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# Metal-Catalyzed Cotrimerization of Arynes and Alkenes

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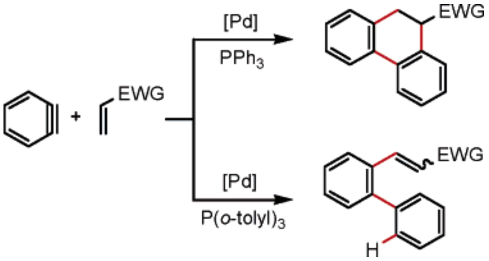
## ABSTRACT



**Cotrimerization of arynes and electron-deficient alkenes selectively affords dihydrophenanthrenes or ortho-olefinated biaryls, depending on the catalytic system employed. Our findings support a mechanism involving benzyne and a metallacycloheptadiene as key intermediates.**

In recent years, the introduction of transition-metal catalysis has significantly broadened the reactivity of arynes.[1,2] In 1998, we found that the generation of benzyne in the presence of catalytic amounts of palladium complexes led to its cyclotrimerization, affording triphenylene.[3] The extension of this [2+2+2] cycloaddition to polycyclic arynes allowed us to synthesize a number of structurally diverse polycyclic aromatic hydrocarbons.[2] We have also shown that palladium complexes can catalyze the cotrimerization of arynes and alkynes with high chemoselectivity.[4a,b] The scope of this methodology was soon extended to related metal-catalyzed cocyclization reactions of arynes with a variety of alkynes,[4c] diynes,[5] allyl derivatives,[6a] and allenes[6b] and with CO.[6c,7] To date, however, the only reported use of alkenes as reaction partners has been the palladium-catalyzed [2+2+2] cycloaddition of arynes to strained bicyclic alkenes.[8] We now report the use of transition-metal complexes to promote the cotrimerization of arynes with acyclic alkenes, which afforded 9,10-dihydrophenanthrenes or ortho-olefinated biphenyls depending on the catalytic system employed.

We first examined the reaction of benzyne and methyl acrylate (**2a**) in the presence of catalytic amounts of palladium complexes. We found that in the presence of an excess of **2a** and 10 mol % of Pd(PPh$_3$)$_4$ the slow generation

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(1) For reviews of aryne reactivity, see: (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.

(2) For a recent review of palladium-catalyzed cycloaddition reactions of arynes, see: Guitián, E.; Pérez, D.; Peña, D. In *Topics in Organometallic Chemistry*; Tsuji, J., Ed.; Springer-Verlag: Weinheim, 2005; Vol. 14, pp 109−146.

(3) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2659.

(4) (a) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **2000**, *65*, 6944. (c) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7280.

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(6) (a) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173. (b) Hsieh, J.-C.; Rayabarapu, D. K.; Cheng, C.-H. *Chem. Commun.* **2004**, 532. (c) Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 12686.

(7) For recent examples of palladium-catalyzed reactions involving arynes besides cycloadditions, see: (a) Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5052. (b) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716. (c) Jayanth, T.-T.; Cheng, C.-H. *Chem. Commun.* **2006**, 894.

(8) Jayanth, T.-T.; Jeganmohan, M.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 8445. Strained bicyclic alkenes are privileged substrates in palladium-catalyzed reactions because the intrinsic strain of these olefins favors their coordination to the metal.

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of benzyne by CsF treatment of *ortho*-(trimethylsilyl)phenyl triflate (**1**) in acetonitrile/toluene at 60 °C led to an 84% yield of a mixture of dihydrophenanthrene **3a** and the ortho-olefinated biaryls (*E*/*Z*)-**4a** (see Scheme 1 and Table 1, entry 1).[9] Compound **3a**, the cotrimerization product resulting from formal [2+2+2] cycloaddition of two benzynes to one alkene, was the major product [**3a**:(*E*)-**4a**:(*Z*)-**4a** = 81:10:9]. Remarkably, it was possible to reduce the amount of catalyst to 2 mol % while maintaining a reasonable 72% yield.[10]

