

Carbocyclization of Aromatic Iodides, Bicyclic Alkenes, and Benzynes Involving a Palladium-Catalyzed C–H Bond Activation as a Key Step

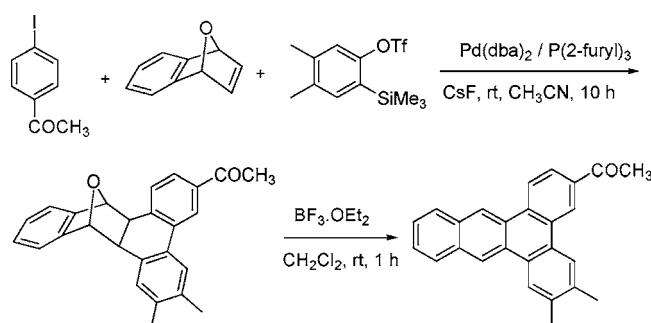
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ABSTRACT



A facile palladium-catalyzed carbocyclization reaction of aromatic iodides, bicyclic alkenes (norbornadiene, norbornene and oxabenzonorbornadiene), and benzynes to furnish various annulated 9,10-dihydrophenanthrene derivatives is described. The carbocyclization products from oxabenzonorbornadiene were further converted to polyaromatic hydrocarbons via a Lewis acid mediated deoxyaromatization reaction.

Palladium-catalyzed carbocyclization is an exceedingly efficient method for preparing polycyclic compounds in one pot.¹ In these reactions, intramolecular insertion of alkynes or alkenes into a palladium–carbon bond is the most common method for the construction of carbocycles. Very recently, carbocyclization involving a C–H bond activation and the formation of a metallacycle as a catalyst intermediate has been proposed.^{2,3,6c} Thus, Catellani and Chiusoli reported a carbocyclization reaction of aryl iodides with two norbornenes,^{3a} Heck and his co-workers^{3b} and Nomura et al.^{3c}

revealed the cocyclotrimerization of aryl halide with two alkynes, and Larock's group has demonstrated a partially intermolecular carbocyclization of 2-halobiaryl with arynes.^{3d} Recently, we also described an intermolecular carbocyclization of an aromatic halide with two benzynes.^{3e} In these

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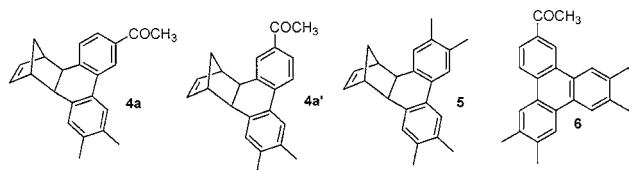
(2) (a) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78 and references therein. (b) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148 and references therein. (c) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527. (d) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *286*, C13. (e) Albrechta, K.; Reisefi, O.; Weberb, M.; Knierima, B.; Meijerea, A. D. *Tetrahedron* **1994**, *50*, 383.

(3) (a) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1982**, *239*, C35. (b) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (c) Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 6836. (d) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716. (e) Jayanth, T. T.; Cheng, C.-H. *Chem. Commun.* **2006**, 894.

(4) (a) Jegannmohan, M.; Cheng, C.-H. *Org. Lett.* **2004**, *6*, 2821. (b) Jegannmohan, M.; Cheng, C.-H. *Synthesis* **2005**, *5*, 1693. (c) Jayanth, T. T.; Jegannmohan, M.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 2921. (d) Hsieh, J.-C.; Cheng, C.-H. *Chem. Commun.* **2005**, 2459. (e) Jayanth, T. T.; Jegannmohan, M.; Cheng, C.-H. *J. Org. Chem.* **2004**, *7*, 8445.

intermolecular reactions, only two different substrates participate. Our continuous interest in carbocyclization and benzyne chemistry⁴ prompted us to explore the possibility of using three different substrates for the benzyne-involved carbocyclization reactions. In this communication, we wish to report a new carbocyclization employing an aryl iodide, a bicyclic alkene, and a benzyne to give an annulated 9,10-dihydrophenanthrene catalyzed by a palladium trifurylphosphine complex and the application of this method in the synthesis of polyaromatic hydrocarbons. The catalytic carbocyclization shows interesting product regiochemistry, providing the basis for the elucidation of catalytic pathways, and involves a facile highly regioselective C–H bond activation promoted by fluoride ion as a key step.^{3d,e}

The three-component carbocyclization of 4-iodoacetophenone (**1a**) with norbornadiene (**2a**) and a benzyne precursor **3a** was carried in the presence of 5 mol % of Pd(dba)₂, 20 mol % of P(2-furyl)₃, and CsF (4 equiv) in CH₃CN at room temperature for 10 h. The reaction gave product **4a** in a 92% isolated yield (Table 1, entry 1).⁵ The regio- and stereochemistry of **4a** was confirmed by its NMR data and NOE experiments. The catalytic reaction is remarkably regio- and stereoselective, giving the exo isomer as the exclusive product (see Supporting Information). In the reaction, the three substrates employed are nearly in a 1:1:1 molar ratio, and yet only **4a** was observed. The other possible carbocyclization products such as **4a'** (see the proposed mechanism), **5**,^{4e} and **6**^{3e} reported previously were not detected.

