reactions (Figure 2). The benefits on the design and the use of these preformed catalysts versus in situ systems were reviewed recently.[20] Of the various precatalysts that we developed and commercialized, **Pd-118** and **Pd-132** stood out to be the two best catalysts of choice based on their air stability, versatility, and high catalytic activity.[20] From the preliminary work on Cu-free Sonogashira reactions, we have realized that the Pd(0) version of **Pd-132**, named **Pd-149**, is a very good catalyst for both aryl and heteroaryl chlorides under Cu-free conditions.[19b] We have also synthesized a mono coordinated Pd-phosphine complex, (η^3-allyl)Pd(L)Cl, using the common ligand, p-$Me_2NC_6H_4(t\text{-}Bu)_2P$ used for making both **Pd-132** and **Pd-149**. Preliminary studies indicated that (η^3-allyl)Pd(L)Cl (**Pd-158**) is more superior than our well-known catalyst, **Pd-118**, for the α-arylation of tetralone.[19a] Therefore, we decided to focus our effort to study the effectiveness of p-$Me_2NC_6H_4(t\text{-}Bu)_2P$-based $L_2Pd(II)$, $L_2Pd(0)$, and LPd(II) catalysts for the Heck alkynation reaction (Cu-free Sonogashira reaction) along with the other well-known catalysts that we have commercialized as controls. This study also provides some insight into the structure−activity relationship with respect to substrates and catalysts as well as the roles of Cu salts, bases, and solvents.

RESULTS AND DISCUSSION

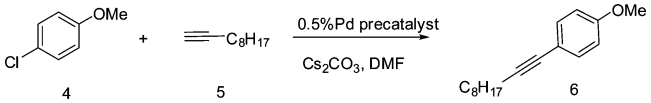
Heck Alkynylation of Aryl Bromides. As Cu has several drawbacks in the manufacture of pharmaceutical materials, we tested air-stable $[p\text{-}Me_2NC_6H_4(t\text{-}Bu)_2P]_2PdCl_2$ (**Pd-132**) for its effectiveness in the coupling of a relatively challenging model substrate, p-bromoanisole, with phenyl acetylene, with and without Cu (Table 1). As reported by Buchwald[12] and Beller,[14] we have also observed that Cu salts have a deleterious effect (56% vs 99% GC yield). The choice of the solvent as well as the base was also important for the success of the coupling. Both DMF and CH_3CN were optimal solvents in comparison to the nonpolar or polar protic solvents. Numerous bases were screened, and only Cs_2CO_3 and K_3PO_4 were proven to be suitable. Addition of different metal salts, such as $ZnCl_2$, to the reaction was also investigated with no significant improvement on conversion. Under optimal conditions, we tested five new generation commercially available catalysts, along with the classical catalyst $Pd(PPh_3)_4$ (see Table 1). Both $[Ph(t\text{-}Bu)_2P]_2PdCl_2$ (**Pd-122**)[21] and (dtbpf)$PdCl_2$ (**Pd-118**)[22] were good (90%); however, both gave slightly lower yield than that of **Pd-132**.[23] Bulky electron-rich tri-t-butylphosphine-based L_2Pd and LPd-based catalysts, $(t\text{-}Bu_3P)_2Pd$ (**Pd-116** (also known as the Fu catalyst)[24] and $[t\text{-}Bu_3P(\mu\text{-}Br)Pd]_2$ (**Pd-113** (Mingos/Hartwig Pd(I) dimer),[25] gave only 73% and 61% yields, respectively (entries 5 and 6). Unlike Hua's observation, under these milder conditions, $(Cy_3P)_2PdCl_2$ (**Pd-114**) gave only 2% yield (entry 8), while interestingly $(PPh_3)_4Pd$ gave 15% yield (entry 7).

Using the optimal conditions from Table 1, a variety of aryl/heteroaryl bromides (17 examples) with various acetylenes were coupled (Table 2). Electron-deficient, electron-rich, and sterically demanding (e.g., 2-bromoxylene) substrates were coupled in excellent yields. An aryl bromide containing a hydroxyl functional group was also successfully coupled (Table 2, entry 6). As heterocyclic moieties are important in the pharmaceutical industry, we have also studied several coupling reactions using heterocyclic bromides containing one or more hetero atoms. Bromopyridines, pyrimidines, and thiophenes were also coupled in excellent yield (Table 2, entries 10−17).

Heck Alkynylation of Aryl and Heteroaryl Chlorides. Because aryl bromide coupling is somewhat well established, the major effort of this study has been focused on challenging aryl chlorides and heterocyclic chlorides containing more than one heteroatom. As mentioned in the Introduction, very limited systematic studies have been conducted on such systems.

It is well established that during the catalytic cycle, $L_nPd(0)$ (n = 1 or 2) is the active catalytic species. Therefore, L_2PdCl_2 complexes, such as **Pd-132**, have to undergo reduction to form the corresponding 14 electron species. Recently, we have developed a novel process for the synthesis and commercialization of $L_2Pd(0)$ precatalysts and have done a preliminary investigation on the use of $Pd[p\text{-}MeNC_6H_4(t\text{-}Bu)_2P]_2$ (**Pd-149**) in the Cu-free Sonogashira coupling of aryl/heteroaryl chlorides.[19b] The precursor to the LPd(0) catalyst, p-$Me_2NC_6H_4(t\text{-}Bu)_2P(\eta^3\text{-allyl})Cl$ Pd (**Pd-158**), was also included in the study for comparison. Table 3 shows the screening results of p-chloroanisole with decyne using three Pd complexes of p-$Me_2NC_6H_4(t\text{-}Bu)_2P$.

Table 3. Heck Alkynylation of p-Chloroanisole Using $L_2Pd(0)$, $L_2Pd(II)$, and LPd(II) Precatalysts, Where L = p-$Me_2NC_6H_4(t\text{-}Bu)_2P$[a]



4 5 6

precatalyst	Pd code	% yield[b]
$Pd[p\text{-}Me_2NC_6H_4(t\text{-}Bu)_2P]_2$	**Pd-149**	95 (90)[c]
$PdCl_2[p\text{-}Me_2NC_6H_4(t\text{-}Bu)_2P]_2$	**Pd-132**	89
$PdCl[p\text{-}Me_2NC_6H_4(t\text{-}Bu)_2P](\eta^3\text{-allyl})$	**Pd-158**	74

[a]Conditions: 0.5 mol % catalyst, Cs_2CO_3, DMF solvent, 100 °C, 7 h. [b]GC yields. [c]Isolated yield in parentheses.

Although the ligand was the same, three catalysts showed different activities when an aliphatic acetylene, such as 1-decyne, was coupled with p-chloroanisole. **Pd-149** was the best catalyst of choice with 95% GC yield (90% isolated). This is because under these conditions, the preactivated catalysts is more active than its corresponding air-stable Pd(II) complex. Interestingly, monoligated palladium complex **Pd-158** has given only 74% yield, although it is supposed to generate a highly active 12 electron-based LPd(0) catalytic species during catalysis. The fact that **Pd-158** (Table 3) was less active than **Pd-132** and **Pd-149** suggests that L_2Pd complexes may not be either dissociating to LPd(0) or the 12 electron LPd(0) species formed is thermodynamically less stable, at least in this class of reactions under these conditions. Results from Table 1, entry 6 versus entry 5, are also in agreement with this observation.

However, when attempting to couple aromatic acetylenes, both **Pd-149** and **Pd-132** afforded no desired product (Table

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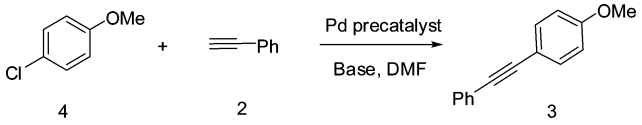
4). Presumably, this is due to the fact that aromatic acetylenes are susceptible to undergo dimerization or oligomerization to form side products if the oxidative addition of aryl halide is relatively more challenging. Inspired by Buchwald's results on the slow addition of aromatic acetylenes,[12] pheylacetylene was added slowly, thereby diluting its initial concentration. Interestingly, **Pd-132** gave 99% GC yield with 90% isolated yield, when the aryl acetylene is added over a period of 6 h. Monitoring the slow addition over a period of 1 and 3 h gave 47% and 75% GC conversion to product, respectively. The Pd(0) complex **Pd-149** did not give any satisfactory results. This could be due to the poor stability of the catalyst under these conditions. These results confirm that both **Pd-132** and **Pd-149** complement each other, depending on the choice of the coupling partners and the reaction conditions employed.