**Scheme 1**

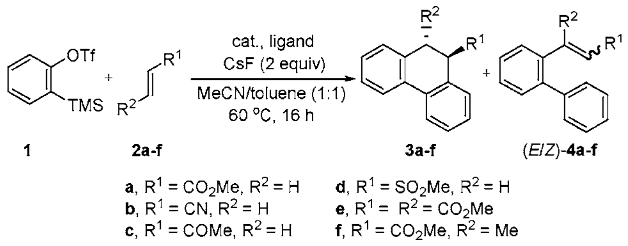


**Table 1.** Metal-Catalyzed Reactions of Benzyne with Alkenes[a]

| entry | 2 | catalyst (%)[b] | ligand (%)[b] | yield (%)[c] | ratio[d] |
|---|---|---|---|---|---|
| 1 | **2a** | $Pd(PPh_3)_4$ (10) | - | 84 | 81:10:9 |
| 2 | **2a** | $Pd_2(dba)_3$ (5) | $PPh_3$ (20) | 95 | **77:14:9** |
| 3 | **2a** | $Pd_2(dba)_3$ (5) | $PPh_3$ (10) | 85 | 20:57:23 |
| 4 | **2a** | $Pd_2(dba)_3$ (5) | P(*o*-tol)$_3$ (20) | 69 | **8:68:24** |
| 5 | **2b** | $Pd_2(dba)_3$ (5) | $PPh_3$ (20) | 52 | 44:34:22 |
| 6 | **2c** | $Pd_2(dba)_3$ (5) | $PPh_3$ (20) | 66 | 80:9:11 |
| 7 | **2d** | $Pd_2(dba)_3$ (5) | $PPh_3$ (20) | 88 | 92:6:2 |
| 8 | **2c** | $Pd_2(dba)_3$ (5) | P(*o*-tol)$_3$ (20) | 71 | 3:60:37 |
| 9 | **2d** | $Pd_2(dba)_3$ (5) | P(*o*-tol)$_3$ (20) | 84 | 33:36:41 |
| 10 | **2e** | $Ni(cod)_2$ (10) | $PPh_3$ (20) | 61 | 100:0:0 |
| 11 | **2f** | $Ni(cod)_2$ (10) | $PBu_3$ (20) | 60 | 51:49:0 |

[a] See Scheme 1. Reactions were performed using 3 equiv of alkene, except entry 5 (1 equiv). [b] Amounts of catalyst and ligand, in mol %, are in parentheses. [c] Combined isolated yields (%) of **3** and (*E*/*Z*)-**4**. Small amounts of triphenylene were also detected (see ref 3). [d] Mole ratio [**3**:(*E*)-**4**:(*Z*)-**4**], as determined by $^1H$ NMR.

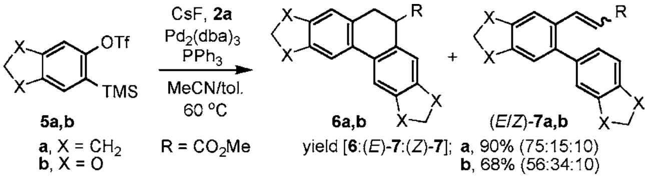
With $Pd_2(dba)_3$ as the catalyst, cotrimerization turned out to be highly dependent on the accompanying auxiliary ligand: the reaction was catalyzed by mixtures of $Pd_2(dba)_3$ and $PPh_3$, but cotrimerization products were not isolated in significant amounts in the absence of phosphine or with bidentate phosphines such as dppe or dppf.[11] Also, whereas the use of a 1:2 Pd/$PPh_3$ ratio afforded results similar to those obtained with $Pd(PPh_3)_4$ (entry 2), decreasing the amount of ligand (1:1 Pd/$PPh_3$ ratio) led to biaryls (*E*/*Z*)-**4a** being the major products (entry 3). An even more pronounced selectivity in favor of **4a** [ratio **3a**:(*E*)-**4a**:(*Z*)-**4a** = 8:68:24] was observed when P(*o*-tolyl)$_3$ was used instead of $PPh_3$ (cf. entries 4 and 2).

Other electrophilic monosubstituted alkenes (**2b**−**d**) also cotrimerized with benzyne in the presence of Pd catalysts (entries 5−7). Alkenes substituted with no electron-withdrawing groups (e.g., ethyl vinyl ether) did not cotrimerize. As in the case of **2a**, the reactions of alkenes **2c** and **2d** could be steered toward the formation of biaryls (*E*/*Z*)-**4c** and (*E*/*Z*)-**4d** by using P(*o*-tolyl)$_3$ as the auxiliary ligand (entries 8 and 9).