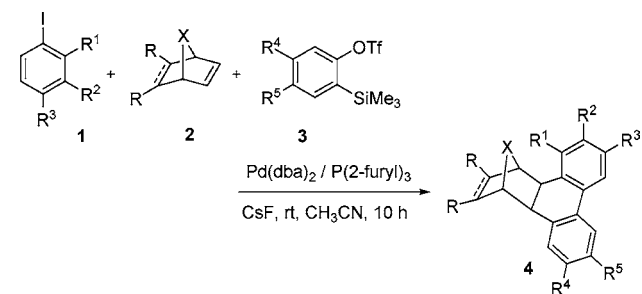


To optimize the present reaction, various palladium complexes with different supporting ligands were examined for the reaction of **1a** with **2a** and **3a** to give **4a** in CH₃CN. Other monodentate phosphine palladium complexes Pd(PPh₃)₄, PdCl₂(PPh₃)₂ and Pd(dba)₂/4P(Cy)₃, /4P(*t*-Bu)₃, /4P(*n*-Bu)₃, and /4P(*o*-tolyl)₃ were active for the reaction but gave **4a** in only 65%, 60%, 45%, 40%, 38%, and 35% yields, respectively. Bidentate phosphine complexes Pd(dba)₂/dppm and dppe are less active, affording **4a** in 25% and 15% yields, respectively. Phosphine-free palladium complexes Pd(dba)₂ and PdCl₂ furnished 15% and 10% yields, whereas Pd(OAc)₂ provided a 75% yield of **4a**. For the reaction of **1a** with **2a** and **3a** in CH₃CN, the Pd(dba)₂/4P(2-furyl)₃ gave the highest yield of 97% (92% isolated). The yield of **4a** was determined

(5) For the stoichiometric palladium carbocyclization reaction of an aryl halide, norbornadiene, and alkynes leading to norbornene annulated 9,10-dihydrophenanthrene, see: (a) Liu, C.-H.; Li, C.-S.; Cheng, C.-H. *Organometallics* **1994**, *13*, 18. (b) Catellani, M.; Marmiroli, B.; Fagnola, M. C.; Acquotti, D. *J. Organomet. Chem.* **1996**, *507*, 157.

(6) (a) Li, C.-S.; Cheng, C.-H.; Liao, F.-L.; Wang, S.-L. *J. Chem. Soc., Chem. Commun.* **1991**, 710. (b) Li, C.-S.; Jou, D.-C.; Cheng, C.-H. *Organometallics* **1993**, *12*, 3945. (c) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Carreno, E. P.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336 and references therein.

Table 1. Results of Carbocyclization Reactions^a



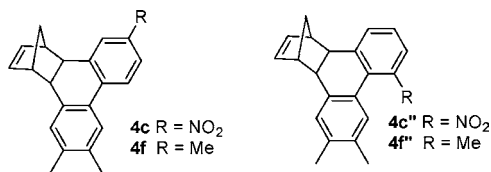
entry	1	2	3	product ^b	yield, (%) ^c
1	1a	2a	3a		4a : R ³ = COCH ₃ 92
2	1b	2a	3a		4b : R ³ = NO ₂ 83
3	1c	2a	3a		4c : R ² = NO ₂ 88
4	1d	2a	3a		4d : R ¹ = NO ₂ 90
5	1e	2a	3a		4e : R ³ = CH ₃ 68
6	1f	2a	3a		4f : R ² = CH ₃ 75
7	1g	2a	3a		4g : R ³ = OCH ₃ 59
8	1h	2a	3a		4h : R ³ = Br 75
9	1i	2a	3a		4i : R ³ = H 79
10	1a	2b	3a		4j : R ³ = COCH ₃ 83
11	1i	2b	3a		4k : R ³ = H 76
12	1j	2b	3a		4l 79
13	1k	2b	3a		4m 75
14	1a	2c	3a		4n 87
15	1a	2a	3b		4o : R ⁴ = R ⁵ = H 89
16	1a	2a	3c		4p : R ⁴ + R ⁵ = - (CH ₂) ₂ - 83
17	1a	2a	3d		4q : R ⁴ + R ⁵ = - OCH ₂ O- 80
18	1a	2a	3e		4r : R ⁴ = Me; 4r' : R ⁵ = Me 85

