

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

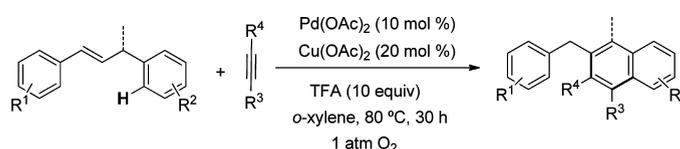
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Received December 23, 2012

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 interest⁸ in various

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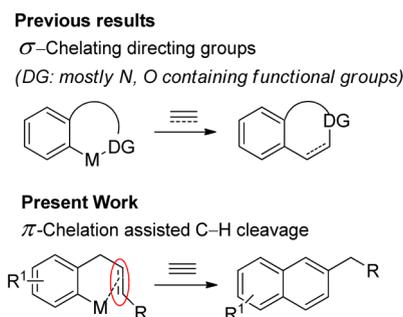
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C–H bond activation and cyclization and the recent success in the use of an allylic C–C double bond as a directing group for *ortho*-alkenylation of arenes^{7d} prompted us to explore the possibility of employing alkyne as a coupling partner in this functional group directed intermolecular C–H activation 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 ¹³C 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 O₂ 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

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	<i>o</i> -xylene	80/24	70
10	O ₂ + Cu(OAc) ₂ /0.25	<i>o</i> -xylene	80/24	81
11	O ₂ + CuCl ₂ /0.25	<i>o</i> -xylene	80/24	40
12	O ₂ + CuO/0.25	<i>o</i> -xylene	80/24	72
13	O ₂ + Cu(BF ₄) ₂ /0.25	<i>o</i> -xylene	80/24	47
14	O ₂ + Cu(OTf) ₂ /0.25	<i>o</i> -xylene	80/24	29
15	O ₂ + Cu(OAc) ₂ /0.05	<i>o</i> -xylene	80/24	80
16	O ₂	<i>o</i> -xylene	80/24	67
17	O ₂ + Cu(OAc) ₂ /0.05	<i>o</i> -xylene	80/24	– ^c
18	O ₂ + Cu(OAc) ₂ /0.05	<i>o</i> -xylene	80/30	89 (85) ^d

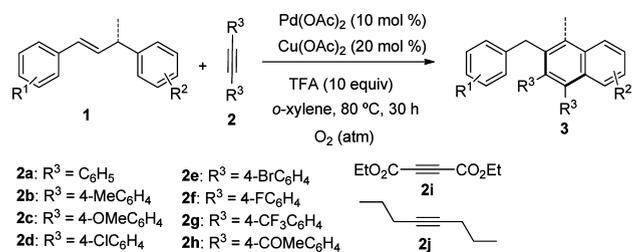
^a Unless otherwise mentioned, all reactions were carried out using **1a** (0.25 mmol) and **2a** (0.30 mmol), TFA (2.5 mmol) and other additives. ^b Yields were determined by the ¹H NMR integration method using mesitylene as the internal standard. ^c TFA not used. ^d Isolated yield based on **1a**.

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

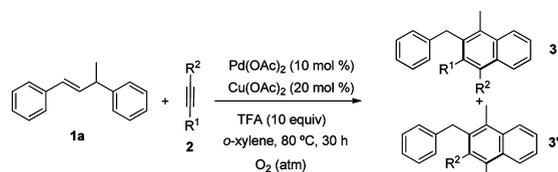


entry	1	2	product 3	yield % ^b
1		2a		85
2	1a	2b		81
3	1a	2c		52
4	1a	2d		82
5	1a	2e		67
6	1a	2f		74
7	1a	2g		76
8	1a	2h		68
9	1a	2i		57
10		2a		63
11		2a		76
12		2a		79
13		2j		56
14		2a		61
15		2a		57
16		2a		53
17		2a	---	--- ^c
18		2a	---	--- ^c

^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 O₂ 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		
2		
3		
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 O₂ 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

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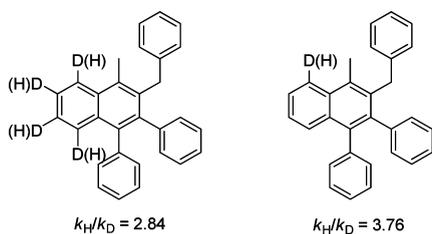


Figure 1. Kinetic isotope effect for the Pd-catalyzed reaction of allylarene **1a** with **2a**.

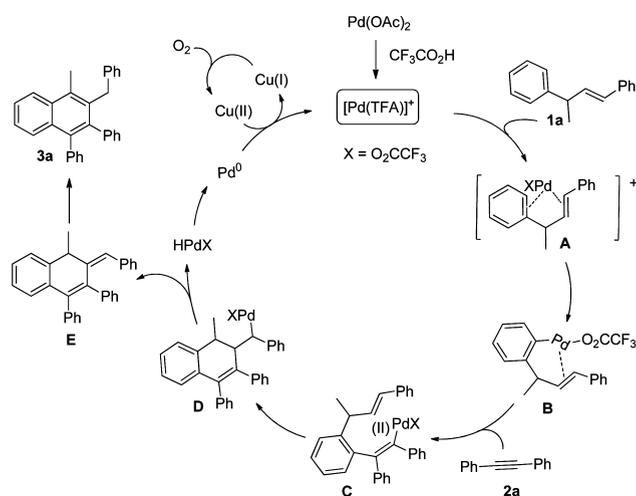
To understand the mechanism of this catalytic reaction, we measured the inter- and intramolecular kinetic isotopic effects (KIE) of the catalytic reaction of **1a** with **2a**. An intermolecular KIE k_H/k_D of 2.84 was observed for the competition reaction of **1a** and deuterium-labeled **1a-d₅** with **2a** (Figure 1). On the other hand, an intramolecular competition experiment of **1a-d₁** 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 $[\text{Pd}(\text{TFA})]^+$ 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,

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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.

Acknowledgment. We thank the National Science Council of the Republic of China (NSC-101-2628-M-007-004) for support of this research.

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.