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Authors: Zhen Li and Wei-Liang Duan

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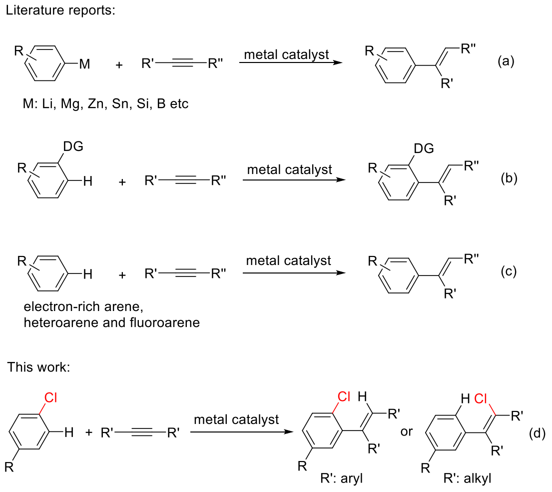
Palladium-Catalysed C–H Alkenylation of Arenes with Alkynes: Stereoselective Synthesis of Vinyl Chlorides via a 1,4-Chlorine Migration

*Zhen Li and Wei-Liang Duan**

Dedicated to Professor Tamio Hayashi on the occasion of his 70th birthday

Substituted alkenes are important intermediates for the preparation of valuable chemicals through a wide range of organic transformations, and their synthetic methods have received a substantial amount of attention over the past decades. Carbometallation of internal alkynes catalysed by various metal catalysts is a direct and efficient approach for the synthesis of multisubstituted alkenes (Scheme 1a).[1,2] However, these reactions require prefunctionalized organometallic reagents. Recently, C–H bond activation has been extensively developed for building complex molecules from simple starting materials via C–H bond cleavage.[3] Directing group (DG)-assisted C–H functionalization strategies have been widely explored, and various arenes have been reacted with alkynes and alkenes to form functionalized alkenes (Scheme 1b).[4] Meanwhile, compounds without DGs have been investigated less frequently and have shown limited success in C–H activation reactions due to their inherent low reactivity and site selectivity.[5,6] With respect to the reactions of arenes without DGs with alkynes, the successful examples are mostly limited to electron-rich arenes or pyridine derivatives (Scheme 1c).[7] For example, Fujiwara and co-workers described the first example of a Pd-catalysed hydroarylation of an activated alkyne with a simple arene or anisole derivative under acid conditions.[8] Nakao and Hiyama et al. reported the highly efficient hydroarylation of a series of heteroarenes and fluoroarenes enabled by a Ni/Lewis acid catalyst system.[9] However, electron-neutral arenes, such as benzene and chloroarenes, have rarely been found to provide good yields and wide functional group tolerance.[10] Herein, we report a DG-free palladium-catalysed hydroarylation reaction of internal alkynes with simple arenes that furnishes the corresponding alkenes or vinyl chlorides via a 1,4-chlorine migration in good yields.

In our previous study, a bidentate ligand (2-OH-1,10-phenanthroline) was developed for the palladium-catalysed oxidative C–H alkenylation of arenes.[11] The use of this ligand enabled the generation of the active palladium catalyst for the C–H bond cleavage of aryl groups. The present study began with the reaction of 1,4-dichlorobenzene with 4-octyne in the presence of palladium acetate and various ligands. The use of 2-OH-1,10-phenanthroline (**L1**) afforded a mixture of hydroarylation product **3a** and alkenyl chloride **4a** in a ratio of 18:60 (Table 1, entry 1). In contrast, the use of 1,10-phenanthroline (**L2**) did not generate any arylation product, and the reaction did not proceed at all (Entry 2). The more flexible 2-OH-1,1´-bipyridine (**L3**) afforded products **3a** and **4a** in relatively low yields (Entry 3). A monoprotected amino acid[12] was also examined, and no desired arylation product was generated (Entry 4). Further screening of the oxidant revealed that 1.0 equiv. of silver carbonate is the optimal choice (Entries 5–11). Control experiments indicated that ligand **L1** and the palladium catalyst are both essential for the progress of the reaction (Entries 12 and 13). The use of different solvents and reaction temperatures did not improve the yield of product (Entries 14–20). Finally, increasing the amount of chloroarene **1a** led to an 81% yield of the product (Entries 21 and 22).



