7280 *J. Am. Chem. Soc.* **2000,** *122,* 7280−7286

# Palladium-Catalyzed Controlled Carbopalladation of Benzyne

**Eiji Yoshikawa, K. V. Radhakrishnan, and Yoshinori Yamamoto***

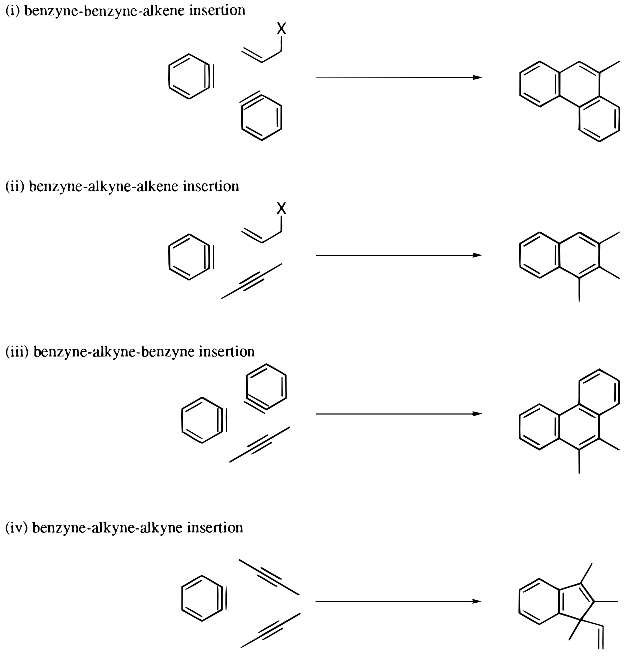
*Contribution from the Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*

*Received April 6, 2000*

**Abstract:** 2-Trimethylsilylphenyl trifluoromethanesulfonate **1a**, a benzyne precursor, reacted with the allylic chlorides **2a−f** in the presence of CsF (2.0 equiv) and $Pd_2(dba)_3$•$CHCl_3$ (2.5 mol %)−dppf (5 mol %) in a 1:1 mixed solvent of $CH_3CN$ and THF to produce the phenanthrene derivatives **3** along with their minor regioisomers **4** in good yields (i) and the reaction of **1a** with **2a** and the internal alkynes **15a**,**c−e** afforded the naphthalene derivatives **16** in moderate yields (ii). The reaction of benzyne precursor **1a** with the alkynes **15a−c**,**f−h** in the presence of $Pd(OAc)_2$ (5 mol %)−(*o*-tolyl)$_3$P (5 mol %) catalyst and CsF (2.0 equiv) in $CH_3CN$ gave the phenanthrene derivatives **17** (iii), whereas the reaction of **1a** with the alkynes **15a**,**b**,**i** in the presence of the same catalysts and CsF in *$CH_3CN$−toluene* gave the indene derivatives **18** in good yields (iv). Detailed mechanistic investigation revealed that the former two reactions i and ii proceed through carbopalladation to free benzyne, while the latter two reactions iii and iv proceed through the nonfree benzyne mechanism, in which the initial step of the catalytic cycle begins with Pd(0) insertion to the Ar−OTf bond of **1**.

## Introduction

Alkynes are frequently used as a substrate for the transition metal catalyzed inter- and intramolecular carbometalation reaction.[1] However, arynes have hardly been utilized in the transition metal *catalyzed* organic synthesis, although *stoichiometric* reactions of zirconium−benzyne and nickel−benzyne complexes were studied.[2] Quite recently, Peña, and co-workers have reported the efficient palladium-catalyzed cyclotrimerization[3a,b] of arynes and cocyclization of arynes with alkynes.[3c] During our continuing studies of the catalytic hydro- and/or carbopalladation of allenes,[4a] enynes,[4b] methylenecyclopropanes,[4e] and alkynes,[4c,d] it occurred to us that arynes may be utilized as a reactive partner in catalytic carbopalladation. We first examined the palladium-catalyzed intermolecular insertion reaction of benzyne into the $\pi$-allylpalladium intermediates and found that the reaction via controlled benzyne−benzyne−alkene insertion (i) took place to give phenanthrene derivatives.[5a] Furthermore, the controlled benzyne−alkyne−alkene insertion (ii) occurred by the three-component coupling reaction, giving naphthalene derivatives.[5a] Then, we examined the co-cyclization of benzyne with alkynes and found that phenanthrene derivatives were obtained via benzyne−alkyne−benzyne insertion (iii).[5b] Concerning the benzyne−alkyne−benzyne insertion, Peña and coworkers reported a similar result almost at the same time.[3c] We now report the full account on the previous communications[5a,b] together with new findings on the unprecedented cocyclization reaction of aryne precursors with alkynes via benzyne−alkyne−alkyne insertion (iv), which produces indene derivatives.


(i) benzyne-benzyne-alkene insertion

(ii) benzyne-alkyne-alkene insertion

(iii) benzyne-alkyne-benzyne insertion

(iv) benzyne-alkyne-alkyne insertion

## Results and Discussion

**Reaction of Benzyne with $\pi$-Allylpalladium Intermediate. (i) Benzyne−Benzyne−Alkene Insertion.** It is well-known that

---

[1] (a) Hegedus, L. S. Transition Metal Organometallics in Organic Synthesis. In *Comprehensive Organometallic Chemistry II*; Able, E. W., Stone, F. G. A., Willkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 1−977. (b) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081−1119.

[2] (a) Buchwald, S. L.; Broene, R. D. Transition Metal Alkyne Complexes: Zirconium-Benzyne Complexes. In *Comprehensive Organometallic Chemistry II*; Able E. W., Stone, F. G. A., Willkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 771−784. (b) Bennett, M. A.; Wenger, E. *Chem. Ber*. **1997**, *130*, 1029−1042.

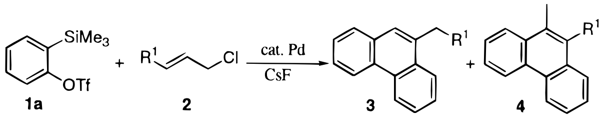
[3] (a) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2659−2661. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L *Org. Lett.* **1999**, *1*, 1555−1557. (c) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc*. **1999**, *121*, 5827−5828.