For the cotrimerization of disubstituted alkenes, nickel-based catalysts turned out to be more efficient than palladium complexes. In particular, the reaction with dimethyl fumarate [(*E*)-**2e**] afforded higher yields with $Ni(cod)_2$/$PPh_3$ (61%, entry 10) than with $Pd_2(dba)_3$/$PPh_3$ (31%). Remarkably, with this alkene, no formation of biaryls **4e** was observed, with *trans*-dihydrophenanthrene (*trans*-**3e**) being the only cotrimerization product. Curiously, dimethyl maleate [(*Z*)-**2e**] afforded only a 10% yield of *trans*-**3e**.[12] Less electrophilic disubstituted alkenes appear to require the use of more electron-rich phosphines. For example, with methyl crotonate [(*E*)-**2f**], the combined yield of *trans*-**3f** and (*E*)-**4f** increased from 6% to 60% when $PPh_3$ was replaced by $PBu_3$ as the auxiliary ligand (entry 11). Notably, (*Z*)-**4f** was not detected in the reaction mixture.[13]

Substituted arynes also cotrimerized with alkenes **2**. Benzynes with five-membered fused rings, generated from **5a** or **5b** (Scheme 2), afforded the corresponding dihydrophenanthrenes **6a**,**b** and ortho-olefinated biaryls **7a**,**b** in good yields under the reaction conditions optimized for the Pd-catalyzed cotrimerization of unsubstituted benzyne and methyl acrylate (**2a**).[14]

**Scheme 2.** Cotrimerization of Substituted Benzynes with **2a**



Plausibly, the mechanism of this reaction is closely related to the one proposed by Cheng and co-workers for the Ni-catalyzed cotrimerization of alkynes and acrylates.[15] For monosubstituted alkenes, it is depicted in Scheme 3. First,

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[9] An excess of the acrylate (3 equiv) was necessary to avoid the formation of triphenylene as the major product.

[10] In the absence of palladium catalyst, none of the cotrimerization products were detected.

[11] Under these conditions, the major reaction products resulted from the cyclotrimerization of benzyne and the [2+2] cycloaddition of benzyne to the alkene.

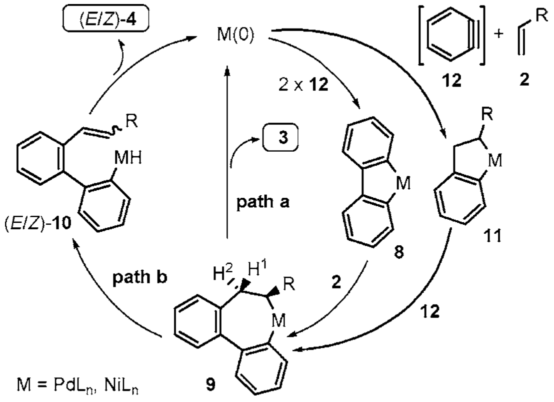
[12] We found that (*Z*)-olefins are poor reaction partners in this cotrimerization. The formation of *trans*-**3e** from (*Z*)-**2e** is due to the partial *Z*/*E* isomerization of the olefin in the reaction mixture.

[13] Geminally disubstituted olefins such as methyl methacrylate or dimethyl itaconate afforded yields below 30% of the corresponding products.

[14] $Pd_2(dba)_3$ (5 mol %), $PPh_3$ (20 mol %). MeCN/toluene; 3:1 for **5a** (16 h), 1:1 for **5b** (30 h). When using P(*o*-tolyl)$_3$ as a ligand: **a**, 73% (4:69:27); **b**, 78% (13:67:20).

[15] Sambaiah, T.; Li, L.-P.; Huang, D.-J.; Lin, C.-H.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3663.

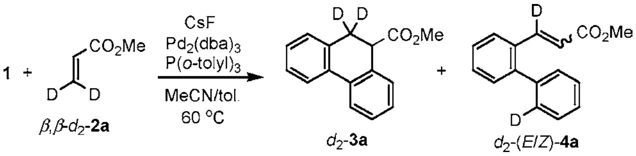
**Scheme 3.** Postulated Mechanism of the Cotrimerization