Scheme 1: Representative procedures for the hydroarylation of alkynes.

With the optimized conditions in hand, we began to examine the substrate scope of the reaction using a range of chloroarenes (Table 2). With respect to the reaction with a dialkylalkyne, various moieties on the aryl ring *para* to the chlorine atom, such as nitro, trifluoromethyl, methyl ester, and methoxyl, were tolerated and afforded the corresponding alkenyl chlorides (**4b**–**4f**) in moderate to good yields (43%–86%). The use of an unsymmetrical 2-octyne afforded two isomers with a ratio of 3 to 1 in 60% yield. In the reaction with a diaryl alkyne, alkene **3** without chlorine migration was formed as the major product.[13] Alkynes bearing electron-donating or electron-withdrawing substituents on the aryl ring, such as methyl, chloro, fluoro, trifluoromethyl, and methoxyl groups, were all smoothly converted to corresponding products (**3h**–**3o**) in moderate to good yields. Electron-rich and electron-deficient arenes,

[*] Z. Li, Prof. Dr. W.-L. Duan
College of Chemistry and Chemical Engineering, Yangzhou University, 180 Siwangting Road, Yangzhou 225002, China
E-mail: duanwl@yzu.edu.cn
Prof. Dr. W.-L. Duan
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences 200032, China

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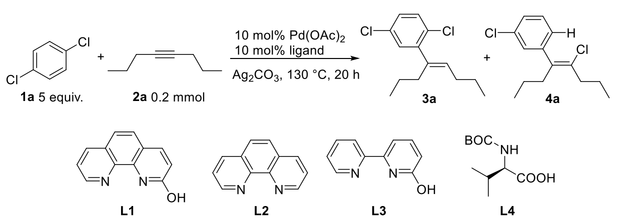
such as 1,4-dimethoxybenzene, 1,4-difluorobenzene, 1-chloro-4-trifluoromethylbenzene, 1-fluoro-4-trifluoromethylbenzene, and 1,3-bis(trifluoromethyl)benzene were also reactive under the current conditions, affording arylation products **3p** to **3t** with up to 94% yield. Table 3 summarizes the results of the reaction of benzene with various internal alkynes under the optimized conditions. Dialkyl alkynes and diaryl alkynes bearing various substituents at the *para*, *meta*, and even *ortho*-positions were all tolerated and generated a variety of trisubstituted alkenes (**5a**–**5k**) in 40% to 91% yield. The use of 1-ethyl-2-phenylacetylene generated the product as a mixture of two isomers (**5la** and **5lb**) in 75% yield. The obtained alkenyl chloride **4c** can be utilized for the preparation of tetrasubstituted alkene through a Pd-catalysed Suzuki coupling reaction (Scheme 2).

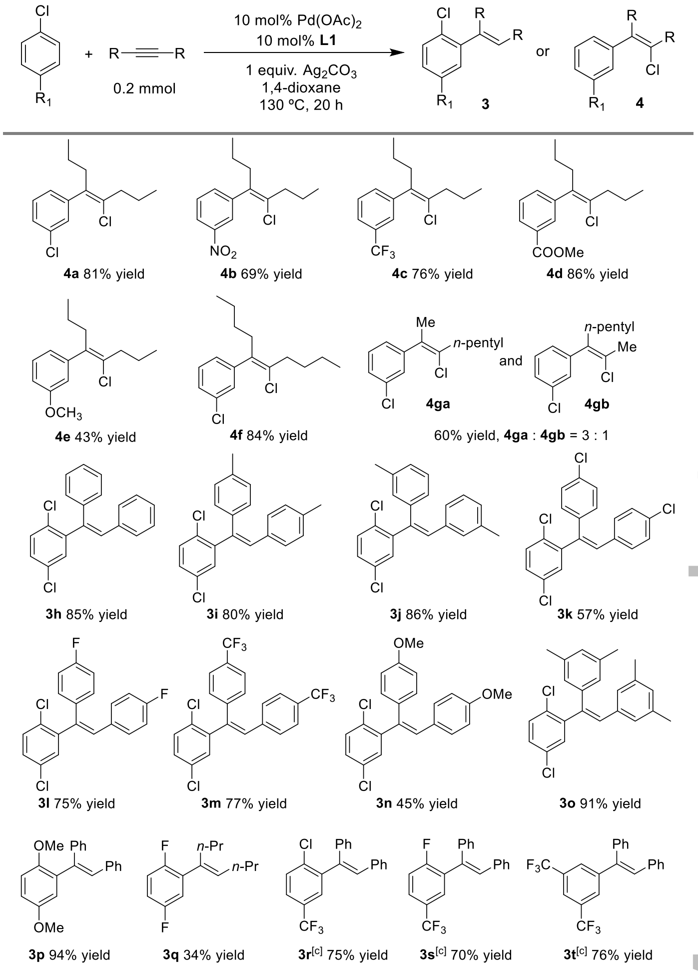
Table 1. Palladium-catalysed reaction of 1,4-dichlorobenzene with 4-octyne.