^a All reactions were carried out using aromatic iodides **1** (1.0 mmol), bicyclic alkenes **2** (1.5 mmol for **2a** and **2c** and 1.0 mmol for **2b**), benzyne precursors **3** (1.1 mmol), Pd(dba)₂ (5 mol %), P(2-furyl)₃ (20 mol %), CsF (4.0 mmol), and CH₃CN (3.0 mL) at room temperature for 10 h. ^b In products **4a–h**, **4r** and **4r'**, only the non-hydrogen substituents are shown in the table. ^c Isolated yields.

on the basis of the ¹H NMR integration method using mesitylene as an internal standard.

The catalytic reaction can be extended to various aromatic iodides **1b–k** (Table 1). Aryl iodides having substituents 4-nitro (**1b**), 3-nitro (**1c**), 2-nitro (**1d**), 4-methyl (**1e**),

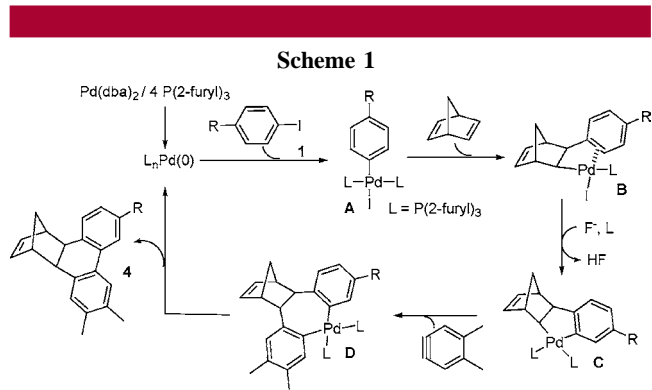
3-methyl (**1f**), 4-MeO (**1g**), 4-Br (**1h**), and iodobenzene (**1i**) all reacted smoothly with **2a** and **3a** to give the corresponding carbocyclization products **4b–i** in 59–90% yields (Table 1, entries 2–9). The results indicate that the reaction is compatible with a wide range of functional groups, but aryl iodides with electron-withdrawing substituents such as nitro and acetyl groups are more reactive, affording higher product yields (entries 1–4). The lowest product yield (59%, entry 7) was observed with iodoanisole **1g**. Chemoselectivity was observed for the carbocyclization of 4-bromo-1-iodobenzene (**1h**) with **2a** and **3a** giving bromo-substituted product **4h** in 75% yield (entry 8). All of these reactions are highly regioselective; only regioisomer **4** was observed in the ^1H NMR spectra of the reaction mixtures. In addition to the above regioselectivity, the reactions of meta-substituted 1-iodo-3-nitrobenzene (**1c**) and 3-iodotoluene (**1f**) with **2a** and **3a** reveal a new interesting regioselectivity. In these reactions, there are two *ortho* positions of **1c** and **1f** for C–H activation, but the activation takes place only at the less hindered *ortho* position, leading only to products **4c** and **4f**, respectively. The other possible regioisomers **4c''** and **4f''** were not observed.



The present protocol can be further applied to other bicyclic alkenes such as oxabenzonorbornadiene (**2b**) and norbornene (**2c**). Treatment of **1a** with **2b** and **3a** under the optimized reaction conditions gave **4j** in 83% yield (entry 10). Similarly, 1-iodobenzene (**1i**), 1-iodonaphthalene (**1j**), and heterocyclic 2-iodothiophene (**1k**) provided **4k**, **4l**, and **4m** in 76%, 79%, and 75% yields, respectively. In addition, **2c** also efficiently reacted with **1a** and **3a** to give product **4n** in 87% yield (entry 14).

Under similar reaction conditions, various benzyne precursors **3b–e** were also tested. Compound **3b** reacted smoothly with **1a** and **2a** to give **4o** in 89% yield (entry 15). Likewise, electron-rich benzyne precursors **3c** and **3d** reacted with **1a** and **2a** to afford **4p** and **4q** in 83% and 80% yields, respectively (entries 16 and 17). As expected, the reaction of 4-methylbenzyne precursor **3e** with **1a** and **2a** gave a mixture of regioisomeric products **4r** and **4r'** in a ca. 50:50 ratio (entry 18).