[4] (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019−6020. (b) Saito, S.; Salter, M. M.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 970−971. (c) Tsukada, N.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2477−2479. (d) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc*. **1998**, *120*, 10262−10263. (e) Tsukada, N.; Shibuya, A.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8123−8124.

[5] (a) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed*. **2000**, *39*, 173−175. (b) Radhakrishnan, K. V.; Yoshikawa, E.; Yamamoto, Y. *Tetrahedron Lett*. **1999**, *40*, 7533−7535. For the reaction of arynes with *bis*-$\pi$-allylpalladium intermediate, see: (c) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 729−731.

10.1021/ja001205a CCC: $19.00

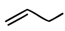
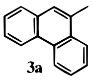
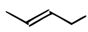
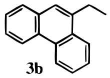
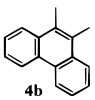
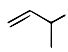
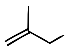
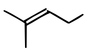
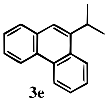
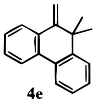
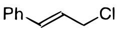
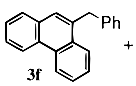
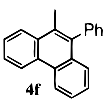
aryl- and vinylpalladiums easily undergo intra- and intermolecular carbopalladation with alkynes via, for example, Heck-type reaction. However, when we started this research, to the best of our knowledge, there was no report on the *intermolecular* carbopalladation of $\pi$-allylpalladium complexes to alkynes, although several examples of the intramolecular reactions were known.[6,7] Quite recently, almost at the same time as our commumication appeared, the intermolecular reaction of alkynes with a $\pi$-allylpalladium complex leading to substituted benzenes has been reported.[8] We thought that, since benzyne is quite a reactive substrate compared to ordinary alkynes, the intermolecular reaction between benzyne and $\pi$-allylpalladium complexes must take place rather readily. The initial experiment revealed that the palladium-catalyzed reaction of allylic chlorides **2** with benzyne precursor **1a**[9,10] produces phenanthrene derivatives **3**, along with their minor regioisomers **4**, in good yields (eq 1).



**1a** **2** **3** **4** (1)

The results are summarized in Table 1. After certain optimization work on the reaction of allyl chloride **2a**, we settled on the following two best methods. **Method A**: Allyl chloride (32.6 mL, 0.4 mmol) was added to a suspension of anhydrous CsF (243 mg, 1.6 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (10.4 mg, 0.01 mmol), and dppf (11 mg, 0.02 mmol) in $CH_3CN$ (1 mL) and THF (1 mL), and the mixture was stirred at room temperature for a few minutes. Benzyne precursor **1a** (182.8 mL, 0.8 mmol) was added and the resulting mixture was stirred at 60 °C for 1 day. The mixture was cooled to room temperature, extracted with ether, dried with $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography, giving **3a** in 69% yield (53.1 mg) (entry 1). **Method B** (larger amounts of **1a** and CsF were used compared to Method A): Allyl chloride (32.6 mL, 0.4 mmol) was added to a suspension of anhydrous CsF (486 mg, 3.2 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (10.4 mg, 0.01 mmol) in $CH_3CN$ (2 mL) and the mixture was stirred at room temperature for 15 min. Four equivalents of **1a** (365.6 mL, 1.6 mmol) was added and the mixture was stirred at 80 °C for 3 h. The same workup procedure as above was used, and **3a** was obtained in 70% yield (53.9 mg) (entry 2). The catalytic system of $Pd_2(dba)_3{\cdot}CHCl_3$ using $PPh_3$ or dppe gave slightly lower yields, and the other catalysts such as $Pd(OAc)_2$ and $Pd(PPh_3)_4$ were not so effective. The reaction of crotyl chloride **2b** with **1a** under the conditions of Method A gave a 58:42 mixture of **3b** and **4b** in 66% combined yield (entry 3). The ratio of **3b** to **4b** increased up to 70:30 under the conditions of Method B (entry 4). The reaction of α-methylallyl chloride **2c** gave a 65:35 mixture of **3b** and **4b** in 70% yield (entry 5). It should be noted that the isomer ratio of the products obtained from the reaction of **2c** is almost the same as that of **2b**. Methallyl chloride **2d** did not produce phenanthrene derivatives at all (entry 6).[15] The reaction of prenyl chloride **2e** under Method A gave an 80:20 mixture of **3e** and **4e** in 44% yield (entry 7), but both the isomer ratio and the chemical yield increased up to >95:5 and 68% yield, respectively, under the conditions of Method B (entry 8). The reaction of cinnamyl chloride **2f** afforded approximately a 7:3 mixture of **3f** and **4f** under the conditions of both methods, but Method B gave a higher chemical yield than Method A (entries 9 and 10).

**Table 1.** Palladium-Catalyzed Reaction of **1a** with **2**

| entry | allylic chloride **2** | | method | product | | | yield %[a] (**3** : **4**)[b] |
|---|---|---|---|---|---|---|---|
| 1 |  | **2a** | A |  | | | 69 |
| 2 | **2a** | | B | **3a** | | | 70 |
| 3 |  | **2b** | A |  | + |  | 66(58 :42) |
| 4 | **2b** | | B | **3b** | | **4b** | 70(70 : 30) |
| 5 |  | **2c** | A | **3b** | | **4b** | 70(65 : 35) |
| 6 |  | **2d** | B | | | | – |
| 7 |  | **2e** | A |  | + |  | 44(80 : 20) |
| 8 | **2e** | | B | **3e** | | **4e** | 68(>95 : 5) |
| 9 |  | **2f** | A |  | + |  | 56(70 :30) |
| 10 | **2f** | | B | **3f** | | **4f** | 71(73 : 27) |

[a] Isolated yield based on **2**. [b] Ratio determined by $^1H$ NMR of the crude product.