Table 4. Results of Catalyst and Condition Optimization in the Heck Alkynylation of *p*-Chloroanisole with Phenylacetylene by Slow Addition of Acetylene[a]



4 2 3

entry	catalyst	addition time	base	% yield[b]
1	**Pd-132**	<1 min	Cs_2CO_3	trace
2	**Pd-132**	<1 min	K_3PO_4	trace
3	**Pd-149**	<1 min	Cs_2CO_3	trace
4	**Pd-149**	<1 min	K_3PO_4	trace
5	**Pd-132**	1 h	Cs_2CO_3	47%
6	**Pd-149**	1 h	Cs_2CO_3	<5%
7	**Pd-132**	3 h	Cs_2CO_3	75%
8	**Pd-149**	3 h	Cs_2CO_3	<10%
9	**Pd-132**	5 h	Cs_2CO_3	>98% (90%)[c]

[a]Conditions: 1.0 mol % catalyst, base, DMF solvent, 100 °C. [b]GC yield. [c]Isolated yield on a 1.0 mmol scale in parentheses.

Having identified **Pd-132** and **Pd-149** as two good catalysts with optimal conditions for the Cu-free Sonogashira reaction of *p*-chloroanisole, we expanded the substrate scope to couple several aryl and heteroaryl chlorides with excellent isolated yields (Table 5). Both electron-rich and electron-deficient aryl chlorides were coupled in excellent yield (91−96%) with aliphatic acetylenes (Table 5, entries 1−3), using **Pd-149** in DMF with Cs_2CO_3 base. An elevated temperature is required for difficult substrates, such as electron rich and sterically hindered aryl chlorides (Table 5, entries 4,5). In such cases, DMF is usually preferred over CH_3CN as a solvent because of its high boiling point. The slow addition of phenylacetylene minimized the side reactions, which delivered a useful synthetic procedure for the coupling of aryl acetylenes with both electron-rich and -deficient aryl chlorides (Table 5, entries 9−11). However, as mentioned earlier, **Pd-132** complements **Pd-149**. Substrates with unprotected free primary amines, alcohols, and amides can be problematic for palladium-catalyzed coupling reactions. However, these catalyst systems have very good functional group tolerance. Meta-substituted chlorophenol (Table 5, entry 13) and aniline (Table 5, entry 15) gave higher yields than their respective para-analogues (Table 5, entry 12), whereas the corresponding ortho-substituted derivatives were inefficient. This poor reactivity might be due to the strong coordination of the ortho-hetero atoms to the palladium species, thereby slowing the rate of the reaction. Alkynes containing polar functional groups also gave the desired products in good yield (Table 5, entries 17,18).

Because of the importance of heterocyclic compounds containing alkyne moieties in the pharmaceutical industry, we have made a special effort in developing routes for a few examples (Table 5, entries 20−30) using the heteroaryl chlorides. Although several groups have reported the cross-coupling of heteroaryl chlorides, a very limited substrate scope has been explored.[10,26,27] In this study, several nitrogen-containing five- or six-membered heterocycles have been coupled in good to excellent yields. Noteworthy is that heteroaryl chlorides such as dimethoxy- and methylthioether-substituted pyrimidine gave very good yield of the desired coupled products. On the basis of selected GC studies, it is observed that in certain cases product decomposition in DMF occurs much faster than that in CH_3CN, especially when the reaction is carried out at higher temperatures. Therefore, for certain heteroaryl chlorides, CH_3CN is the solvent of preference.

Aryl-substituted propargylic alcohols are versatile building blocks, as these structural motifs are present in several drugs on the market.[28] Although they can be synthesized by the 1,2 addition of terminal alkynes to carbonyls, the Sonogashira reaction is a very practical and diversified way to construct propargylic alcohols with different aryl substituents. Several catalysts have been utilized for coupling aryl iodides and bromides with propargylic alcohols in good yield.[6,29] However, the corresponding aryl chlorides in comparison to the bromides are far more challenging to couple with terminal propargylic alcohols, as these reactions tend to undergo unpredictable rearrangements. Under the conditions (Table 5, methods A, B) developed for simple alkynes, no desired coupling product was isolated in satisfactory yields. To determine the optimal reaction conditions for propargyl systems, further screening was conducted with the use of a milder K_3PO_4 base. Coupled product was obtained in 72% isolated yield in DMF (Table 5, entry 31).

Having established a protocol for propargyl systems, we have extended the method to ethynylestradiol systems (Scheme 2), as these types of compounds are capable of binding to estrogen receptors (ER) with high affinity. These derivatives have been studied as diagnostic reagents for breast cancer treatments.[30] We were able to functionalize the alkyne of the propagylic moiety by selectively coupling with challenging aryl or heteroaryl chlorides in the presence of unmasked polar functional groups.

Understanding the Structure−Activity Relationships (SAR) of L_2Pd (L = *p*-$Me_2NC_6H_4$(*t*-Bu_2)P Catalysts. Because $L_2Pd(0)$ is presumably the active catalytic species based on the results from Table 3, we decided to compare the activity of **Pd-149** with the other new generation $L_2Pd(0)$ catalysts as well as the classical Pd(0) catalyst, $Pd(PPh_3)_4$ (Table 6). While $Pd(PPh_3)_4$ is the least active catalyst (Table 6, entry 6), the other catalysts containing electron-rich/bulky ligands also performed poorly (Table 6, entries 3−5). The catalyst that showed the second best activity was **Pd-148** (Table 6, entry 2). This is somewhat understandable as the Me_2N group at the para position makes the catalyst more electron-rich for **Pd-149** in comparison to **Pd-148**. It is surprising to note that the Pd(0) catalyst **Pd-116** gave only modest conversion under these conditions (Table 6, entry 3). Although **Pd-141** is sterically bulkier than **Pd-116** based on the cone angle data,[31] it was one of the least active catalysts for this model system.

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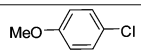
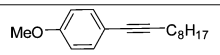
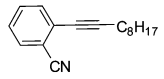
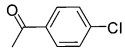
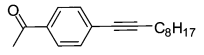
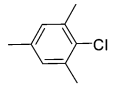
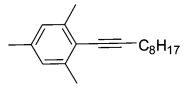
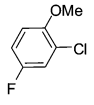
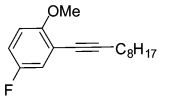
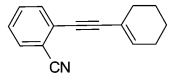
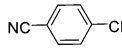
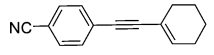
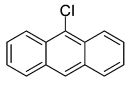
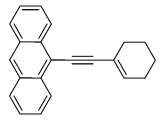
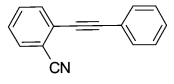
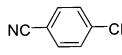
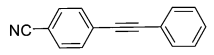
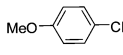
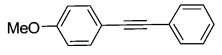
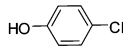
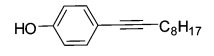
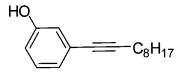
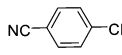
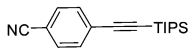
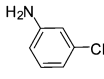
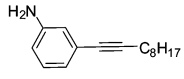
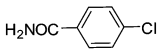
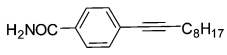
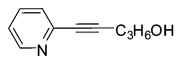
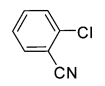
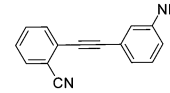
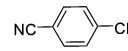
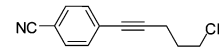
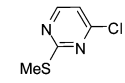
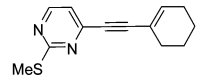
Table 5. Pd-132- and Pd-149-Catalyzed Cu-Free Coupling of Aryl Chlorides with Terminal Alkynes[b]

entry	method	Ar-Cl	product	% yield[a]
1	A			90
2	A			96
3	A			91
4	A			84
5	A			90
6	A			97
7	A			94
8	A			84
9	C			92
10	C			89
11	C			90
12	A			67
13	A			75
14	A			81
15	A			79
16	A			87
17	B			80
18	C			72
19	A			90
20	B			91
21	B			78
22	B			90
23	B			85
24	B			95
25	B			93
26	B			76
27	B			79
28	B			87
29	B			86
30	B			83
31	D			72

[a]Isolated yield on a 1.0 mmol scale. [b]Conditions: (A) 0.5−1.5 mol % **Pd-132**, Cs_2CO_3, DMF, 90−110 °C, 4−8 h. (B) 0.5−1.5 mol % **Pd-149**, CH_3CN, 90 °C, 4−8 h. (C) 0.5−1.5 mol % **Pd-132**, DMF, 90 °C, slow addition of arylacetylene during reaction, 5 h. (D) 1 mol % **Pd-132**, K_3PO_4, DMF, 90 °C, 6 h.