Entry	L	Base (equiv.)	Solvent	T [°C]	Yield **3a**/**4a** [%][a]
1	**L1**	Ag_2CO_3(1)	1,4-dioxane	130	18/60
2	**L2**	Ag_2CO_3(1)	1,4-dioxane	130	n.r.
3	**L3**	Ag_2CO_3(1)	1,4-dioxane	130	6/6
4	**L4**	Ag_2CO_3(1)	1,4-dioxane	130	n.r.
5	**L1**	AgOAc(1)	1,4-dioxane	130	46/18
6	**L1**	$AgNO_3$(1)	1,4-dioxane	130	trace
7	**L1**	$Cu(OAc)_2$(1)	1,4-dioxane	130	8/14
8	**L1**	Cs_2CO_3(1)	1,4-dioxane	130	n.r.
9	**L1**	Ag_2CO_3(0.5)	1,4-dioxane	130	26/49
10	**L1**	Ag_2CO_3(1.5)	1,4-dioxane	130	24/56
11	**L1**	Ag_2CO_3(2.0)	1,4-dioxane	130	10/57
12	-	Ag_2CO_3(1)	1,4-dioxane	130	n.r.
13[b]	**L1**	Ag_2CO_3(1)	1,4-dioxane	130	n.r.
14	**L1**	Ag_2CO_3(1.0)	DME	130	14/21
15	**L1**	Ag_2CO_3(1.0)	DMF	130	24/16
16	**L1**	Ag_2CO_3(1.0)	MeCN	130	12/22
17	**L1**	Ag_2CO_3(1.0)	THF	130	21/28
18	**L1**	Ag_2CO_3(1.0)	*t*-Amyl-OH	130	17/15
19	**L1**	Ag_2CO_3(1.0)	1,4-dioxane	140	24/65
20	**L1**	Ag_2CO_3(1.0)	1,4-dioxane	120	12/23
21[c]	**L1**	Ag_2CO_3(1.0)	1,4-dioxane	130	17/65
22[d]	**L1**	Ag_2CO_3(1.0)	1,4-dioxane	130	9/82(81[e])

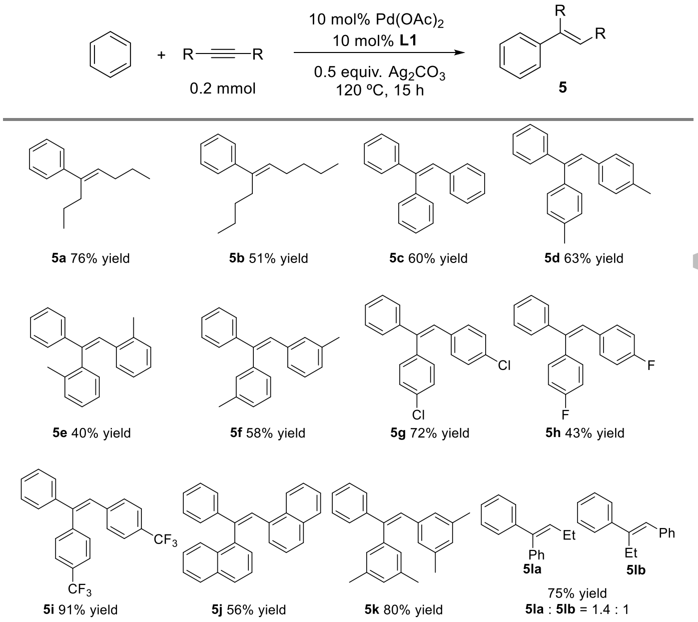
[a] Yields were determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [b] No Pd cat. [c] 10 equiv. of **1a** was used. [d] 34 equiv. of **1a** was used. [e] Isolated yield.