A plausible mechanism for this unprecedented intermolecular benzyne−benzyne−alkene insertion reaction is shown in Scheme 1. Initially $\pi$-allylpalladium chloride **5** would be formed from Pd(0) and **2a**. Benzyne **6**, which is generated from the reaction of CsF and **1a**,[13] would insert into **5** to afford the arylpalladium intermediate **7**. In the case of substituted allylic chlorides **2b**−**c**,**e**−**f**, two regioisomers **12** and **13** would be produced at this

---

(6) (a) Oppolzer, W. Transition Metal Allyl Complexes: Intermolecular Alkene and Alkyne Insertion. In *Comprehensive Organometallic Chemistry II*; Able, E. W., Stone F. G. A., Willkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 905−921. (b) Oppolzer W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38−52. (c) Keese, R.; Grept, R. G. G.; Herzog, B. *Tetrahedron Lett.* **1992**, *33*, 1207−1210. (d) Larock, R. C.; Takagi, K.; Burkhart, J. P.; Hershberger, S. S. *Tetrahedron* **1986**, *42*, 3759−3762. (e) Inoue, Y.; Ohuchi, K.; Kawamata, T.; Ishiyama, J.; Imaizumi, S. *Chem. Lett.* **1991**, 835−836.

(7) The intermolecular insertion reaction of alkynes into $\pi$-allyl nickel complexes is known: (a) Camps, F.; Moretó, J. M.; Pagès, L. *Tetrahedron* **1992**, *48*, 3147−3162. (b) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911−4920. (c) Gómez, G. G.; Moretó, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 878−879.

(8) Tsukada, N.; Sugawara, S.; Inoue, Y. *Org. Lett.* **2000**, *2*, 655−657.

(9) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211−1214.

(10) A new hypervalent iodine−benzyne precursor, (phenyl)[2-(trimethylsilyl)phenyl]iodonium triflate, was reported recently. (a) Kitamura, T.; Yamane, M. *J. Chem. Soc., Chem. Commun.* **1995**, 983−984. (b) Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674−11679. The use of this benzyne precursor in our Pd reactions gave a complex mixture of products.

(11) An unidentified compound having $M^+$ (282) was obtained in low yield: this molecular weight corresponds to a molecule consisting of three benzynes and one $CH_2{=}CH(CH_3)CH_2$.

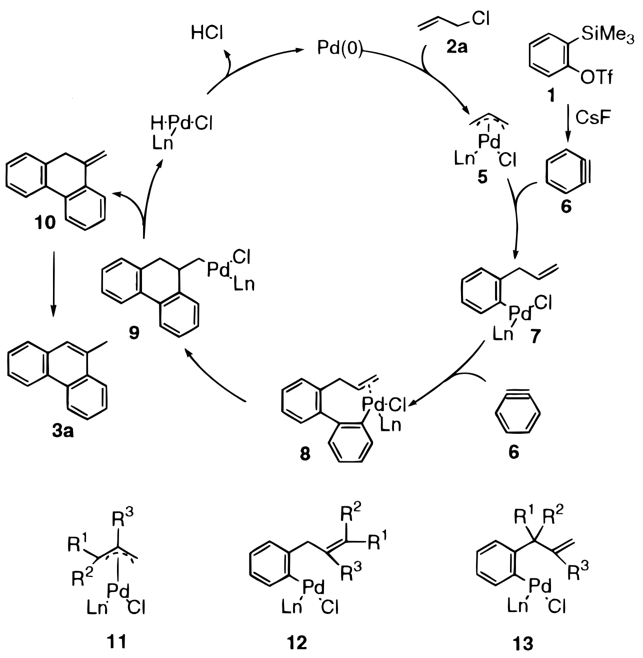
(12) A mixture of **2a** (1.0 equiv), **1a** (1.0 equiv), and **15a** (2.0 equiv) was stirred at 60 °C for 1 day in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), dppf (10 mol %), and CsF (2.0 equiv) in $CH_3CN$/THF (1/1). Then, again CsF (2.0 equiv) was added and the resulting mixture was stirred at 60 °C for 1 day.

(13) For transition metal mediated cyclotrimerization of alkynes which produces vinylcyclopentadienes, see: (a) Reinheimer, H.; Moffat, J.; Maitlis, P. M. *J. Am. Chem. Soc.* **1970**, *92*, 2285−2294.(b) Inoue, Y.; Itoh, Y.; Hashimoto, H. *Chem. Lett.* **1978**, 633−634. (c) Inoue, Y.; Itoh, Y.; Haruo, K.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3329−3333. (d) Kong, K.-C.; Cheng, C.-H. *J. Chem. Soc., Chem. Commun.* **1991**, 423−424. (e) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941−1946.

(14) It is reasonable to assume that the isomer ratio is not influenced strongly by the stereoelectronic effect of the Me group at the C-4 position of the methylbenzyne **6b** (see eq 10).

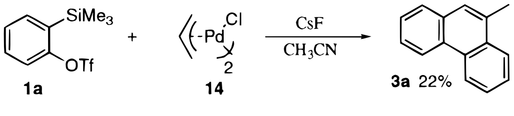
(15) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, 47, 2101−2108.

**Scheme 1**



stage. Second benzyne insertion into **7** would produce **8** and subsequent carbopalladation to alkene would afford the cyclized intermediate **9**. $\beta$-Hydride elimination from **9** would give HPdCl species and **10**, which would undergo isomerization to 9-methylphenanthrene **3a**. In the case of the substituted allylic chlorides, benzyne **6** would react predominantly at the less substituted terminus of the $\pi$-allylpalladium complexes **11** to produce **12** preferentially over its regioisomer **13**. Accordingly, **3b**,**e**−**f** were in general formed predominantly over their isomers **4b**,**e**−**f**, respectively. Formation of **4e** strongly supports the $\beta$-elimination−rearrangement processes (**9**−**10**−**3**) in the proposed mechanism; the rearrangement of the double bond of **4e** to form the phenanthrene ring is not possible. As is apparent from the result of the experiment with **2d**, the carbopalladation step (**8**−**9**) would be hampered if there is a substituent, such as Me, at the R$^3$ position of **11**. Even if the carbopalladation proceeds in the reaction of **2d** and a palladium intermediate corresponding to **9** is formed, there is no proton at the $\beta$-position of Pd in the intermediate, so there is no chance to regenerate palladium catalyst by $\beta$-hydride elimination. Therefore, the phenanthrene derivatives were not obtained from the reaction of **2d**.