These results have further prompted us to determine the X-ray structure of **Pd-149** (Figure 3), which reveals that it has Pd−P bond lengths similar to those of the other $L_2Pd(0)$ complexes reported in Table 7. However, it has the smallest P−Pd−P angle (174.7°) (Table 7, entry 1), while **Pd-116** and **Pd-141** have shown perfectly linear (180°) structures (Table 7, entries 3,5). Interestingly, the second most active catalyst **Pd-148** (Table7, entry 2) also has a slightly bent structure (176.8°). The X-ray structure of **Pd-150** is not reported, but the closest is $[(Fc)(t\text{-}Bu)_2]_2Pd$, which also has a P−Pd−P bond angle of 180°. By analyzing the combined data from Tables 6 and 7, one can infer that the "bent" $L_2Pd(0)$ species tend to be more active than the linear Pd complexes containing monodentate ligands. This observation has been discussed in Hartwig's text book that "$L_2Pd(0)$ bent into a less stable

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Scheme 2. Coupling of Ethynylestradiol with Aryl and Heteroaryl Chlorides under Cu-Free Conditions

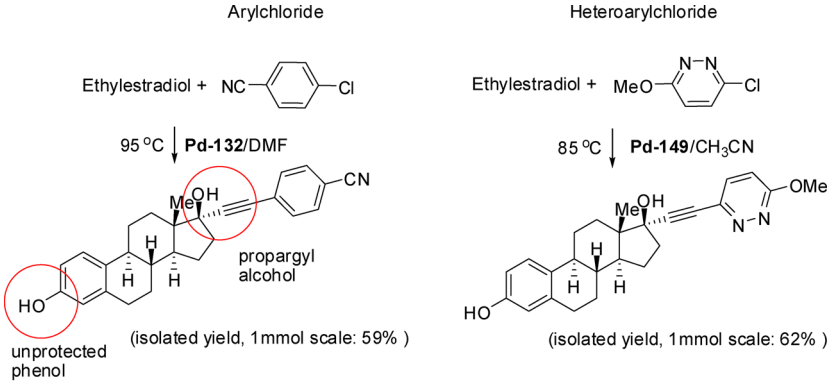
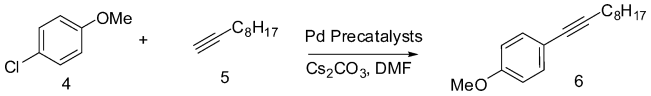


Table 6. Ligand Effect in $L_2Pd(0)$ Complexes for Copper-Free Sonogashira Reaction[a]



entry	catalyst	% yield[b] 1 h	% yield[b] 7 h
1	Pd[*p*-$Me_2NC_6H_4$(*t*-Bu)$_2$P]$_2$ (**Pd-149**)	75	95
2	Pd[Ph(*t*-Bu)$_2$P]$_2$ (**Pd-148**)	30	69
3	Pd(*t*-Bu_3P)$_2$ (**Pd-116**)	15	48
4	Pd(QPhos)$_2$ (**Pd-150**)	5	20
5	Pd[(*o*-Tol)$_3$P]$_2$ (**Pd-141**)	<5	<5
6	Pd(Ph_3P)$_4$ (**Pd-101**)	<5	<5

[a]Conditions: 1 mol % catalyst, Cs_2CO_3, DMF solvent, 100 °C. [b]GC yield.

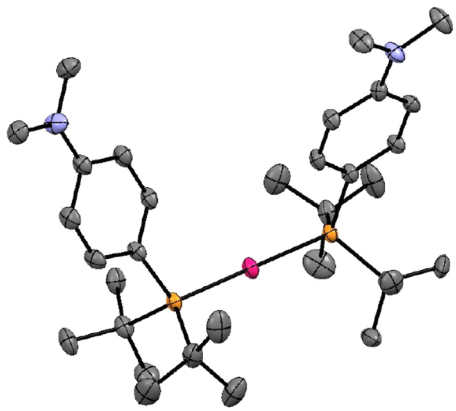


Figure 3. Single-crystal X-ray structure of **Pd-149**. Hydrogen atoms are omitted for clarity. The thermal ellipsoids correspond to 50% probability.

conformation than the linear $L_2Pd(0)$ fragment, the frontier orbitals are more available for coordination and addition."[32]

From these preliminary data, we believe that the electronic and steric properties of the catalysts as well as the P–Pd–P bond angles have an important impact on the Heck alkynylation reaction.[33] However, more detailed studies are required to fully understand the catalyst activation and reactivity.

Table 7. Comparison of Bond Angle and Bond Length of Pd[*p*-$Me_2NC_6H_4$(*t*-Bu)$_2$P] with Other $L_2Pd(0)$ Complexes

entry	complex	Pd code	Pd–P bond lengths	P–Pd–P angle
1	Pd[*p*-$Me_2NC_6H_4$(*t*-Bu)$_2$P]$_2$	**Pd-149**	2.299(3); 2.299(2)[a]	174.7(0)
2	Pd[Ph(*t*-Bu)$_2$P]$_2$	**Pd-148**	2.282(4); 2.273(4)[b]	176.8(1)
3	(*t*-Bu_3P)$_2$Pd	**Pd-116**	2.285(3); 2.285(3)[c]	180.0(0)
4	[(Fc)(*t*-Bu)$_2$]$_2$Pd	N/A	2.276(4); 2.276(4)[d]	180.0(0)
5	[(*o*-Tol)$_3$P]$_2$Pd	**Pd-141**	2.276(1); 2.276(1)[e]	180.0(0)

[a]See ref 34. [b]See ref 35. [c]See ref 36. [d]See ref 37. [e]See ref 38.

More Insight into the Copper Effect. There is a belief that commercially available palladium salts such as palladium dichloride or palladium acetate may contain a very small amount of copper that would accelerate the conventional Sonogashira reaction even without the addition of copper.[39,1d] If that is the case, addition of Cu should enhance the coupling. However, on the contrary, we observed a significant negative Cu effect for both **Pd-132** and **Pd-149** catalyst systems (Table 8).

In the presence of 2 mol % copper iodide, both bromo- and chloro-anisole were inhibited to couple with acetylene using both **Pd-132** and **Pd-149** catalysts (Table 8, entries 2,4,6). When KI was used as an additive, no negative effect was observed in the coupling of bromoanisole to the product in high yield, ruling out iodide as an inhibitor[40](Tables 8 and 9). At the same time, other copper salts also inhibited the reaction (Table 8, entries 7,8,10). The concentration of copper in the reaction is also identified to be important (Table 9). It should be noted that the acetylene was almost completely consumed by **Pd-149** with the formation of conjugated addition product of acetylene, whereas almost no conversion of acetylene was observed when **Pd-132** was used. The reaction listed in Table 8 was also studied by varying the amount of Cu (Table 9). This observation is similar to what Buchwald and Beller observed for various biaryl ligands.[12,14] Recently, Schoenebeck et al. discovered that Cu(I)X (X = Br, I) species can readily oxidize electron-rich (*t*-Bu_3P)$_2$Pd(0) (**Pd-116**) to a dinuclear Pd(I) complex, [(*t*-Bu_3P)BrPd]$_2$ (**Pd-113**), with the formation of a Cu-cubane, (Cu(*t*-Bu_3P)X)$_4$.[41] They also found that **Pd-113** polymerizes acetylene, rather than promoting the cross

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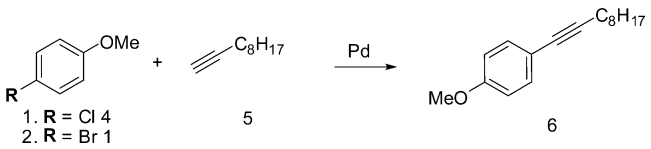
Table 8. Cu Effect in Sonogashira Reaction in the Presence of Pd-132 and Pd-149[a]



entry	R	catalyst	additive	temp (°C)	% yield[b]
1	Br	**Pd-132**	none	90	>95%
2	Br	**Pd-132**	CuI	90	<10%
3	Cl	**Pd-132**	none	110	90%
4	Cl	**Pd-132**	CuI	110	<10% (<10%)[c]
5	Cl	**Pd-149**	none	95	94%
6	Cl	**Pd-149**	CuI	95	<5% (95%)[c]
7	Br	**Pd-132**	CuBr	90	5%
8	Br	**Pd-132**	CuCl	90	3%
9	Br	**Pd-132**	KI	90	95%
10	Cl	**Pd-132**	CuBr, KI	90	<5%

[a]Conditions: 0.5 mol % catalyst, 2 mol % additive, DMF solvent, 100 °C. [b]GC yield. [c]GC conversion of acetylene in parentheses.

