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Pd-Catalyzed π-Chelation Assisted *ortho*-C−H Activation and Annulation of Allylarenes with Internal Alkynes

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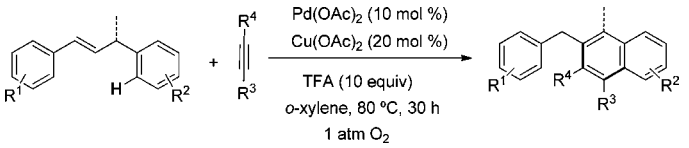
ABSTRACT



The synthesis of highly substituted naphthalenes from allylarenes and alkynes is described. This reaction proceeds via π-coordination of an allylic carbon−carbon double bond to the Pd(II) center and is followed by *ortho* selective C−H bond activation.

Transition-metal-catalyzed C−H bond functionalization has become a prevailing method for the construction of carbon−carbon and carbon−heteroatom bonds.[1] In general, the selectivity of C−H functionalization is controlled by the chelating functional groups.[2] Recently, Rh(III) and Ru(II)-catalyzed C−H functionalization followed by annulation with unsaturated molecules has been extensively used for the synthesis of various heterocyclic and carbocyclic compounds.[3,4] However, similar reactions involving palladium(II)-catalyzed C−H activation followed by oxidative coupling with alkynes are less well-studied, and only limited examples were reported.[5] While a variety of functional groups have been intensively investigated as the directing groups for C−H bond activation,[1,2] most of these groups involve σ-coordination to the metal catalysts. It is known that C−C multiple bonds readily coordinate with metal catalysts through π-chelation and facilitate selective C−H activation and intramolecular cyclizations.[6] Intermolecular C−H coupling reactions assisted by π-chelating C−C multiple bonds are rarely documented in literature.[7] Our ongoing interest[8] in various

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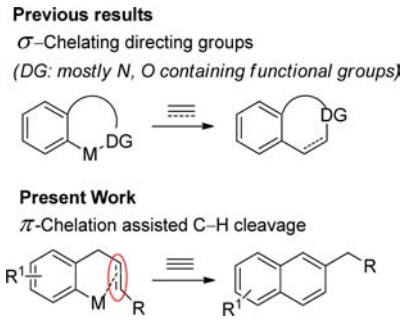
C−H bond activation and cyclization and the recent success in the use of an allylic C−C double bond as a directing group for *ortho*-alkenylation of arenes[7d] prompted us to explore the possibility of employing alkyne as a coupling partner in this functional group directed intermolecular C−H activation reaction and cyclization. Here, we report the synthesis of substituted naphthalenes by Pd-catalyzed reaction of allylarenes with internal alkynes (Scheme 1). It is noteworthy that substituted naphthalenes are important units in many bioactive compounds,[9] and the design of new direct C−H activation methods leading to the synthesis of naphthalenes is highly challenging.[10]

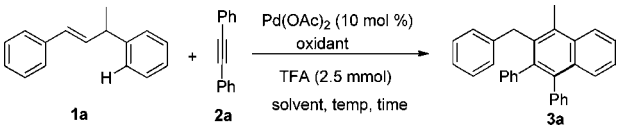
Scheme 1. Modes of Chelation in C−H Activation



We started our investigation using allylarene **1a** and diphenylacetylene (**2a**) as the substrates. Treatment of **1a** (0.25 mmol) with **2a** (0.30 mmol) in the presence of $Pd(OAc)_2$ (0.025 mmol) and trifluoroacetic acid (TFA) (2.5 mmol) in dichloromethane under one oxygen atmosphere at room temperature for 24 h gave substituted naphthalene derivative **3a** in 20% yield (Table 1, entry 1). The structure of **3a** was confirmed by its ^1H and ^{13}C NMR, mass data and single crystal X-ray structural determination. As a result of our devoted optimization study, we found that the reaction of **1a** (1 equiv), **2a** (1.2 equiv), $Pd(OAc)_2$ (10 mmol %), $Cu(OAc)_2$ (20 mol %) and TFA (10 equiv) in *o*-xylene at 80 °C for 30 h under one O_2 atmosphere gave **3a** in 85% isolated yield (for the detailed optimization study see Table 1 and the Supporting Information).

