

Communications to the Editor

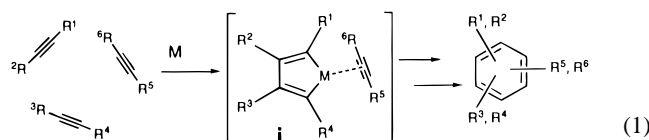
**First Intermolecular Regiospecific
Palladium-Catalyzed Enyne–Diyne [4 + 2]
Cross-Benzannulation Reaction**

Vladimir Gevorgyan, Akira Takeda, and
Yoshinori Yamamoto*

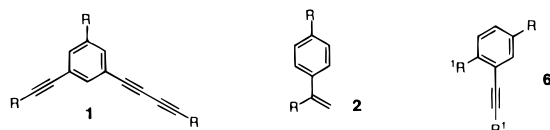
Department of Chemistry, Graduate School of Science
Tohoku University, Sendai 980-77, Japan

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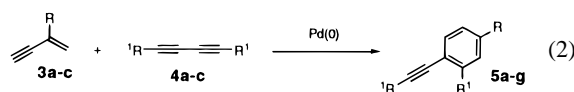
Since the earliest example of thermal trimerization of acetylene to benzene reported by Berthelot in 1866,¹ and the first transition-metal-catalyzed version of this reaction demonstrated by Reppe in 1948,² the [2 + 2 + 2] cycloaddition of acetylenes was extensively studied by number of research groups and became a vast field three decades ago. A large number of transition metal catalysts, as well as Ziegler-type catalysts,³ give rise to this reaction.⁴ Although this approach becomes one of the most powerful methods to assemble a benzene ring, it suffers from serious chemo- and regioselectivity problems which normally lead to complex mixtures of products, thus severely limiting the synthetic utility of this reaction (eq 1).⁵ Vollhardt



succeeded to solve these problems for several types of *intramolecular*⁶ or *partially intramolecular*⁷ modes of cyclotrimerization: three new bonds were formed under the cobalt catalysis affording cyclophane-type aromatic products in chemo- and regioselective manner.^{6,7} Two complementary regioselective *intermolecular* methods for constructing benzene skeleton under palladium catalysis were reported recently: the formation of 1,3,5-unsymmetrical benzenes **1** *via* cyclotrimerization of terminal diynes⁸ and the synthesis of 1,4-disubstituted benzenes **2** *via* [4 + 2] homo-dimerization of conjugated enynes.⁹ We



now report the first example of *intermolecular* enyne–diyne [4 + 2] cross-benzannulation reaction: the reaction of enynes **3** with diynes **4** affording regioselectively 1,2,4-trisubstituted benzenes **5** in high to quantitative yields with none of the regioisomers **6** being produced (eq 2).



Various different ways of the orientation of acetylenes are possible for assembling an intermediate **i**, since three new bonds are formed in [2 + 2 + 2] cyclotrimerization (eq 1).⁴ It occurred to us that in the case where a conjugated enyne **3** would react with alkyne in a [4 + 2] cycloaddition manner,¹⁰ this reaction could be more regioselective than the [2 + 2 + 2] mode of cycloaddition since only the regioselectivity of two bond formation remains questionable. After trying a number of alkynes in a role of enyne partner in the [4 + 2] cycloaddition, we discovered that conjugated diynes **4** underwent regioselective cross-cycloaddition with **3**. The reaction of 2-methyl-1-buten-3-yne (**3a**) with dodeca-5,7-diyne (**4a**) in the presence of 5 mol % Pd(PPh₃)₄ in THF gave **5a**¹³ in 89% yield (entry 1, Table 1). No traces of **6** were detected by NMR and capillary GLC analyses of crude reaction mixtures. The enyne–diyne cross-annulation reaction of enynes **3b,c** appeared to be much faster than the corresponding enyne–enyne homo-dimerization,¹⁴ thus an equimolar amount of hexyl- (**3b**) and benzyl- (**3c**) enyne reacted with **4a,b** not only in regio-, but also in chemoselective manner affording the cross-annulation products **5d–f**, exclusively (entries 4–6). In contrast, a 2–5-fold excess of volatile and less-reactive **3a** (toward diynes **4**) was needed to drive the reaction to complete conversion of **4** (entries 1–3).¹⁶ Bulky diyne **4c** reacted with enynes rather slower than **4a,b**, thus the slow addition of the enynes **3a,c** was employed in order to avoid its dimerization (entries 3 and 7).

Apparently, the fact of *regiospecific* two bonds formation

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(7) See, for example: (a) Halterman, R. L.; Nguyen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1985**, *107*, 1379. (b) Berris, B. C.; Hovakeemian, G. H.; Lai, Y.-H.; Mestdagh, H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1985**, *107*, 5670. (c) Helson, H. E.; Vollhardt, K. P. C.; Yang, Z.-Y. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 114. (d) Grigg, R.; Scott, R.; Stevenson, P. *Tetrahedron Lett.* **1982**, *23*, 2691.

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(10) Although scattered data on related processes such as thermal^{11,12} or Lewis acid mediated¹¹ *intramolecular* enyne–yne [4 + 2] cycloaddition reactions were recently reported, the more synthetically useful *intermolecular* enyne–yne cross-benzannulation¹³ still remained unemployed.

(11) Danheiser, R. L.; Gould, A. E.; Fernandez de la Predilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514.

(12) Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218.

(13) The structure of *para*-oriented **5** was unambiguously confirmed by 500 MHz NOE and COLOC NMR analyses. For details see the Supporting Information.

(14) The *homo*-dimerization of enynes has been recently reported, see ref 9.