Table 9. Concentration Effect of Cu in Pd-132-Catalyzed Reaction of Chloroanisole with 1-Decyne[a]

% CuI	% yield
0.1	85
0.5	59
2	10
5	<5

[a]Conditions: 1.5 mol % **Pd-132**, DMF, 100 °C, 6 h.

coupling of aryl halides in the Sonogashira reaction. From these findings, we can infer that Cu salts can act as an oxidizing agent with electron-rich $L_2Pd(0)$ species (**Pd-149**) in the coupling catalytic cycle, but also can inhibit the formation of the active Pd(0) species from Pd(II) precatalyst (**Pd-132**).

Why Is Aryl Chloride Coupling with Aryl Acetylene Difficult? Understanding the Mechanism. On the basis of the literature reports[12] and from our in-house study, slow addition of aryl acetylenes (Table 4) is required to achieve high yields of the desired coupled product when unactivated aryl chlorides are used. Typically, one pot addition leads to very low yield of the coupled product at the expense of the acetylene being consumed. However, there are no reported studies on the fate of acetylenes in these cases. Therefore, we report the results of some preliminary mechanistic investigations to understand this anomaly under copper-free conditions.

A major side product isolated under the one-pot addition conditions was identified to be the conjugated head-to-head addition product, *E*-enyne (Scheme 3, **11**) when **Pd-132** was used as a catalyst. Under elevated temperature, this styrene analogue could be more reactive than the phenyl acetylene, leading toward undesired polymerization. Interestingly, there are no other regio- and stereoisomers of conjugated enynes detected or isolated from the reaction. Trost's group has done a tremendous amount of work on palladium-catalyzed alkyne dimerization reactions.[42] In many cases, they observed a head-to-tail addition of terminal alkynes in the presence of TDMPP (TDMPP = $P[(2,6\text{-}OMe)_2C_6H_3]_3$) ligand in conjunction with $Pd(OAc)_2$. Gevorgyan et al. later observed the formation of an enyne product with opposite regioselectivity, using TDMPP with a different palladium source (allylpalladium chloride dimer) and base.[43] Several head-to-head aryl *E*-enynes were prepared under these conditions, whereas ortho-substituted aryl acetylenes gave the product (*E*-enyne) in low to no yield. An agostic interaction between the palladium and ortho protons of the aromatic ring in the substrate is proposed to be responsible for facilitating the conjugate addition, following anti-Markovnikov selectivity. The above work inspired us to envision that if the side reaction in the coupling of aryl acetylenes with aryl chlorides is also caused by a similar agostic interaction, the undesired dimerization should be inhibited by ortho-substitutions on the aryl acetylene ring.

Table 10 shows the control experiments done on the Cu-free Sonogashira coupling of *p*-chlorotoluene with unsubstituted and ortho-disubstituted arylacetylenes: (a) phenyl acetylene and (b) 2,4,6-trimethylphenyl acetylene. The desired coupling product was isolated in 72% yield (>85% GC conversion of aryl chloride) within 4 h, when 2,6-dimethylphenyl acetylene was used, while the unsubstituted phenyl acetylene gave only 12% yield of the coupled product with nonselective formation of the enyne dimer.

To better understand the enyne formation reaction, a deuterium labeling study has been conducted, which revealed that both olefin protons are from the acetylene substrate (Scheme 4). When the oxidation step is challenging, acetylene coordination takes preference, which leads to the formation of the enyne. That is why we see coupled product with aryl bromides and activated aryl chlorides, where oxidative addition takes preference over acetylene coordination.

On the basis of the above experimental studies, a reported mechanism of Cu-free Sonogashira reaction by Soheili and co-workers from Merck, and a recent computational study by García-Melchor et al.,[9d,44] we propose the following plausible mechanisms for aryl acetylene participated Heck alkynylation of aryl chlorides and the corresponding side reaction (Scheme 5). The desired catalytic cycle starts with the oxidative addition of an aryl chloride to the active Pd(0) species. This is followed by the acetylene coordination and the subsequent deprotonation in the presence of a base. Once the acetylene is rearranged from π to δ bonding, the product is reductively eliminated. On the other hand, with challenging aryl chloride substrates, oxidative addition becomes the turnover-limiting step; acetylene coordination takes preference over aryl halide addition to the $L_nPd(0)$ to form a palladium hydride intermediate. This species further interacts with another molecule of phenylacetylene to undergo a carbopalladation (insertion) rearrangement, which is

Scheme 3. Challenges Associated with the Coupling of Unactivated Aryl Chloride with Phenyl Acetylene

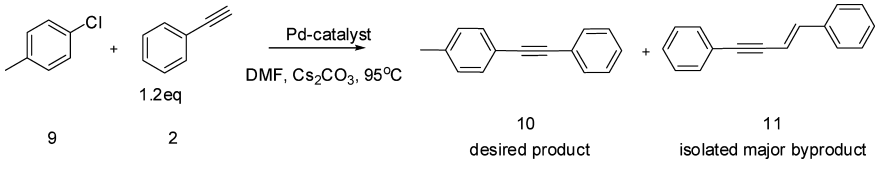


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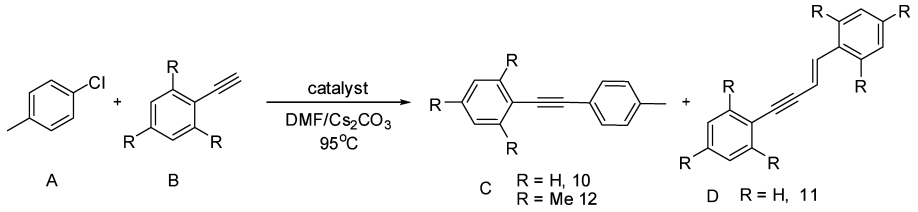
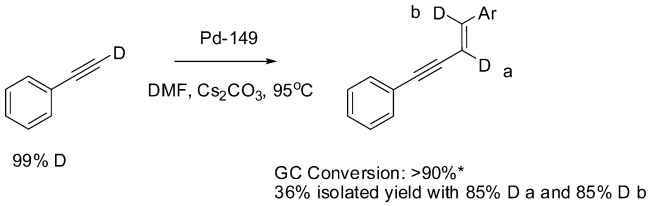
Table 10. Ortho-Disubstitution Effect of Aryl Acetylene in the Heck Alkynylation[a]



entry	R	C:D (GC ratio)	yield of C (%)[b]	yield of D (%)[b]
1	H	1:1	12 (32)[c]	16
2	Me	>99:1	72 (85)[c]	

[a]Conditions: Aryl halide (1.6 mmol), alkyne (2.0 mmol), Cs_2CO_3 (2.4 mmol), toluene (2.0 mL) using 1 mol % **Pd-149**. [b]Isolated yield. [c]GC conversion of A.

Scheme 4. Deuterium Labeled Acetylene Giving the *E*-Enyne via Head-to-Tail Addition



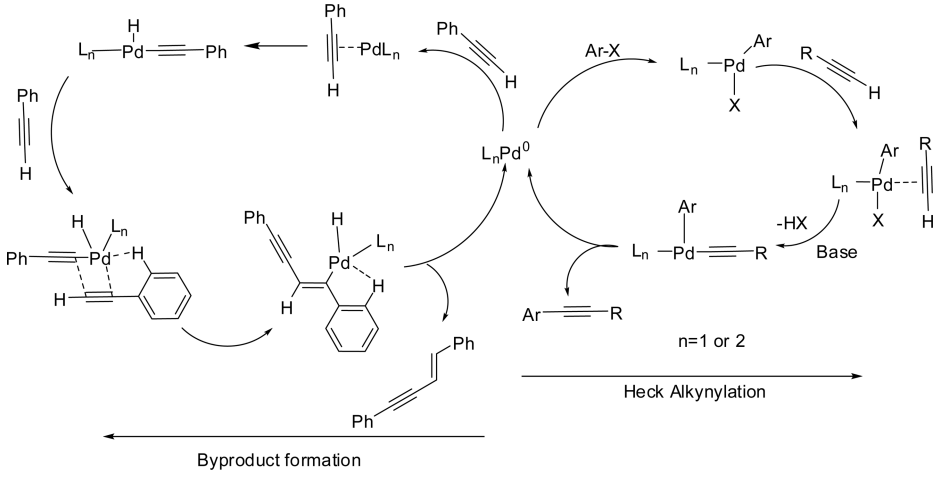
regioselectively controlled by the agostic interaction of the ortho protons. Reductive elimination provided the enyne byproduct with regeneration of the $L_nPd(0)$ catalyst.