The observed regiochemistry and the known palladium chemistry provide the basis for the proposed mechanism shown in Scheme 1. The first step is likely the oxidative addition of **1** to the Pd(0) species to give arylpalladium(II) intermediate **A**. Next is the coordination of alkene to the palladium intermediate, followed by the insertion into the aryl–Pd bond, forming an intramolecular (η^2 -arene)palladium(II) species **B**.⁶ Subsequent C–H activation promoted by F[–] to give a cyclometalated species **C**,^{5a} insertion of benzyne, and reductive elimination give the final product and regenerate the catalyst. The proposed intermediates **B**



and **C** are strongly supported by the isolation of similar complexes previously.^{5a,6} In addition, we were able to prepare **C** (R = H and L = PPh₃) from iodobenzene, Pd(dba)₂/4PPh₃ in the presence of CsF in acetonitrile in 69% yield. Further treatment of **C** with benzyne precursor gave the carbocyclization product **4i** in 75% yield.

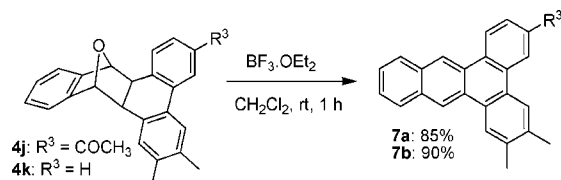
The insertion sequence of bicyclic alkene and benzyne into the Pd–carbon bond is vital in determining the regiochemistry of carbocyclization products **4**. For example, the structure of product **4a** can be accounted for precisely by the insertion order in Scheme 1, but if benzyne is first inserted into the Pd–aryl bond,^{3c} a different isomeric product **4a'** will be formed. The observation of **4a–r** exclusively shows that bicyclic alkene insertion into the Pd–aryl bond occurs prior to benzyne insertion in the present catalytic reaction.

The present catalytic reaction is similar in reaction conditions to the palladium-catalyzed [2 + 2 + 2] cocyclotrimerization reaction of two benzynes with a bicyclic alkene to give the cocyclotrimerization product **5**.^{4e} The absence of **5** in the present reaction indicates that the oxidative addition of aryl iodide to palladium(0) complex is faster than the formation of palladacycle from the oxidative coupling of benzyne and bicyclic alkene.

The selection of phosphine ligands is important to the success of the catalytic reaction. The results of optimization studies show that bidentate phosphine palladium complexes are less active than monodentate ones. This is likely due to the fact that a coordinated bidentate phosphine will block the coordination of the aryl group in intermediate **B** to the palladium(II) center and thus hinder the further C–H bond activation to give intermediate **C** in Scheme 1. Among the monodentate phosphine ligands tested, more π -acidic phosphines appear to give higher product yields, and P(2-furyl)₃ is most effective for the present catalytic reaction. The results may be rationalized on the basis of the C–H bond activation step (**B** to **C**). A more π -acidic ligand on intermediate **B** will enhance the proton acidity and assist the removal of the proton by F[–] ion to give **C**.

The carbocyclization products from oxabenzonorbornadiene **4j** and **4k** undergo deoxyaromatization reaction in the presence of BF₃·OEt₂ (1.5 equiv) in CH₂Cl₂ at room temperature for 1 h, providing polyaromatic hydrocarbons **7a** and **7b** in 85% and 90% yields (Scheme 2). It is interesting to note that most of these polycyclic aromatic hydrocarbons show strong photoluminescence in the solid

Scheme 2



state and in solutions and are potentially useful as electroluminescent and photoluminescent materials.⁷

In conclusion, we have developed a new palladium-catalyzed, highly regio- and stereoselective carbocyclization of aryl iodides, bicyclic alkenes, and arynes to give various annulated 9,10-dihydrophenanthrene derivatives efficiently,

(7) (a) Shih, H.-T.; Shih, H.-S.; Cheng, C.-H. *Org. Lett.* **2001**, *6*, 881.
 (b) Shih, H.-T.; Shih, H.-S.; Cheng, C.-H. *Adv. Mater.* **2002**, *14*, 1409.

providing the construction of three different C–C bonds in one pot. The catalytic reaction involves an interesting reaction sequence of the substrates and facile fluoride-promoted C–H bond activation. The carbocyclization products from oxabenzonorbornadiene can be further applied for the synthesis of highly substituted aromatic hydrocarbons via a deoxyaromatization reaction. Further extension of these annulation reactions into different multiple carbon–carbon and carbon–hetero bonds are in progress.

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Supporting Information Available: Preparation details, characterization data of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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