the coordination of the metal complex to two benzynes (**12**), followed by oxidative coupling, would afford metallacycle **8**. Then, insertion of the alkene into a carbon−metal bond would lead to metallacycloheptadiene **9**, which could evolve in two ways. Following path **a**, reductive elimination of the metal could produce dihydrophenanthrene **3**.[16] Following path **b**, $\beta$-hydride elimination could afford (*E*/*Z*)-**10**, which would subsequently produce biaryls (*E*/*Z*)-**4** by reductive elimination, the final *E*/*Z* isomerism of **4** depending on which hydrogen is involved in the $\beta$-H elimination step.[17] Path **b** would be favored by coordination vacancies on the metal due to the bulk of phosphines such as P(*o*-tolyl)$_3$ (entries 4, 8, and 9) or to the use of a 1:1 Pd/ligand ratio (entry 3). A similar mechanism via metallacycle **11** instead of **8** is also likely,[18] although the detection of small amounts of the benzyne cyclotrimer triphenylene in the reaction mixtures suggests that **8** is formed as an intermediate. Similar metallacycles have recently been proposed as intermediates in related Pd-catalyzed synthesis of ortho-olefinated biaryls.[19]

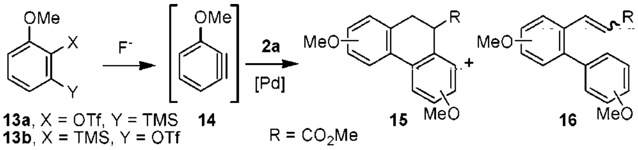
To rule out an alternative mechanism initiated by oxidative addition of the aryl triflate to Pd(0),[20] we performed additional experiments, the results of which strongly support a mechanism involving benzyne as the reactive species. First, we found that in the absence of a fluoride source the starting materials remained unaltered, even in the presence of other bases. Second, cotrimerization of benzyne with deuterium-labeled $\beta,\beta$-$d_2$-**2a** (Scheme 4) produced the expected mixture of $d_2$-**3a** and $d_2$-(*E*/*Z*)-**4a**, which in our opinion suggests that the synthesis of biaryls **4** proceeds via $\beta$-hydride elimination from metallacycle **9**.

**Scheme 4.** Cotrimerization with Deuterium-Labeled Acrylate



Third and most conclusively, under our standard conditions (entry 2, Table 1), the reactions of acrylate **2a** with regioisomeric triflates **13a**,**b**, both of which are precursors of 3-methoxybenzyne (**14**, Scheme 5), afforded identical mixtures of dihydrophenanthrenes **15** and biaryls **16**, with the same isomer ratios as determined by GC/MS. A mechanism via oxidative addition would produce different isomers from **13a** and **13b**.[21]

**Scheme 5.** Cotrimerization of 3-Methoxybenzyne



In conclusion, this work shows for the first time that arynes can undergo palladium- and nickel-catalyzed cotrimerization with acyclic alkenes, selectively affording dihydrophenanthrenes or ortho-olefinated biaryls depending on the catalyst used. Remarkably, our findings support a mechanism based on metal-catalyzed cycloaddition of benzyne involving a metallacycloheptadiene as the key intermediate.

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**Supporting Information Available:** Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Alternatively, compound **3** could be produced via [4+2] cycloaddition of metallacycle **8** and the alkene, followed by reductive elimination of the metal. However, this pathway is unlikely because it initially requires the loss of the aromaticity of compound **8**.

(17) Control experiments showed that there is not isomerization between (*E*)- and (*Z*)-**4a** under the reaction conditions. Bearing in mind the requirement that the H should be syn to the metal, elimination of $H^1$ would afford the (*E*)-isomer, whereas the $\beta$-H elimination of $H^2$ would produce (*Z*)-**4**. In fact, when $H^2$ was replaced by a methyl group (**2f**, entry 11, Table 1), only (*E*)-**4f** was obtained.

(18) The predominant formation of metallacycle **11** is feasible, considering the excess of alkene present in the reaction mixture (3 equiv) compared to the maximum amount of benzyne−metal complex possible at any stage in the reaction (10 mol %). Metallacycles related to **11** have been isolated by reaction of electron-deficient alkenes with aryne−nickel complexes. See: Bennett, M. A.; Wenger, E. *Chem. Ber.* **1997**, *130*, 1029.

(19) (a) Satoh, T.; Jones, W. D. *Organometallics* **2001**, *20*, 2916. (b) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326. (c) Masselot, D.; Charmant, J. P. H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 694.

(20) This alternative has been proposed by Yamamoto and co-workers for some Pd-catalyzed cyclizations of triflate **1** with alkynes (see ref 4c).

(21) See Supporting Information for details.