Therefore, a one-pot addition of acetylene could be possible for coupling of most aryl acetylenes with activated aryl bromide substrates. Coupling is also possible for challenging aryl chlorides with ortho-substituted aryl acetylenes under one-pot addition conditions. However, in many cases, the slow addition of ortho-unsubstituted aryl acetylenes is necessary for coupling unactivated aryl chlorides to control the concentration of the acetylene, thereby preventing the self-conjugated addition reaction catalyzed by the palladium catalyst. So to speak, it is necessary to tweak the reaction conditions by understanding the nature of the catalyst and substrates.

CONCLUSION

We have identified that the *p*-$Me_2NC_6H_4P(t\text{-}Bu)_2$ ligand and its palladium(0) and (II) complexes as active catalysts or precatalysts for the Heck alkynylation of aryl chlorides without the assistance of copper salts. By slightly varying the reaction conditions, a wide variety of aryl bromides, aryl chlordes, and heteroaryl chlorides have been coupled with both aryl and aliphatic acetylenes in good to excellent yields. Noteworthy is that unstable terminal propargylic alcohols can also be coupled with unactivated aryl chlorides in good yields. Because both **Pd-132** (air-stable) and **Pd-149** (air-sensitive)[45] are commercially available in multikilogram quantities, these are promising catalysts for large-scale coupling processes. Our structure–activity relationship (SAR) study suggests that the smaller P–Pd–P bond angle of **Pd-149** in comparison to the other similar $L_2Pd(0)$ might be an important factor in deciding the activity of the catalyst. We also support Buchwald's observation that Cu is detrimental with the new generation bulky electron-rich Pd-phosphine-based catalytic systems. For coupling aryl acetylenes containing no ortho substitution, slow addition is required to prevent the formation of enyne byproducts, while ortho-substituted aryl acetylenes selectively form the desired coupling products without significant process variations. A catalytic cycle for Heck alkynylations and byproduct formation is proposed. A detailed study on mechanism is underway.

Scheme 5. Proposed Mechanism for the Byproduct Formation during the Cu-Free Sonogashira Coupling Reaction (Heck Alkynylation) Using $L_nPd(0)$ Where n = 1 or 2



dx.doi.org/10.1021/jo302195y | J. Org. Chem. XXXX, XXX, XXX–XXX

EXPERIMENTAL SECTION

General Experimental Details. Unless otherwise stated, all reactions were carried out under nitrogen atmosphere in 20 mL 12-space Radley carousels with magnetic stirring. Anhydrous DMF and CH_3CN used in the study were purchased from commercial sources. Cs_2CO_3 and K_3PO_4 were grounded into fine powder before use. All reactions were monitored by GC or silica gel TLC plates. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Proton and carbon-13 chemical shifts were reported relative to $CDCl_3$ peaks as internal standards (^1H, δ = 7.27, ^{13}C, δ = 77.26 ppm), while $^{31}P\{^1H\}$ NMR spectra were externally referenced to 85% H_3PO_4. MS were obtained on a high-resolution GC/MS. Compounds were purified with Teledyne isco combiflash Rf or silica gel flash column with ethyl acetate and hexane as eluent. Elemental analyses were performed by an outside lab.

General Procedure for Copper-Free Sonogashira Coupling of Aryl Bromide with Alkyne. An oven-dried Schlenk tube was charged with Cs_2CO_3 (3 mmol) and Pd catalyst (7.5 μmol, 0.5 mol %) and sealed under nitrogen. It was then degassed three times (vacuum and nitrogen), followed by the stepwise injection of aryl bromide (1.5 mmol), alkyne (1.8 mmol), and anhydrous acetonitrile (2 mL) under N_2 atmosphere. The resulting pale yellow suspension was stirred at the desired temperature for the indicated period of time. The reaction mixture was allowed to cool to room temperature, followed by the addition of water (10 mL) to dissolve the inorganic salts. It was later extracted with diethyl ether (3 × 4 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to purify by flash chromatography using silica gel catridge with 10% ether/hexane solvent combination to isolate the desired product. The known compounds were characterized by comparing their NMR data with those reported. The other ones were fully characterized by NMR, elemental, and GC/MS. The NMR spectra of the isolated products are provided in the Supporting Information.

(Table 2, Entry 1) Diphenyl Acetylene.[46] The general procedure afforded the title compound (248 mg) in 93% isolated yield (yellowish solid).

(Table 2, Entry 2) 1-Phenyl-1-octyne.[13] The general procedure afforded the title compound (251 mg) in 90% isolated yield (yellowish solid).

(Table 2, Entry 3) 1-Cyclohexene Phenyl Acetylene.[47] The general procedure afforded the title compound (237 mg) in 87% isolated yield (yellowish solid).

(Table 2, Entry 4) 4-Methoxyphenyl Phenyl Acetylene.[29] The general procedure afforded the title compound (268 mg) in 86% isolated yield (yellowish solid).

(Table 2, Entry 5) 4-(Phenyl-1-ynyl)benzonitrile.[48] The general procedure afforded the title compound (277 mg) in 91% isolated yield (yellowish solid).

(Table 2, Entry 6) 3-Hydroxylphenyl Phenyl Acetylene.[49] The general procedure afforded the title compound (250 mg) in 86% isolated yield (yellowish solid).

(Table 2, Entry 7) 4-Acetylphenyl Phenyl Acetylene.[50] The general procedure afforded the title compound (293 mg) in 88% isolated yield (yellowish solid).

(Table 2, Entry 8) 2,6-Dimethylphenyl Phenyl Acetylene.[11] The general procedure afforded the title compound (284 mg) in 92% isolated yield (yellowish solid).

(Table 2, Entry 9) 4-tert-Butylphenyl Phenyl Acetylene.[51] The general procedure afforded the title compound (325 mg) in 93% isolated yield (yellowish solid).

(Table 2, Entry 10) 2-Pyridine Phenyl Acetylene.[13] The general procedure afforded the title compound (240 mg) in 89% isolated yield (yellowish solid).

(Table 2, Entry 11) 1-(2-Pyridine)-1-octyne.[52] The general procedure afforded the title compound (241 mg) in 86% isolated yield (yellowish solid).

(Table 2, Entry 12) 1-Cyclohexene (2-Pyridine) Acetylene.[53] The general procedure afforded the title compound (250 mg) in 91% isolated yield (yellowish solid).

(Table 2, Entry 13) 3-Pyridine Phenyl Acetylene.[54] The general procedure afforded the title compound (250 mg) in 93% isolated yield (yellowish solid).

(Table 2, Entry 14) 2-Thiophene Phenyl Acetylene.[13] The general procedure afforded the title compound (248 mg) in 90% isolated yield (yellowish solid).

(Table 2, Entry 15) 3-Thiophene Phenyl Acetylene.[55] The general procedure afforded the title compound (254 mg) in 92% isolated yield (yellowish solid).

(Table 2, Entry 16) 3,5-Pyrimidine Phenyl Acetylene.[56] The general procedure afforded the title compound (250 mg) in 93% isolated yield (yellowish solid).

(Table 2, Entry 17) 2,6-Pyrimidine Phenyl Acetylene.[56] The general procedure afforded the title compound (250 mg) in 93% isolated yield (yellowish solid).

Procedure for Copper-Free Sonogashira Reaction (Method A and Method B). A Radley tube was charged with 2 equiv of Cs_2CO_3(2 mmol, 648 mg), 0.5−1.5 mol % palladium catalysts, followed by aryl chloride (1 mmol), 1.5 mL of DMF (method A), or 1.5 mL of CH_3CN (method B) under an atmosphere of nitrogen. Using a syringe, 1.2 equiv of the respective actylene was injected into the tube via septum. The reaction was heated to 90−105 °C under stirring for 4−7 h. All reactions were monitored by GC or TLC plates. Products were purified by Combiflash auto chromatographic system using a mixture of hexanes and ethyl acetate as the eluent.

Procedure for Copper-Free Sonogashira Reaction of Arylacetylenes (Method C). A Radley tube was charged with 2 equiv of Cs_2CO_3 (2 mmol, 648 mg), 0.5−1.5 mol % palladium catalyst, and aryl chloride (1 mmol), followed by the addition of 1.5 mL of DMF under an atmosphere of nitrogen. The reaction mixture was heated to 90−105 °C and with stirring, followed by the addition of 1.2 equiv of actylenes via a syringe pump over a period of 3−5 h. After the addition of acetylene, the reaction was further stirred for an additional hour. All reactions were monitored by either GC or TLC plates. Products were purified by a Combiflash auto chromatographic system using a mixture of hexanes and ethyl acetate as the eluent.