Table 2. Palladium-catalysed reaction of arenes with internal alkynes.[a,b]

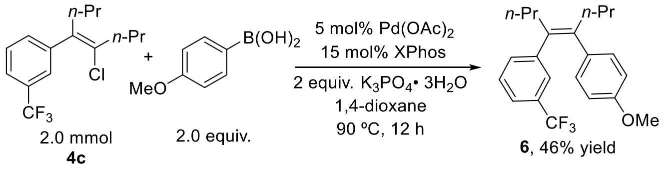


[a] All the reactions were conducted with 0.20 mmol of alkynes and 1 g of arenes in 1.0 mL of 1,4-dioxane unless specifically noted. [b] Isolated yield. [c] The reaction was conducted at 140 ℃.

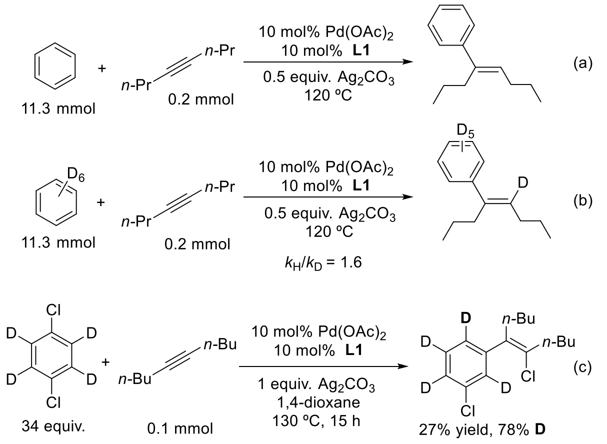
Table 3. Palladium-catalysed reaction of benzene with internal alkynes.[a,b]



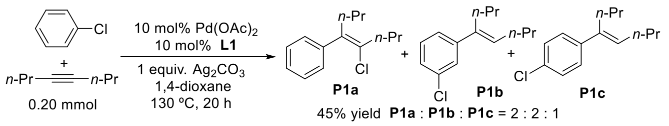
[a] All the reactions were conducted with 0.20 mmol of alkyne in 1.0 mL of benzene unless specifically noted. [b] Isolated yield.



Scheme 2. Pd-catalysed Suzuki coupling reaction for the preparation of tetrasubstituted alkene.

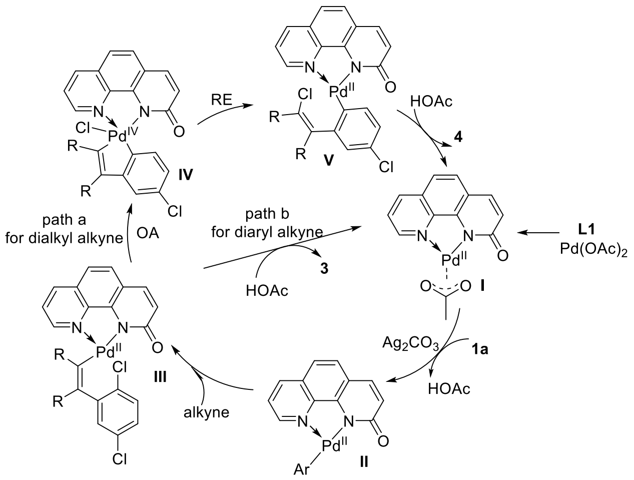


Scheme 3. Experiments with isotopically labelled compounds.



Scheme 4. C-H alkenylation of chlorobenzene with 4-octyne.