Having the optimized reaction conditions in hand, we tested the scope of allyl arenes **1** and alkynes **2**, and the results are shown in Table 2. Both diarylalkynes having an electron-donating and electron-withdrawing group on the

Table 1. Optimization Studies for the Pd-Catalyzed *ortho*-C−H Activation and Annulation of Allyl Arenes[a]



1a 2a 3a

entry	O_2 (1 atm) + oxidant/mmol	solvent (1.5 mL)	temp (°C)/ time (h)	yield (%)[b]
1	O_2	DCM	rt/24	20
2	O_2	DCE	50/24	27
3	O_2	toluene	50/24	30
4	O_2 + $Cu(OAc)_2$/0.125	toluene	50/24	35
5	O_2 + $Cu(OAc)_2$/0.25	toluene	50/24	43
6	$Cu(OAc)_2$/0.25	toluene	50/24	47
7	$Cu(OAc)_2$/0.25	toluene	80/24	67
8	$Cu(OAc)_2$/0.25	toluene	100/24	46
9	$Cu(OAc)_2$/0.25	*o*-xylene	80/24	70
10	O_2 + $Cu(OAc)_2$/0.25	*o*-xylene	80/24	81
11	O_2 + $CuCl_2$/0.25	*o*-xylene	80/24	40
12	O_2 + CuO/0.25	*o*-xylene	80/24	72
13	O_2 + $Cu(BF_4)_2$/0.25	*o*-xylene	80/24	47
14	O_2 + $Cu(OTf)_2$/0.25	*o*-xylene	80/24	29
15	O_2 + $Cu(OAc)_2$/0.05	*o*-xylene	80/24	80
16	O_2	*o*-xylene	80/24	67
17	O_2 + $Cu(OAc)_2$/0.05	*o*-xylene	80/24	–[c]
18	**O_2 + $Cu(OAc)_2$/0.05**	***o*-xylene**	**80/30**	**89 (85)**[d]

[a] Unless otherwise mentioned, all reactions were carried out using **1a** (0.25 mmol) and **2a** (0.30 mmol), TFA (2.5 mmol) and other additives. [b] Yields were determined by the ^1H NMR integration method using mesitylene as the internal standard. [c] TFA not used. [d] Isolated yield based on **1a**.

arene rings reacted with **1a** under the standard reaction conditions to give the corresponding products **3** in good to excellent yields (Table 2). Thus, treatment of *p*-Me and *p*-OMe substituted diphenylacetylenes **2b** and **2c** with **2a** gave the desired naphthalene derivatives **3b** and **3c** in 81 and 52% yields, respectively (entries 2−3). *p*-Cl, -Br and -F substituted diphenylacetylenes underwent the reaction with **1a** smoothly to offer products **3d**, **3e** and **3f** in 82, 67 and 74% yields, respectively (entries 5−7). Trifluoromethyl and acetyl substituted diarylalkynes gave the desired naphthalenes **3g** and **3h** in 76 and 68% yields (entries 7−8). Electron-deficient diethyl acetylenedicarboxylate (**2i**) and aliphatic alkyne 4-octyne (**2j**) also underwent the cyclization reaction with **1a** to give naphthalene derivatives in 57 and 56% yield, respectively (entries 9 and 13). Next, we examined the scope of allyl arenes. Thus, 4-Cl substituted allylarene **1b** reacted with **2a** to afford **3j** in 63% yield (Table 2, entry 10). Similarly, 3-Cl and 3-OMe substituted allyl arenes **1c** and **1d** gave **3k** and **3i** in 76 and 79% yields, respectively (entries 11−12). For substrates with a substituent at *meta* position, the C−H activation occurs only at the less hindered *ortho* position. Presumably, the regioselectivity was controlled by the steric effect of *meta*-substituent (entries 11−12). Substrates **1e**−**g** without a methyl group on the aliphatic chain also reacted efficiently with **2a** to give the expected naphthalene products in good

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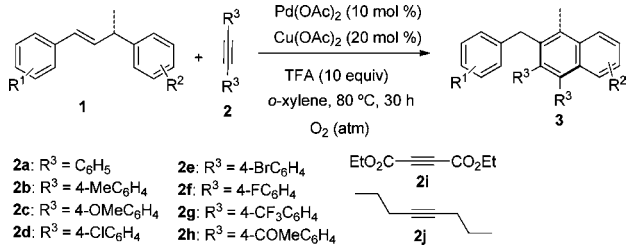
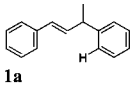
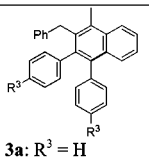
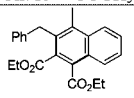
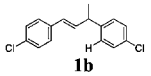
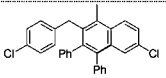
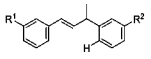
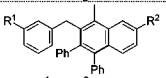
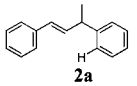
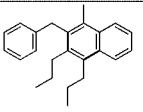
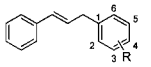
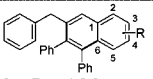
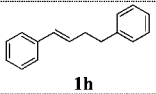
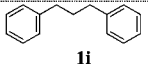
Table 2. Scope of Symmetrical Alkynes **2** in Pd-Catalyzed C−H Activation of Allylarenes **1**[a]