Procedure for Copper-Free Sonogashira Reaction (Method D). A Radley tube was charged with 2 equiv of K_3PO_4 (2 mmol, 425 mg), 0.5−1.5 mol % palladium catalyst, and aryl chlorides (1 mmol). 1.5 mL of DMF under a nitrogen atmosphere was injected, followed by the addition of 1.5 equiv of propargyl alcohol. The reaction was heated to 95 °C with stirring and kept for 7 h. All reactions were monitored by either GC or TLC plates. Products were purified on a Combiflash auto chromatographic system using a mixture of hexanes and ethyl acetate as the eluent.

(Table 5, Entry 1) 1-(Dec-1-ynyl)-4-methoxybenzene. The general procedure method A in Table 5 with 0.5 mol % catalyst afforded the title compound (220 mg) in 90% isolated yield. ^1H NMR ($CDCl_3$): δ (ppm) 7.32 (d, J = 6.8 Hz, 2H), 6.81 (d, J = 7.5 Hz, 2H), 3.78 (s, 3H), 2.38 (t, J = 6.8 Hz, 2H), 1.59 (m, 2H), 1.21−1.41 (m, 10H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 159.0, 132.8, 116.4, 113.8, 88.8, 80.3, 55.2, 32.0, 29.2, 29.2, 29.0, 28.9, 22.7, 19.4, 14.1. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.28; H, 10.04.

(Table 5, Entry 2) 2-(Dec-1-ynyl)benzonitrile. The general procedure method A in Table 5 with 0.5 mol % catalyst afforded the title compound (230 mg) in 96% isolated yield (yellowish solid). ^1H NMR ($CDCl_3$): δ (ppm) 7.60 (d, J = 7.2 Hz, 1H), 7.50 (m, 2H), 7.33 (m, 1H), 2.48 (t, J = 7.2 Hz, 2H), 1.68 (m, 2H), 1.50 (m, 2H), 1.32 (m, 8H), 0.89 (t, J = 6.4, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 132.3, 132.5, 132.2, 128.1, 127.5, 117.7, 115.4, 98.0, 77.2, 31.8, 29.2, 29.1, 28.9, 28.4, 22.7, 19.6, 14.1. Anal. Calcd for $C_{17}H_{21}N$: C, 85.33; H, 8.84. Found: C, 84.92; H, 9.31.

(Table 5, Entry 3) 1-Octyl (4-Acetonphenone) Acetylene. The general procedure method A in Table 5 with 0.5 mol % catalyst afforded the title compound (233 mg) in 91% isolated yield. ^1H NMR ($CDCl_3$): δ (ppm) 7.83 (dd, J = 2.0, 6.8 Hz, 2H), 7.42 (dd, J = 1.6, 6.4 Hz, 2H), 2.54 (s, 3H), 2.39 (t, J = 7.2 Hz, 2H), 1.57 (m, 2H), 1.42 (m, 2H), 1.26−1.28 (m, 8H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 197.1, 135.6, 131.5, 129.1, 128.1, 94.3, 80.0, 31.8, 29.1, 29.01,

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28.9, 28.5, 26.4, 22.56, 19.5, 14.0. Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.20; H, 9.69.

(Table 5, Entry 4) 2-(Dec-1-ynyl)-1,3,5-trimethylbenzene. The general procedure method A in Table 5 with 0.5 mol % catalyst afforded the title compound (215 mg) in 84% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 6.88 (s, 2H), 2.54 (t, J = 6.8 Hz, 2H), 2.44 (s, 6H), 2.31 (s, 3H), 1.69 (m, 2H), 1.55 (m, 2H), 1.21−1.37 (m, 8H), 0.95 (t, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 139.8, 136.5, 127.4, 120.9, 98.0, 78.2, 31.9, 29.3, 29.1, 28.9, 22.66, 21.2, 21.0, 19.7, 14.1. Anal. Calcd for $C_{19}H_{28}$: C, 88.99; H, 11.01. Found: C, 88.96; H, 10.99.

(Table 5, Entry 5) 2-(Dec-1-ynyl)-4-fluoro-1-methoxybenzene. The general procedure method A in Table 5 with 1 mol % catalyst afforded the title compound (236 mg) in 90% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.06 (dd, J = 3.2 8.8 Hz, 1H), 6.89 (td, J = 3.2, 8.4 Hz, 1H), 6.74 (dd, J = 4.4, 8.8 Hz, 1H), 3.82 (s, 3H), 2.44 (t, J = 6.8 Hz, 2H), 1.61 (m, 2H), 1.44 (m, 2H), 1.29 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 157.6, 156.2, 156. 2, 155.2, 119.9, 119.7, 115.1, 114.9, 114.5, 114.4, 111.53, 111.4, 95.7, 75.8, 75.7, 56.3, 31.8, 29.1, 29.1, 28.8, 28.6, 22.6, 19.6, 14.1. Anal. Calcd for $C_{17}H_{23}FO$: C, 77.82; H, 8.84; Found: C, 77.90; H, 9.22.

(Table 5, Entry 6) 2-(Cyclohexenylethynyl)benzonitrile. The general procedure method A in Table 5 with 1 mol % catalyst afforded the title compound (201 mg) in 97% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.58 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 4.4 Hz, 2H), 7.31 (m, 1H), 6.33 (m, 1H), 2.33 (m, 2H), 2.63 (m, 2H), 1.65−1.68 (m, 2H), 1.58−1.64 (m, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) 137.7, 132.5, 132.2, 131.9, 127.9, 127.6, 120.2, 117.6, 115.1, 98.1, 83.2, 28.8, 25.9, 22.2, 21.4. MS(EI) m/z: 207 (M^+).

(Table 5, Entry 7) 4-(Cyclohexenylethynyl)benzonitrile. The general procedure method A in Table 5 with 1 mol % catalyst afforded the title compound (195 mg) in 94% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.54 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 6.25 (m, 1H), 2.13−2.21 (m, 4H), 1.59−1.68 (m, 4H). ^{13}C NMR ($CDCl_3$): δ (ppm) 137.2, 132.0, 131.9, 129.0, 120.3, 118.6, 110.9, 95.9, 85.4, 29.1, 25.9, 22.2, 21.4. MS (EI) m/z: 207 (M^+).

(Table 5, Entry 8) 9-(Cyclohexenylethynyl)anthracene. The general procedure method A in Table 5 with 1 mol % catalyst afforded the title compound (237 mg) in 84% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.58 (d, J = 8.4 Hz, 2H), 8.40 (s, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.58 (t, J = 6.4 Hz, 2H), 7.52 (t, J = 6.8 Hz, 2H), 6.50 (s, 1H), 2.52 (m, 2H), 2.29 (m, 2H), 1.84 (m, 2H), 1.76 (m, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) 135.4, 132.4, 131.2, 128.6, 127.0, 126. 9, 126.3, 125.6, 121.3, 118.0, 103.1, 83.8, 29.6, 26.0, 22.5, 21.6. Anal. Calcd for $C_{22}H_{18}$: C, 93.57; H, 6.43. Found: C, 93.35; H, 6.26.

(Table 5, Entry 9) 2-(Phenylethynyl)benzonitrile. The general procedure method C in Table 5 with 1 mol % catalyst afforded the title compound (187 mg) in 92% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.59 (m, 1H), 7.56 (m, 3H), 7.52 (m, 1H), 7.36 (m, 4H). ^{13}C NMR ($CDCl_3$): δ (ppm) 132.7, 132.4, 132.1, 132.0, 129.2, 128.5, 128.2, 127.3, 122.1, 117.5, 115.4, 96.0, 85.6. MS(EI) m/z: 203 (M^+).

(Table 5, Entry 10) 4-(Phenylethynyl)benzonitrile. The general procedure method C in Table 5 with 1 mol % catalyst afforded the title compound (177 mg) in 87% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.61 (d, J = 5.6 Hz, 2H), 7.59 (d, J = 6.4 Hz, 2H), 7.54 (dd, J = 2.4, 6.4 Hz, 2H), 7.36 (m, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 132.0, 132.0, 131.7, 129.0, 128.4, 128.2, 122.19, 118.4, 111.5, 93.7, 87.6. MS(EI) m/z: 203 (M^+).