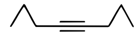
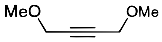
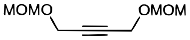
As mentioned above, the lack of an example for the *intermolecular* carbopalladation of $\pi$-allylpalladium complexes toward alkynes was strange for us. Accordingly, the reaction of $\pi$-allylpalladium chloride dimer **14** with 4-octyne was examined under various reaction conditions. However, no addition products were obtained, instead the starting materials were recovered. On the other hand, the reaction of **14** (1.0 equiv) with **1a** (1.0 equiv) in the presence of CsF (2.0 equiv) in $CH_3CN$ at room temperature gave **3a** in 22% yield (eq 2). This result



(2)

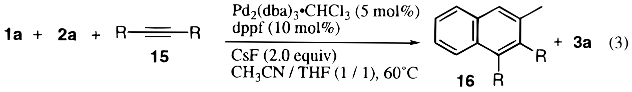
clearly indicates the very high reactivity of benzyne triple bond, compared to the ordinary one, toward the $\pi$-allyl−Pd bond.

**Table 2.** Palladium-Catalyzed Benzyne−Alkyne−Alkene Insertion

| entry | $R-\equiv-R$ **15** | product yields, %[a] **16** | **3a** |
|---|---|---|---|
| 1 |  **15a** | 47 | 3 |
| 2 |  **15c** | 50 | 4 |
| 3 |  **15d** | 53 | 4 |
| 4[b] | $EtO_2C-\equiv-CO_2Et$ **15e** | 37 | 3 |

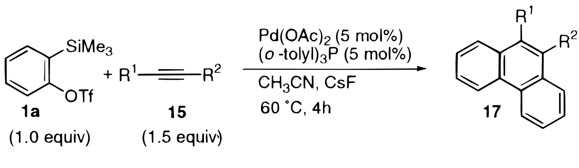
[a] Isolated yield was based on **2a**. [b] Hexaethyl mellitate was also formed.

**(ii) Benzyne−Alkyne−Alkene Insertion.** Encouraged by the successful controlled insertion of benzyne−benzyne−alkene, we next examined the controlled insertion of benzyne−alkyne−alkene. The results are summarized in Table 2. The reaction of **1a** (1.0 equiv), **2a** (1.0 equiv), and 4-octyne **15a** (2.0 equiv) under the slightly modified conditions[12] of Method A gave **16a** in 47% yield along with small amounts (3%) of **3a** (entry 1). Other internal alkynes **15c**−**e** reacted similarly to give the corresponding naphthalene derivatives **16c**−**e**, respectively, along with small amounts of **3a** (entries 2−4). As mentioned above, the insertion of $\pi$-allylpalladium chloride **5** into the ordinary alkynes **15** would be very sluggish compared to the insertion to benzyne, leading to the formation of **7** at the first stage of carbopalladation. The second stage of carbopalladation takes place via the Heck-type arylpalladation, so that alkynes can participate in this step. Especially in the presence of excess amounts of the alkynes, the alkyne insertion can take place selectively compared to the second benzyne insertion. When a terminal alkyne, such as phenyl acetylene, was used instead of the internal alkynes **15**, a small amount of diphenylacetylene was obtained. Accordingly, the alkyne component of the benzyne−alkyne−alkene insertion is limited to internal alkynes.



(3)

**Reaction of Benzyne with Alkynes in the Presence of Palladium Catalyst. (iii) Benzyne−Alkyne−Benzyne Insertion.** Since it became clear that alkynes could be incorporated into the sequential insertion starting from benzyne, we next studied the reaction of benzyne with alkynes. Optimization experiments were carried out on the reaction of **1a** with **15a**. After a number of trials, we found that the reaction in the presence of a Pd(OAc)$_2$/(*o*-tolyl)$_3$P catalytic system at 60 °C in $CH_3CN$ gave the best result, affording the phenanthrene derivative **17a** in 63% yield along with trace amounts of triphenylene (entry 1). The results with several different alkynes are summarized in Table 3. The other symmetrically substituted alkynes **15b** and **15c** reacted similarly to give the corresponding phenanthrene derivatives **17b** and **17c**, respectively, in good yields (entries 2 and 3). The unsymmetrically substituted alkynes **15f**−**h** gave the products **17f**−**h** in good yields (entries 4−6).



(4)

**Table 3.** Palladium-Catalyzed Reaction of **1a** with **15** in $CH_3CN$

| entry | alkyne **15** | $R^1$ | $R^2$ | product **17** | yield, %$^a$ |
|---|---|---|---|---|---|
| 1 | **15a** | *n*-Pr | *n*-Pr | **17a** | $63^b$ |
| 2 | **15b** | *n*-pentyl | *n*-pentyl | **17b** | $67^b$ |
| 3 | **15c** | $CH_2OMe$ | $CH_2OMe$ | **17c** | $59^b$ |
| 4 | **15f** | Ph | $CH_3$ | **17f** | 67 |
| 5 | **15g** | Ph | $CH_2CH_3$ | **17g** | 63 |
| 6 | **15h** | Ph | $COCH_3$ | **17h** | 76 |

[a] Isolated yield based on **1a**. [b] Trace amounts of triphenylene were also formed.

Because of the structural characteristics of phenanthrenes, even if the carbopalladation to unsymmetric alkynes proceeds in nonregioselective manner, regioisomeric phenanthrene products are not obtained. When we completed this work, an article by Peña et al.[3c] appeared which described the synthesis of phenanthrenes and naphthalenes by cocyclization of arynes with alkynes. According to this report, electron deficient alkynes, such as DMAD, gave phenanthrene derivatives in the presence of $Pd(Ph_3P)_4$, while with $Pd_2(dba)_3$, they afforded naphthalene derivatives in good yields. It is interesting to note that with other alkynes studied, they did not observe any selectivity in the formation of phenanthrenes and triphenylene. Phenanthrene derivatives were obtained, albeit in low yields, in the case of electron-rich alkynes. It is noteworthy that our method, utilizing the $Pd(OAc)_2$-(*o*-tolyl)$_3$P catalyst system, afforded the phenanthrene derivatives exclusively in good yields regardless of the electronic nature of the alkynes.