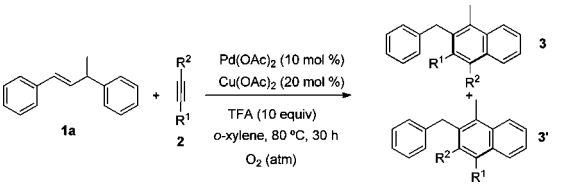


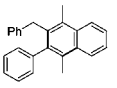
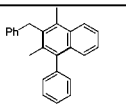
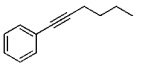
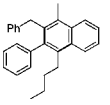
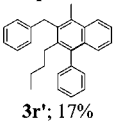
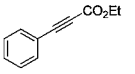
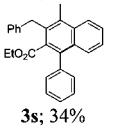
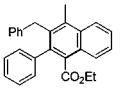
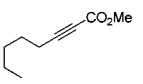
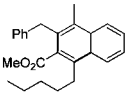
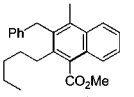
entry	1	2	product 3	yield %[b]
	 1a			
1	1a	2a	3a: R^3 = H	85
2	1a	2b	3b: R^3 = CH_3	81
3	1a	2c	3c: R^3 = OCH_3	52
4	1a	2d	3d: R^3 = Cl	82
5	1a	2e	3e: R^3 = Br	67
6	1a	2f	3f: R^3 = F	74
7	1a	2g	3g: R^3 = CF_3	76
8	1a	2h	3h: R^3 = $COCH_3$	68
9	1a	2i	 3i	57
10	 1b	2a	 3j	63
		2a		
11	1c: R^1 = R^2 = Cl	2a	3k: R^1 = R^2 = Cl	76
12	1d: R^1 = R^2 = OMe	2a	3l: R^1 = R^2 = OMe	79
13	 2a	2j	 3m	56
				
14	1e: R = 4-Me	2a	3n: R = 4-Me	61
15	1f: R = 4-C$(CH_3)_3$	2a	3o: R = 4-C$(CH_3)_3$	57
16	1g: R = 2-Me	2a	3p: R = 2-Me	53
17	 1h	2a	—	---[c]
18	 1i	2a	—	---[c]

[a] Unless otherwise mentioned, all reactions were carried out using **1** (0.25 mmol), **2** (0.30 mmol), $Pd(OAc)_2$ (0.025 mmol), $Cu(OAc)_2$ (0.05 mmol), TFA (2.5 mmol) and *o*-xylene (1.5 mL) at 80 °C under O_2 atmosphere for 30 h. [b] Isolated yields. [c] No characteristic products were observed.

yields (entries 14−16). We also examined the possibility of a butenylic C−C double bond as a director for the C−H bond activation reaction with **2a**. However, we did not observe any C−H functionalization product (entry 17).

Table 3. Scope of Unsymmetrical Alkynes **2** in Pd-Catalyzed C−H Activation of Allylarenes **1a**[a]



entry	alkyne **2**	product 3[b,c]	
1	 2k	 3q; 55%	 3q'; 14%
2	 2l	 3r; 45%	 3r'; 17%
3	 2m	 3s; 34%	 3s'; 20%
4	 2n	 3t; 64%	 3t'; 4%

[a] Unless otherwise mentioned, all reactions were carried out using **1a** (0.25 mmol), alkyne **2** (0.30 mmol), $Pd(OAc)_2$ (0.025 mmol), $Cu(OAc)_2$ (0.05 mmol), TFA (2.5 mmol) and *o*-xylene (1.5 mL) at 80 °C under one O_2 atmosphere for 30 h. [b] Isolated yields. [c] Regioisomers were determined by ^1H NMR.

Similarly, no expected product was observed for the reaction of **2a** with 1,3-diphenylpropane (**1i**) without an olefinic C−C double bond; the starting materials remain unchanged (entry 18). These results evidence the assistance of allylic double bond in the present Pd-catalyzed reaction.