(Table 5, Entry 11) 1-Methoxy-4-(phenylethynyl)benzene. The general procedure method C in Table 5 with 1 mol % catalyst afforded the title compound (187 mg) in 91% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.50 (d, J = 6.0 Hz, 2H), 7.47 (d, J = 6.8 Hz, 2H), 7.33 (m, 3H), 6.85 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 159.6, 133.0, 131.4, 128.2, 127.9, 123.6, 115.4, 114.0, 89.3, 88.0, 55.2. MS(EI) m/z: 208 (M^+).

(Table 5, Entry 12) 4-(Dec-1-ynyl)phenol. The general procedure method A in Table 5 with 1.5 mol % catalyst afforded the title compound (145 mg) in 67% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.29 (d, J = 6.4 Hz, 2H), 6.75 (d, J = 6.0 Hz, 2H), 5.16 (s, 1H), 2.38 (m, 2H), 1.60 (m, 2H), 1.46 (m, 2H), 1.32 (m, 8H), 0.89 (t, J = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 155.0, 133.1, 116.5, 115.3, 88.9, 80.2, 31.9, 29.2, 29.14, 29.0, 28.9, 22.7, 19.4, 14.1. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.08; H, 9.74.

(Table 5, Entry 13) 3-(Dec-1-ynyl)phenol. The general procedure method A in Table 5 with 1.5 mol % catalyst afforded the title compound (172 mg) in 75% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.15 (t, J = 8.0 Hz, 1H), 6.97 (dd, J = 7.6, 1.2 Hz, 2H), 6.88 (dd, J = 1.2 Hz, 1H), 6.75 (dt, J = 8.0, 1.6 Hz, 1H), 5.55 (s, 1H), 2.38 (t, J = 7.2 Hz, 2H), 1.56−1.64 (m, 2H), 1.46 (m, 2H), 1.31 (m, 8H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 155.2, 129.5, 125.4, 124.4, 118.4, 115.0, 90.8, 80.3, 31.9, 29.2, 29.2, 20.0, 28.8, 22.7, 19.4, 14.1. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.25; H, 9.37.

(Table 5, Entry 14) 4-((Triisopropylsilyl)ethynyl)benzonitrile. The general procedure method A in Table 5 with 0.5 mol % catalyst afforded the title compound (229 mg) in 81% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.58 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 1.11 (s, 18H), 1.09 (m, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 132.5, 131.9, 128.3, 118.4, 111.6, 105.1, 96.4, 18.6, 18.5, 11.23. MS (EI) m/z: 283 (M^+ − 43).

(Table 5, Entry 15) 3-(Dec-1-ynyl)aniline. The general procedure method A in Table 5 with 1.5 mol % catalyst afforded the title compound (180 mg) in 79% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.06 (t, J = 8 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.73 (s, 1H), 6.60 (d, J = 8 Hz, 1H), 3.62 (s, 2H), 2.39 (t, J = 7.2 Hz, 2H), 1.62 (m, 2H), 1.45 (m, 2H), 1.28−1.33 (m, 8H), 0.92 (t, J = 6.8, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 146.2, 129.1, 124.9, 122.0, 118.1, 114.6, 89.9, 80.7, 31.9, 29.2, 29.2, 29.0, 28.8, 22.7, 19.4, 14.1. Anal. Calcd for $C_{16}H_{23}N$: C, 83.79; H, 10.11. Found: C, 83.67; H, 10.17.

(Table 5, Entry 16) 4-(Dec-1-ynyl)benzamide. The general procedure method A in Table 5 with 1.5 mol % catalyst afforded the title compound (224 mg) in 87% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.70 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.41 (s, 2H), 2.38 (t, J = 7.2 Hz, 2H), 1.57 (m, 2H), 1.40 (m, 2H), 1.22−1.28 (m, 8H), 0.86 (t, J = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 169.3, 131.7, 128.9, 128.1, 127.3, 93.6, 80.0, 31.8, 29.2, 29.1, 28.9, 28.6, 22.6, 19.5, 14.1. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01. Found: C, 78.96; H, 8.85.

(Table 5, Entry 17) 5-(Pyridin-2-yl)pent-4-yn-1-ol. The general procedure method B in Table 5 with 1 mol % catalyst afforded the title compound (129 mg) in 80% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 8.24 (d, J = 1.6 Hz, 1H), 7.52 (td, J = 8.0, 1.2 Hz, 1H), 7.27 (dd, J = 8.0, 1.2 Hz, 1H), 7.09 (td, J = 8.0, 1.2 Hz, 1H), 4.0 (s, 1H), 3.73 (t, J = 6.0 Hz, 2H), 2.50 (t, J = 8.8 Hz, 2H), 1.82 (q, J = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) 149.5, 143.6, 136.2, 126.9, 122.4, 90.8, 80.4, 60.9, 31.2, 15.9. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88. Found: C, 74.43; H, 6.92.

(Table 5, Entry 18) 2-((3-Aminophenyl)ethynyl)benzonitrile. The general procedure method C in Table 5 with 1 mol % catalyst afforded the title compound (157 mg) in 72% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.65 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.56 (m, 1H), 7.39 (m, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.02 (m, 1H), 6.72 (m, 1H), 6.70 (d, J = 8.0 Hz, 1H), 3.78 (s, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) 146.6, 132.6, 132.4, 132.1, 129.4, 128.2, 127.4, 122.7, 122.2, 118.1, 117.7, 116.3, 115.2, 96.5, 85.1. Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62. Found: C, 82.29; H, 4.73.

(Table 5, Entry 19) 4-(5-Chloropent-1-ynyl)benzonitrile. The general procedure method A in Table 5 with 1 mol % catalyst afforded the title compound (183 mg) in 90% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.55 (d, J = 6.8 Hz, 2H), 7.45 (d, J = 6.8 Hz, 2H), 3.69 (t, J = 6.4 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.05 (q, J = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) 132.2, 131.95, 128.6, 118.5, 111.1, 93.25, 80.3, 43.6, 31.1, 17.0. MS (EI) m/z: 203 (M^+).

(Table 5, Entry 20) 4-(Cyclohexenylethynyl)-2-(methylthio)-pyrimidine. The general procedure method B in Table 5 with 1 mol % catalyst afforded the title compound (238 mg) in 91% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 8.42 (d, J = 5.21 Hz, 1H), 6.96 (d, J = 5.2 Hz, 1H), 6.41 (m, 1H), 2.56 (s, 3H), 2.23 (m, 2H), 2.17 (m, 2H),

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1.61−1.69 (m, 4H). ^{13}C NMR ($CDCl_3$): δ (ppm) 173.0, 156.7, 151.4, 139.69, 119.7, 118.3, 96.1, 84.7, 28.6, 26.0, 22.1, 21.3, 14.1. Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13. Found: C, 67.53; H, 6.26.

(Table 5, Entry 21) 5-(Dec-1-ynyl)-1,3-dimethyl-1H-pyrazole. The general procedure method B in Table 5 with 1 mol % catalyst afforded the title compound (181 mg) in 78% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 6.08 (m, 1H), 3.82 (s, 3H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.62 (m, 2H), 1.45 (m, 2H), 1.31 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 150.2, 129.4, 111.4, 100.5, 72.3, 39.5, 34.7, 32.0, 31.9, 31.7, 31.3, 25.5, 22.3, 16.9, 16.2. Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41. Found: C, 77.31; H, 10.56.

(Table 5, Entry 22) 3-(Cyclohexenylethynyl)-6-methoxypyridazine. The general procedure method B in Table 5 with 1 mol % catalyst afforded the title compound (193 mg) in 90% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.33 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 6.29 (m, 1H), 4.09 (s, 3H), 2.21 (m, 2H), 2.11 (m, 2H), 1.56−1.64 (m, 4H). ^{13}C NMR ($CDCl_3$): δ (ppm) 163.2, 144.2, 137.6, 132.2, 120.0, 116.4, 94.1, 83.3, 54.9, 28.7, 25.8, 22.2, 21.4. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59. Found: C, 72.82; H, 6.48.

(Table 5, Entry 23) 2-(Dec-1-ynyl)pyrimidine. The general procedure method B in Table 5 with 1.5 mol % catalyst afforded the title compound (183 mg) in 85% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.64 (d, *J* = 4.8 Hz, 2H), 7.15 (t, *J* = 4.8 Hz, 1H), 2.43 (t, *J* = 7.2 Hz, 2H), 1.61 (m, 2H), 1.41 (m, 2H), 1.22−1.25 (m, 8H), 0.83 (t, *J* = 5.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 157.1, 153.4, 119.3, 90.8, 80.0, 31.8, 29.1, 29.0, 29.0, 28.0, 22.6, 19.2, 14.0. Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32. Found: C, 77.56; H, 9.34.