**(iv) Benzyne−Alkyne−Alkyne Insertion**. On the continuation of this study, we found a dramatic solvent effect. As mentioned above, all the previous reactions using **1a** were carried out in a rather polar solvent such as $CH_3CN$. When the reaction of benzyne precursor **1a** and 4-octyne **15a** in the presence of CsF and $Pd(OAc)_2$/(*o*-tolyl)$_3$P was carried out in a 1:1 mixed solvent of $CH_3CN$ and toluene, the indene derivative **18a**,[13] a 1:2 adduct of benzyne and **15a**, was obtained in 66% yield along with trace amounts of the isomeric product **19a** in which the double bond of the side chain isomerized from C-1 to C-2. No trace amount of the phenanthrene product **17a** was detected by $^1H$ NMR and capillary GC-mass analyses of the crude reaction mixture. It should be mentioned also that the indene derivatives were not obtained in the absence of toluene (see Table 3). The use of $Pd_2(dba)_3 \cdot CHCl_3$/(*o*-tolyl)$_3$P, instead of $Pd(OAc)_2$/(*o*-tolyl)$_3$P, did not show high selectivity on the product distribution and gave a mixture of the phenanthrene, indene, and isomeric indene derivatives **17a**, **18a**, and **19a**. The results are summarized in Table 4. The reaction of the alkyl-substituted internal alkynes **15a** and **15b** proceeded smoothly to afford the indene derivatives **18a** and **18b** in 68% and 65% yields, respectively (entries 1 and 2). However, the methyl ether substituted alkyne **15c** did not produce the indene derivative **18c** but the phenanthrene derivative **17c** in 50% yield (entry 3). On the other hand, **15i**, which has a longer methylene chain between the oxygen atom and the triple bond, gave the indene derivative **18i** in 58% yield along with trace amounts of **17i**. These results indicate that the oxygen atom at the propargyl position prevents the formation of indene derivatives **18** (vide post).

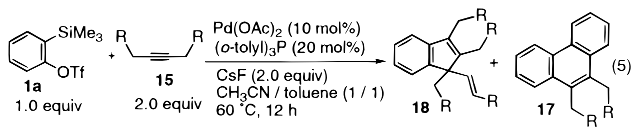
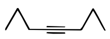
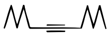
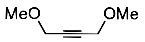
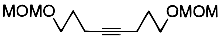
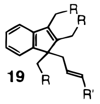


**Table 4.** Palladium-Catalyzed Reaction of **1a** with **15** in $CH_3CN$ and Toluene

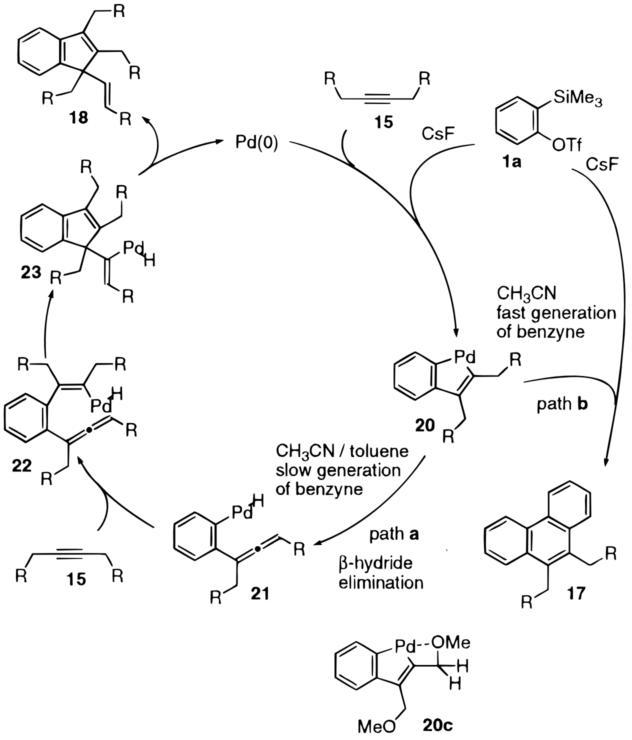
| entry | alkyne **15** | product yields, %$^a$ | |
|---|---|---|---|
| | | **18** | **17** |
| 1 |  **15a** | $68^b$ | 0 |
| 2 |  **15b** | $65^b$ | 0 |
| 3 |  **15c** | 0 | 50 |
| 4 |  **15i** | $58^b$ | trace |

[a] Isolated yields were based on **1a**.
[b] Trace amounts of **19** were also formed.