To obtain more information to understand the reaction mechanism, reactions of an alkyne with deuterium-labelled benzene and benzene in separate vessels were conducted to determine the kinetic isotope effect (KIE). A KIE of 1.6 was obtained, which indicates that the C–H bond cleavage may be the rate-limiting step (Scheme **3a** and **3b**).[14] Deuterated 1,4-dichlorobenzene was also reacted with 4-decyne, and the corresponding alkenyl chloride was obtained in 27% yield with 78% D atom incorporation at the position para to the Cl atom on the aromatic ring (Scheme **3c**). Chlorobenzene was also reacted with 4-octyne under the optimal conditions, and a mixture of alkenyl chloride **P1a**, *meta*-Cl substituted product **P1b**, and *para*-Cl substituted product **P1c**, in a ratio of 2:2:1 was formed in 45% combined yield (Scheme **4**).[15]



Scheme 5. The proposed catalytic cycle.

A proposed catalytic cycle is shown in Scheme 5. Ligand **L1** first reacts with Pd(OAc)$_2$, generating intermediated **I**[11]. **I** bears only one acetate anion on the palladium atom and a vacant coordination site could easily be generated for the incoming substrate. Then, C–H bond cleavage of the 1,4-chlorobenzene occurs to afford aryl palladium species **II** in the presence of silver carbonate. Next, the insertion of alkyne **2** into the aryl palladium bond afforded alkenyl palladium intermediate **III**. In the case of a dialkyl alkyne, the generated palladium intermediate, which has greater electron density, undergoes oxidative addition with the cleavage of the C–Cl bond to form Pd(IV) species **IV** via pathway a. The reductive elimination from Pd(IV) **IV** along with the construction of the alkenyl C–Cl bond completes the 1,4-chlorine migration[16,17], affording aryl Pd(II) species **V**. Protonolysis of **V** with acetic acid turns over the catalytic cycle with the formation of chlorine migration product **4** and regeneration of Pd catalyst **I**. With respect to the diaryl alkyne, formed alkenyl Pd(II) intermediate **III** mainly directs the hydrolysis via pathway b, affording product **3** without a 1,4-halide shift.

In summary, we have described a ligand-promoted palladium-catalysed C–H activation of simple arenes without directing groups with internal alkynes. The alkenyl chlorides resulting from a 1,4-chlorine migration and trisubstituted alkenes were obtained in moderate to good yields.

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[17] For selected examples of palladium-catalysed reaction involving halide-migration, see: a) G. Zhu, Z. Zhang, *J. Org. Chem.* **2005**, *70*, 3339; b) S. G. Newman, M. Lautens, *J. Am. Chem. Soc*. **2011**, *133*, 1778; c) H. Liu, C. Li, D. Qiu, X. Tong, *J. Am. Chem. Soc*. **2011**, *133*, 6387; d) C. M. Le, P. J. C. Menzies, D. A. Petrone, M. Lautens, *Angew. Chem*. **2015**, *127*, 256; *Angew. Chem. Int. Ed*. **2015**, *54*, 254; e) C. M. Le, T. Sperger, R. Fu, X. Hou, Y. H. Lim, F. Schoenebeck, M. Lautens, *J. Am. Chem. Soc*. **2016**, *138*, 14441.

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C–H Activation

Zhen Li and Wei-Liang Duan*

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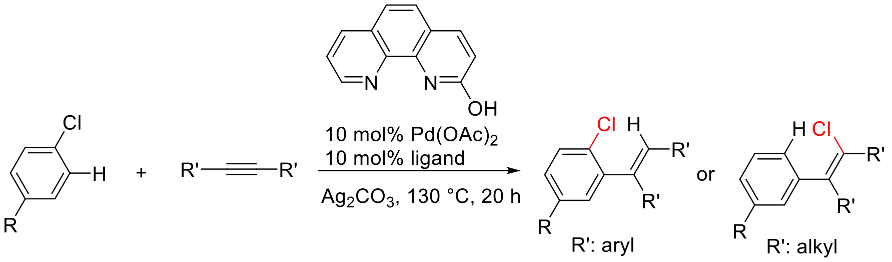
Palladium-Catalysed C–H Alkeylation of Arenes with Alkynes: Stereoselective Synthesis of Vinyl Chlorides via a 1,4-Chlorine Migration

C-H activation of arenes without directing groups



A directing group-free, ligand-promoted palladium-catalysed C-H arylation of internal alkynes with simple arenes was developed, and alkenyl chlorides via 1,4-chlorine migration or trisubstituted alkenes were produced in moderate to good yields depending on the type of alkyne.