(Table 5, Entry 24) Methyl 6-(Dec-1-ynyl)nicotinate. The general procedure method B in Table 5 with 0.5 mol % catalyst afforded the title compound (259 mg) in 95% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 9.12 (t, *J* = 1.2 Hz, 1H), 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.41 (dd, *J* = 8.0, 0.8 Hz, 1H), 3.92 (s, 3H), 2.45 (t, *J* = 7.2 Hz, 2H), 1.63 (m, 2H), 1.44 (m, 2H), 1.28 (m, 8H), 0.87 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 165.5, 151.0, 147.7, 137.0, 126.2, 124.2, 81.0, 94.0, 52.4, 31.8, 29.1, 29.1, 29.0, 28.2, 22.6, 19.5, 14.1. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.53; H, 8.37.

(Table 5, Entry 25) 2-(Cyclohexenylethynyl)-4,6-dimethoxypyrimidine. The general procedure method B in Table 5 with 1 mol % catalyst afforded the title compound (227 mg) in 91% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 6.32 (m, 1H), 5.86 (s, 1H), 3.86 (s, 6H), 2.17 (m, 2H), 2.06 (m, 2H), 1.52−1.58 (m, 4H). ^{13}C NMR ($CDCl_3$): δ (ppm) 171.0, 151.5, 138.8, 119. 7, 89.6, 88.6, 86.0, 54.1, 28.6, 25.9, 22.1, 21.3. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60. Found: C, 68.82; H, 6.77.

(Table 5, Entry 26) 2-(Cyclohexenylethynyl)pyrimidine. The general procedure method B in Table 5 with 1 mol % catalyst afforded the title compound (227 mg) in 91% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.56 (m, 2H), 7.06 (m, 1H), 6.30 (m, 1H), 2.02 (m, 2H), 2.12 (m, 2H), 1.48−1.53 (m, 4H). ^{13}C NMR ($CDCl_3$): δ (ppm) 157.1, 153.5, 139.4, 119.5, 119.2, 90.2, 85.8, 29.0, 25.9, 22.0, 21.2. Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57. Found: C, 78.04; H, 6.32.

(Table 5, Entry 27) 5-(Dec-1-ynyl)-1,3-dimethyl-4-nitro-1H-pyrazole. The general procedure method B in Table 5 with 1 mol % catalyst afforded the title compound (213 mg) in 79% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 3.85 (s, 3H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.48 (s, 3H), 1.66 (m, 2H), 1.48 (m, 2H), 1.26−1.30 (m, 8H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 145.3, 133.3, 126.2, 106.2, 67.2, 37.6, 31.7, 29.1, 29.0, 28. 8, 28.0, 22.6, 19.9, 14.0, 13.8. Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.95; H, 8.36. Found: C, 6.49; H, 8.33.

(Table 5, Entry 28) 2-(Dec-1-ynyl)-3-(trifluoromethyl)quinoxaline. The general procedure method B in Table 5 with 0.5 mol % catalyst afforded the title compound (290 mg) in 87% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.18 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.81−7.91 (m, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.71 (m, 2H), 1.52 (m, 2H), 1.25−1.33 (m, 8H) 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 143.5, 143.2, 142.7, 138.3, 136.5, 132.6, 131.2, 129.8, 128.8, 122.38, 119.5, 100.4, 76.3, 31.8, 29.7, 29.1, 29.0, 28.8, 27.9, 22.6, 19.7, 14.0. Anal. Calcd for $C_{19}H_{21}F_3N_2$: C, 68.25; H, 6.33. Found: C, 68.71; H, 6.42.

(Table 5, Entry 29) 5-(Dec-1-ynyl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde. The general procedure method B in Table 5 with 1 mol % catalyst afforded the title compound (223 mg) in 86% isolated yield. ^{1}H NMR ($CDCl_3$): δ (ppm) 9.89 (s, 1H), 3.82 (s, 3H), 2.51 (t, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.62 (q, *J* = 8.0 Hz, 2H), 1.44 (m, 2H), 1.26−1.31 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 184.5, 144.5, 132.5, 121.7, 103.6, 66.9, 36.8, 31.8, 29.1, 28.8, 28.9, 28.2, 22.6, 19.6, 14.0, 13.3. Anal. Calcd for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29. Found: C, 74.02; H, 9.37.

(Table 5, Entry 30) 2-(Dec-1-ynyl)thiophene. The general procedure method B in Table 5 with 1 mol % catalyst afforded the title compound (183 mg) in 83% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.17 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.12 (d, *J* = 3.2 Hz, 1H), 6.93 (dd, *J* = 5.2, 3.2 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.63 (m, 2H), 1.45 (m, 2H), 1.32 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 130.8, 126.7, 125.8, 124.3, 94.6, 73.7, 31.8, 29.2, 29.1, 29.0, 28.6, 22.7, 19.7, 14.1. Anal. Calcd for $C_{14}H_{20}S$: C, 76.30; H, 9.15. Found: C, 76.32; H, 9.07.

(Table 5, Entry 31) 4-(3-Hydroxy-3-methylnon-1-ynyl)-benzonitrile. The general procedure method D in Table 5 with 1 mol % catalyst afforded the title compound (183 mg) in 72% isolated yield (yellowish solid). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.56 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 2.29 (s, 1H), 1.72 (m, 2H), 1.51 (s, 3H), 1.46 (m, 2H), 1.23−1.34 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 132.2, 131.9, 127.9, 118.4, 111.6, 97.7, 81.7, 68.7, 43.6, 31.7, 29.6, 29.4, 24.7, 22.6, 14.0. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29. Found: C, 80.31; H, 7.96.

Compound **7**. Using the general procedure described as method D in Table 5, 2 mol % catalyst loading afforded the title compound in 59% isolated yield (250 mg) as a yellowish white solid. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.58 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.65 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.57 (d, *J* = 2.8 Hz, 1H), 5.9 (s, 1H), 2.78 (m, 2H), 2.50 (m, 1H), 2.30−2.45 (m, 2H), 2.1−2.2 (m, 2H), 1.82−1.88 (m, 4H), 1.70 (m, 1H), 1.26−1.49 (m, 3H), 0.93 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 153.8, 138.17, 132.2, 132.0, 132.0, 128.0, 126.4, 118. 5, 115.4, 113.0, 111.4, 97.6, 84.6, 80.5, 50.1, 47.8, 43.7, 39.6, 39.1, 33.1, 29.6, 27.5, 26.3, 23.2, 12.9. Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85. Found: C, 81.49; H, 7.01.

Compound **8**. Using the general procedure described as method D in Table 5, 2 mol % catalyst loading afforded the title compound in 62% (250 mg) isolated yield as a yellowish white solid. ^{1}H NMR ($CDCl_3$): δ (ppm) 8.64 (s, 1H), 7.45 (d, *J* = 9.2 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.69 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 4.10 (s, 3H), 3.40 (s, 1H), 2.67 (m, 2H), 2.43 (m, 1H), 2.09 (m, 2H), 1.89 (m, 1H), 1.66−1.76 (m, 5H), 1.22−1.34 (m, 4H), 0.89 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 163.8, 154.6, 143.0, 137.6, 132.9, 131.52, 126.3, 117.5, 115.4, 112.9, 97.5, 81.6, 80.4, 55.2, 49.8, 47.82, 42.9, 39.3, 38.9, 33.1, 29.7, 27.16, 26.3, 22.8, 12.9. Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98. Found: C, 73.89; H, 7.04.

Compound **11**, *(E)-But-1-en-3-yne-1,4-diyldibenzene.*[57] ^{1}H NMR ($CDCl_3$): δ (ppm) 7.46−7.48 (m, 2H), 7.40−7.43 (m, 2H), 7.28−7.36 (m, 6H), 7.04 (d, *J* = 16 Hz, 1H), 6.38 (d, *J* = 16 Hz, 1H). MS (EI) *m*/*z*: 204 (M^+).

Compound **12**, *1,3,5-Trimethyl-2-(p-tolylethynyl)benzene.*[33] Using the general procedure described as method A in Table 5, 1 mol % catalyst loading afforded the title compound in 72% isolated yield ((250 mg) as a yellowish white solid. ^{1}H NMR ($CDCl_3$): δ (ppm) 7.50 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 2H), 6.95 (s, 2H), 2.55 (s, 6H), 2.43 (s, 3H), 2.36 (s, 3H). MS (EI) *m*/*z*: 234 (M^+).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C NMR spectra of all of the compounds synthesized in this work, along with the X-ray crystal data in cif

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format of **Pd-149**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest: The catalysts used in this study are commercially available from Johnson Matthey.

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