**19a**: R = Et, R′ = Me
**19b**: R = *n*-Bu, R′ = *n*-Pr
**19i**: R = $(CH_2)_2OMOM$, R′ = $CH_2OMOM$

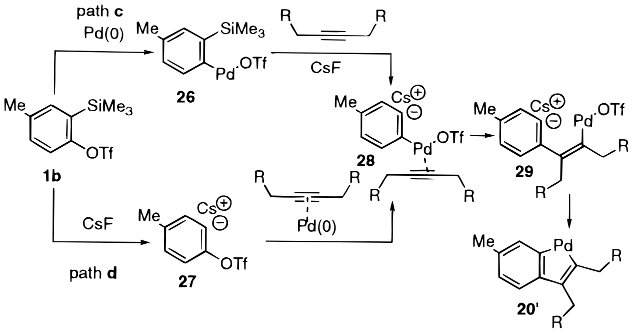
**Scheme 2**

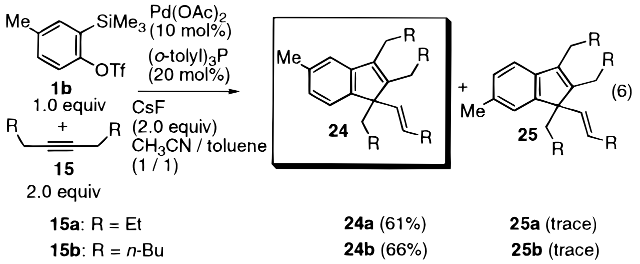


We propose the following plausible mechanism for the observed palladium-catalyzed cocyclization of benzyne and alkynes (Scheme 2). Initially, the reaction between Pd(0), the alkyne **15**, and benzyne generated from **1a** and CsF would afford the palladacycle **20**. The fate of the intermediate **20** depends on the solvent system. In the case of the $CH_3CN$/toluene solvent system, the reaction would proceed through path **a**. *β*-Hydride elimination of **20** would produce the allenyl intermediate **21**. A second alkyne insertion into the aryl−Pd bond of **21** would produce **22**. Subsequent carbopalladation of the alkenyl−Pd bond to the aryl-substituted double bond of the allenyl moiety of **22** would give **23**. The reductive elimination of Pd(0) would give the indene derivative **18.** The regioisomeric minor product **19** would arise by the isomerization of the double bond of **18** in the presence of a palladium hydride species. On the other hand, in the case of $CH_3CN$, the reaction would proceed through path **b**. The palladacycle **20** would react with free benzyne to give the phenanthrene derivatives **17**. The reaction pathway (either **a** or **b**) is controlled primarily by the generation rate of benzyne. The generation rate of benzyne depends on the amount of fluoride ion in solution, that is, it depends on the solubility of CsF. Therefore, in the case of $CH_3CN$ solvent, enough fluoride ion would exist in the reaction medium and a sufficient amount of benzyne is supplied prior to the $\beta$-hydride elimination of palladacycle **20**. Accordingly the reaction proceeds through path **b** to produce the phenanthrene derivatives **17**. One may raise a question that, if sufficient amounts of benzyne exist, the palladacycle built via benzyne−benzyne combination may be formed instead of the benzyne−alkyne counterpart **20**. Excess amounts of alkynes **15** exist already in the medium when benzyne is generated, and perhaps therefore the mixed palladacycle **20** is produced. The reaction conditions and catalyst system would be too weak to form the corresponding alkyne−alkyne combination. Actually, the reaction of **15a** under the same reaction conditions ($Pd(OAc)_2$, (*o*-tolyl)$_3$P, 60 °C, $CH_3CN$/toluene) did not give any cyclization products but resulted in recovery of **15a**. On the other hand, in the case of $CH_3CN$/toluene, insufficient amounts of fluoride ion exist in the medium due to low solubility of CsF, and thus palladacycle **20** would not be able to wait further supply of benzyne but undergo $\beta$-hydride elimination. This postulate is supported by the experimental result of **15c** (entry 3). In the case of the methyl ether substituted alkyne **15c**, presumably it is not easy to eliminate a $\beta$-hydrogen from palladacycle **20c** because of the coordination of an oxygen of the methoxy group to palladium (Scheme 2), so that **20c** would be able to wait further supply of benzyne and produce **17c** selectively regardless of the polarity of the solvent system. The structures of **18** were determined unambiguously by $^1H$ and $^{13}C$ NMR analyses (decoupling, NOE, H−C COSY, and COLOC).

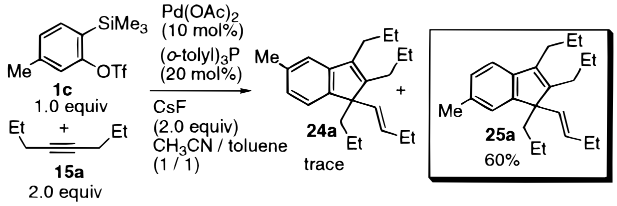
**Reaction of Substituted Benzyne Precursors. Is Benzyne Free?** The above explanation of the marked solvent effect upon the product distribution and the proposed reaction processes shown in Scheme 2 seemed to be reasonable. However, with further study of the palladium-catalyzed cocyclization of *substituted benzyne precursors* with alkynes, we encountered a very interesting and unexpected finding. The reaction of the 4-methyl-substituted benzyne precursor **1b** with 4-octyne **15a** under the same reaction conditions as above ($CH_3CN$/toluene system) produced regioselectively the indene derivative **24a** in 61% yield along with a trace amount of the regioisomer **25a** (eq 6). The reaction of 6-dodecyne **15b** proceeded similarly and produced **24b** selectively in 66% yield. If the reactions proceed via free methyl-substituted benzyne, an approximately 1:1 mixture of **24** and **25** should be obtained.[14] To reveal the reason for this high regioselectivity, the following controlled experiment was performed. The reaction of 5-methyl-substituted benzyne precursor **1c**, which is expected to generate the same aryne as in the case of **1b** if a free benzyne is intervened, with **15a** gave regioselectively **25a** in 60% yield along with a trace amount of **24a** (eq 7). It is now clear that the reaction of **1b** gives **24a** while that of **1c** affords the regioisomeric product **25a**. The above experimental results indicate that the reactions did not proceed via free benzyne.

**Scheme 3**





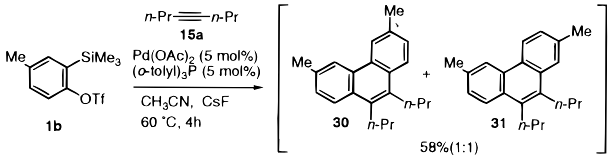
(6)



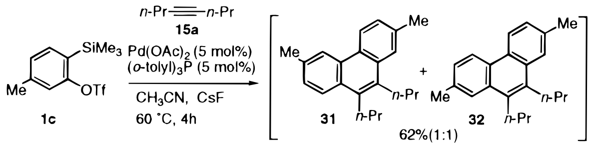
(7)