To further explore the scope of the reaction, we tested the reaction of unsymmetrical alkynes with **1a** under the standard reaction conditions, and the results are given in Table 3. The reaction of 1-phenylpropyne (**2k**) with **1a** gave a 4:1 ratio of regioisomers **3q** and **3q′** in 69% overall yield (Table 3, entry 1). Similarly, hex-1-ynylbenzene (**2l**) and ethyl phenylpropiolate (**2m**) reacted with **1a** to give 2.6:1 and 1.6:1 mixture of regioisomers **3r** + **3r′** and **3s** + **3s′** in 62 and 51% yields (entries 2, 3). Methyl oct-2-ynoate (**2n**) also underwent the cyclization reaction with **1a** to give the desired naphthalenes in 68% yield with a 95:5 ratio of the regioisomers (entry 4). These results suggest that the electronic effects are playing the major role in the observed regioselectivity. The aryl−Pd intermediate more likely adds to the carbon−carbon triple bond with the Pd group to the more electron rich end, which is in agreement with the previous annulation reactions.[11]

(11) Huang, Q.; Larock, R. C. *Org. Lett.* **2002**, *4*, 2505.

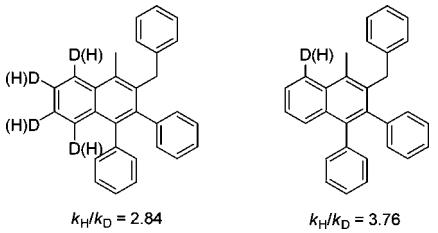
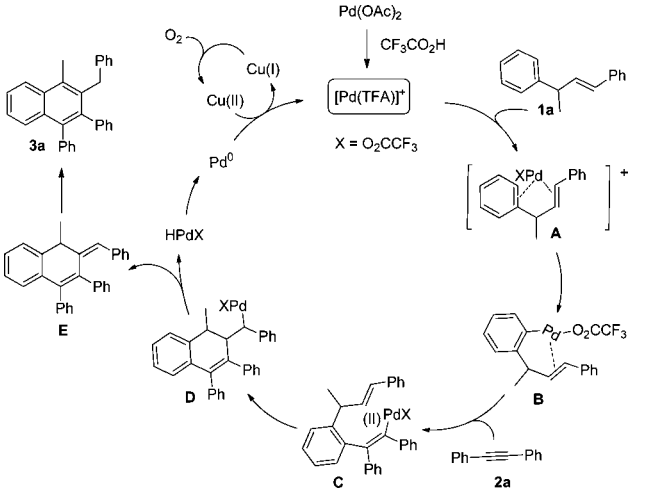


Figure 1. Kinetic isotope effect for the Pd-catalyzed reaction of allylarene **1a** with **2a**.

To understand the mechanism of this catalytic reaction, we measured the inter- and intramolecular kinetic isotopic effects (KIE) of the catalytic reaction of **1a** with **2a**. An intermolecular KIE k_H/k_D of 2.84 was observed for the competition reaction of **1a** and deuterium-labeled **1a**-d_5 with **2a** (Figure 1). On the other hand, an intramolecular competition experiment of **1a**-d_1 with **2a** showed a k_H/k_D of 3.76. The large difference of inter- and intramolecular KIE values implies that the C−C double bond coordination occurs prior to C−H palladation in the catalytic cycle.[12] If palladation takes place before the C−C double bond coordination, similar KIE values for the inter- and intramolecular competitions should be observed.[12] The large KIE value of 3.76 suggests that cleavage of the C−H bond is the rate-limiting step.

On the basis of the experiment results and known transition-metal-catalyzed C−H activation reactions,[7d,e,11] a possible mechanism employing **1a** and **2a** as the substrates is proposed to account for the present catalytic reaction (Scheme 2). The highly electrophilic cationic palladium species $[Pd(TFA)]^+$ is expected to be generated in the presence of TFA.[13] This cationic species should greatly facilitate the coordination of C−C double bond and enhance the metalation of aromatic C−H bond. Thus,

Scheme 2. Proposed Mechanism for Pd-Catalyzed C−H Activation and Annulation Reaction



the coordination of the C−C double bond in **1a** and then the C−C π-bond between the *ortho*- and *ipso*-carbons to Pd(II) center to give intermediate **A** are expected.[14] Subsequent cyclometalation leads to the formation of Pd(II) σ-aryl complex **B**. Addition of arylpalladium species **B** to the carbon−carbon triple bond of **2a** gives the vinylpalladium intermediate **C**. Intramolecular *cis*-addition of vinylpalladium **C** to the allylic carbon−carbon double bond generates an alkylpalladium species **D**. β-Hydride elimination of **D** followed by isomerization gives the final naphthalene **3**.

In summary, we have developed an efficient method for the synthesis of substituted naphthalenes via a palladium-catalyzed C−H activation and annulation of allylarenes with alkynes. This reaction proceeds through the π-coordination of the allylic carbon−carbon double bond to Pd(II) and *ortho*-selective C−H bond activation. The reaction has the advantage of using environmentally friendly oxygen as a terminal oxidant.

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Supporting Information Available. General experimental procedure, characterization details, and crystal data (CIF) for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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