A plausible mechanism for the observed regioselective reactions is shown in Scheme 3. The insertion of Pd(0) into the C−OTf bond of **1b** gives the Pd(II) intermediate **26** (path **c**). As soon as the trimethylsilyl group is removed by CsF, the coordination of alkyne to Pd(II) can take place to form the alkyne complex **28**. The carbopalladation of the aryl−Pd bond to the triple bond of alkyne gives **29**, which is further converted to the palladacycle **20′**. The palladacycle **20′** follows the reaction course shown in Scheme 2 (path **a**) to give **24**. Alternatively, the desilylation of **1b** by the reaction with CsF takes place first to produce **27**, which reacts with Pd(0) and alkyne to give the alkyne complex **28**. One may argue that the desilylation can take place in the latter stage of the reaction sequences, for example, just before the palladacycle formation. Why do we prefer to put the desilylation step at an earlier stage? The following experimental results support our proposal. The benzyne precursor **1b** did not react with 4-octyne **15a** even in the presence of palladium catalyst if CsF is not present in the reaction medium. In the absence of CsF, the starting material **1a** was recovered. On the other hand, it is reported that iodobenzene reacts with 3-hexyne in the presence of palladium catalyst to give a 1:3 addition product of iodobenzene and 3-hexyne via carbopalladation of phenylpalladium iodide to 3-hexyne.[13e] The difference between the previous observation on the reaction of iodobenzene and our observation on the reaction of **1a** seems to be due to the steric hindrance of the trimethyl silyl group present in **1a**, which may prevent the insertion of Pd(0) into C−OTf bond or prevent the carbopalladation step.

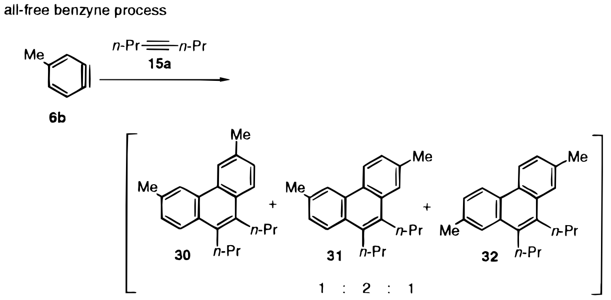
Now, it is clear that the indene derivatives **18** in eq 5 are not produced through free benzyne but through the Pd(0) insertion−carbopalladation sequence. An important question is whether the phenanthrene derivatives **17** in eq 4 are produced via free benzyne or not. To help clarify this point, we carried out the reactions of **1b** and **1c** with **15a** under the reaction conditions using $CH_3CN$ alone (eq 8 and 9). The reaction of **1b** with **15a** gave an approximately 1:1 mixture of two phenanthrene derivatives, assigned tentatively to **30** and **31**, in 58% yield, while the reaction of **1c** afforded an approximately 1:1 mixture of two phenanthrene derivatives, assigned to **31** and **32**, in 62% yield; it should be noted that the structural assignment is quite tentative since the three products **30**, **31**, and **32** could not be isolated in pure form. By GC-mass (15 m × 0.25 mm capillary column cross-linked 5% phenyl methyl siloxane, SPB-5), the three products could be separated and those mass numbers (M$^{+}$= 290) corresponded to a compound made from two molecules of the benzyne and one molecule of **15a**. Further, it was confirmed by GC-mass analysis that one of the two isomeric products in eq 8 was also produced in eq 9. By these observations, we assigned the structure **30**−**32** to the three products. If the reaction does not proceed through the Pd(0) insertion−carbopalladation sequence as mentioned in Scheme 3, and if the reaction proceeds through the free benzyne **6b**, an approximately 1:2:1 mixture of **30**, **31**, and **32** should be obtained both from **1b** and from **1c** (eq 10). Accordingly, the experimental results clearly indicate that the cocyclization does not proceed through the all-free benzyne process.



(8)

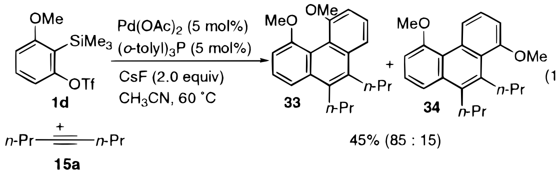


(9)

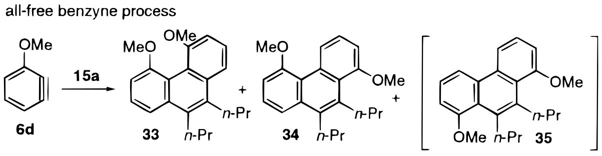


(10)

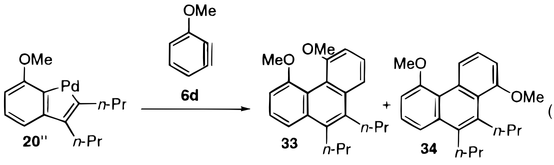
A crucially weak point of the above conclusion was that the isomeric phenanthrene products could not be isolated in a pure form and thus the structural determination of the products was quite ambiguous. Accordingly, we next examined the reaction of **1d** with **15a** in CH$_3$CN solvent. An 85:15 mixture of **33** and **34** was obtained in 45% combined yield (eq 11). The two isomeric phenanthrenes were separated and the structural determination of the products was carried out unambiguously by $^1$H and $^{13}$C NMR, NOE experiments, GC-mass, and HRMS analysis. If the all-free benzyne process is operative, a mixture of **33**, **34**, and **35** should be obtained (eq 12). Therefore, the experimental result clearly indicates that the reaction shown in eq 11 proceeds through a nonfree benzyne mechanism. Most probably, at the beginning of the cocyclization, the Pd(0) insertion−carbopalladation mechanism takes place to give the palladacyclopentadiene intermediate **20″** (eq 13). Then the second stage would be the cocyclization between **20″** and free benzyne **6d** (eq 13). This mechanism can explain very well the experimental result shown in eq 11. Since palladacycle **20″** is a Pd(II) species, it is very difficult to assume that such Pd(II) intermediate undergoes insertion between the Ar−OTf bond of **1d**. Accordingly, the second MeO−phenyl framework of **33** and **34** must come from the free benzyne species **6d** (eq 13).



(11)



(12)



(13)

The reaction of **1b** with allyl chloride **2a** under the conditions shown in Table 1, Method A, gave a mixture of the regioisomeric phenanthrene products. The same regioisomeric products with same isomer ratio were obtained in the reaction of **1c** with **2a**. However, here also the products could not be isolated in pure form, but were separated and analyzed only by GC-mass. The reaction of **1b** with **2a** and 4-octyne **15a** under the conditions shown in eq 3 gave an approximately 1:1 mixture of two regioisomeric naphthalene products, and the same result was obtained from the reaction of **1c**. These results suggest that the reactions of the benzyne precursors **1** with allyl chloride **2a** under the conditions shown in eqs 1 and 3 proceed via an all-free benzyne process.

## Conclusion

(i) The phenanthrene derivatives **3** can be synthesized from the benzyne precursor **1a** and allylic chlorides **2** in the presence of Pd catalyst; in certain cases, the isomeric phenanthrenes **4** are produced as a byproduct. (ii) The naphthalene derivatives **16** can be prepared from **1a**, allyl chloride **2a**, and alkynes **15**. (iii) The phenanthrene derivatives **17** can be synthesized by the palladium-catalyzed reaction of **1a** with alkynes **15** in CH$_3$CN, whereas (iv) the indene derivatives **18** can be obtained by the similar reaction in CH$_3$CN−toluene. The former reactions i and ii proceed through the all-free benzyne process, while the latter reactions iii and iv proceed via the Pd(0) insertion−carbopalladation process,. in which the nonfree benzyne mechanism is operative at the initial step.

The free benzyne mechanism is operative if the aryne precursors **1** interact with the Pd(II) species, such as $\pi$-allylpalladiums, arylpalladiums, and palladacycles. In Scheme 1, presumably, Pd(0) rapidly reacts with allyl chlorides **2**, instead of reacting with **1**, to be converted to Pd(II) species. However, in Scheme 2, Pd(0) can interact with **1**, leading to the nonfree benzyne mechanism. In conclusion, the product distribution and mechanism in the benzyne−Pd catalytic reaction are highly dependent upon the reaction conditions and Pd species present in the catalytic cycle.

## Experimental Section

**Preparation of 3 (Method A)**: The preparation of **3a** is representative. Allyl chloride (32.6 mL, 0.4 mmol) was added to a suspension of anhydrous CsF (243 mg, 1.6 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ (10.4 mg, 0.01 mmol), and dppf (11 mg, 0.02 mmol) in CH$_3$CN (1 mL) and THF (1 mL), and the mixture was stirred at room temperature for 5 min. Benzyne precursor **1a** (182.8 mL, 0.8 mmol) was added and the resulting mixture was stirred at 60 °C for 1 day. The mixture was cooled to room temperature, extracted with ether, dried with MgSO$_4$, and concentrated. The product was purified by column chromatography (silica gel, eluent−hexane), giving **3a** in 69% yield (53.1 mg)

**Preparation of 3 (Method B)**: The preparation of **3a** is representative. Allyl chloride (32.6 mL, 0.4 mmol) was added to a suspension of anhydrous CsF (486 mg, 3.2 mmol) and $Pd_2(dba)_3$•$CHCl_3$ (10.4 mg, 0.01 mmol) in $CH_3CN$ (2 mL) and the mixture was stirred at room temperature for 15 min. Four equivalents of **1a** (365.6 mL, 1.6 mmol) was added and the mixture was stirred at 80 °C for 3 h. The same workup procedure as above was used, and **3a** was obtained in 70% yield (53.9 mg).

**Preparation of 16**: The preparation of **16a** is representative. Allyl chloride (32.6 mL, 0.4 mmol) and 4-octyne **15a** (118.5 mL, 0.8 mmol) were added to a suspension of anhydrous CsF (122 mg, 0.8 mmol), $Pd_2(dba)_3$•$CHCl_3$ (20.8 mg, 0.02 mmol), and dppf (22 mg, 0.04 mmol) in $CH_3CN$ (1 mL) and THF (1 mL), and the mixture was stirred at room temperature for 5 min. Benzyne precursor **1a** (91.4 mL, 0.4 mmol) was added and the resulting mixture was stirred for 12 h at 60 °C. Again, anhydrous CsF (122 mg, 0.8 mmol) was added to the reaction mixture and the resulting mixture was stirred for 12 h at 60 °C. The mixture was cooled to room temperature, extracted with ether, dried over with $MgSO_4$, and concentrated. The product was purified by column chromatography (silica gel, eluent−hexane), giving **16a** in 47% yield (42.7 mg)

**Preparation of 17**: The preparation of **17a** is representative. The benzyne precursor **1a** (91.4 mL, 0.4 mmol) was added to a suspension of anhydrous CsF (122 mg, 0.8 mmol), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol), and (*o*-tolyl)$_3$P (6 mg, 0.02 mmol) in $CH_3CN$ (2 mL). 4-Octyne **15a** (88.5 mL, 0.6 mmol) was then added and the mixture was stirred for 4 h at 60 °C. When the reaction was complete (monitored by TLC and GC), the solvent was evaporated and the residue was purified by column chromatography (silica gel, eluent−hexane), giving 9,10-dipropylphenanthrene **17a** in 63% yield (33.2 mg).

**Preparation of 18, 24, and 25**: The preparation of **18a** is representative. The benzyne precursor **1a** (0.4 mmol) was added to a suspension of anhydrous CsF (0.8 mmol), $Pd(OAc)_2$ (8.8 mg, 0.04 mmol), and (*o*-tolyl)$_3$P (24 mg, 0.08 mmol) in a $CH_3CN$ (1 mL)/toluene (1 mL) solvent system. 4-Octyne **15a** (118 mL, 0.8 mmol) was then added and the mixture was stirred for 12 h at 60 °C. When the reaction was complete (monitored by TLC and GC), the solvent was evaporated and the product was purified by column chromatography (silica gel, eluent−hexane), giving the indene derivative **18a** in 68% yield (80.5 mg).

**Supporting Information Available:** $^1$H NMR spectra and characterization data of **1b**−**c**, **3a**−**b**, **3e**−**f**, **4b**, **4e**−**f**, **16a**, **16c**−**e**, **17a**−**c**, **17g**−**h**, **18a**−**b**, **18i**, **19a**, **24a**−**b**, **25a**, **33**, and **34** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001205A