(15) The preparation of **5a** is representative. A mixture of **3a** (0.6 mmol), **4a** (0.5 mmol), and Pd(PPh₃)₄ (5 mol %) in THF (2 mL) was refluxed under an argon atmosphere. Reaction course was monitored by capillary GLC analysis. After the reaction was complete (12 h for **5a**), the mixture was filtered through a short column (silica gel) and concentrated. Purification by column chromatography (silica gel, hexane eluent) gave 101 mg of **5a** (89%) and 8 mg of **4a** (10%). The good scalability of this reaction was demonstrated with an essentially quantitative preparation of **5b** (homogeneous by ¹H NMR and GLC analyses, isolated yield) in a 5 mmol scale under the mentioned reaction conditions.

(16) The excess of enyne **3a** underwent *homo*-dimerization, affording **2**, see also footnote c of Table 1.

(1) Berthelot, M. C. *R. Acad. Sci.* **1866**, *62*, 905.
(2) Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Justus Liebigs Ann. Chem.* **1948**, *560*, 1.

(3) (a) Meriwether, L. S.; Clothup, E. C.; Kennerly, G. W.; Reusch, R. N. *J. Org. Chem.* **1961**, *26*, 5155. (b) Reikhsfel'd, V. O.; Makovetskii, K. L. *Russ. Chem. Rev.* **1966**, *35*, 510.

(4) For recent reviews, see: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539–644. (b) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081–1119. (c) Trost, B. M. *Science* **1991**, *254*, 1471–1477. (d) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92.

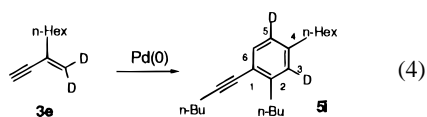
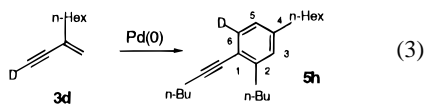
(5) See, for example: (a) Colman, J. P.; Kang, J. W.; Little, W. F.; Sullivan, M. F. *Inorg. Chem.* **1968**, *7*, 1298. (b) Ferreri, R. A.; Wolf, A. P. *J. Phys. Chem.* **1984**, *88*, 2256. (c) Borrini, A.; Diversi, P.; Ingrassio, G.; Lucherini, A.; Serra, G. *J. Mol. Catal.* **1985**, *30*, 181. (d) Yasuda, H.; Nakamura, A. *Rev. Chem. Intermed.* **1986**, *6*, 365.

Table 1. Palladium Catalyzed Enyne–Diene Cross-Benzannulation¹⁵

entry	R	R ¹	Product 5	Yield (%) ^a
1	Me (3a) ^{b,c}	n-Bu (4a)		89 (10) ^d
2	Me (3a) ^{b,c}	Ph (4b)		>99
3	Me (3a) ^{c,e,f}	TMS (4c)		92
4	n-Hex (3b)	n-Bu (4a)		60 ^g (36) ^d
5	Bn (3c) ^h	n-Bu (4a)		89
6	Bn (3c)	Ph (4b)		86
7	Bn (3c) ⁱ	TMS (4c)		80

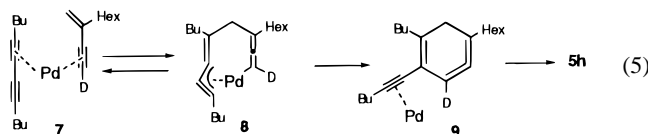
^a Isolated yields based on diyne **4**, except for where otherwise indicated. ^b Two equivalents of **3a** were utilized. ^c Excess of **3a** underwent homodimerization affording the byproduct **2**.⁹ ^d Recovery of **4** (%). ^e Five equivalents of **3a** were utilized. ^f Compound **3** was added in five portions. ^g NMR yield. ^h One-half equivalents of **3c** were added in 10 portions. ⁱ Two and a half equivalents of **3c** were added during 14 h with syringe pump.

observed in all cases of enyne–diene cycloaddition reactions¹⁷ (eq 2, Table 1) eliminated involvement of the traditional transition-metal-assisted mechanism of alkynes trimerization (eq 1).⁴ Indeed, if the mentioned mechanism is operative, the formation of the two regioisomers **5** and **6** is unavoidable. As a part of mechanistic study of this palladium-catalyzed enyne–diene cross-benzannulation, the deuterium analogues **3d,e** were employed in the reaction with diyne **4a**. Accordingly, the cross-benzannulation of **3d** afforded **5h** in 64% yield with a deuterium atom attached to the C-6 position of benzene ring (eq 3), and cycloaddition of **3e** gave **5i** (eq 4) in 61% yield with deuterium atoms at C-3 and C-5 positions of ring, exclusively. The results



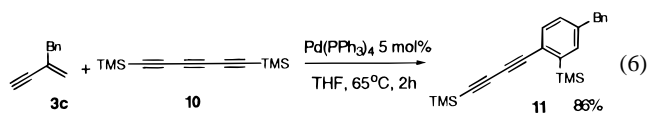
on deuterium labeling experiments, taken together with the fact of

regiospecific formation of *para*-oriented regioisomer **5**, encouraged us to propose the following mechanistic rationale for this reaction (eq 5). The reversible coordination of palladium with



enyne and diyne **7** would produce palladacycle **8**,¹⁸ stabilized by coordination of Pd atom with neighboring η^3 -propargyl moiety.¹⁹ The reductive elimination of palladium from **8** would form strained cyclic cumulene **9**,²⁰ which *via* sigmatropic rearrangement would be transformed into cross-annulation product **5h**.

As a final remark on our investigation, we disclose our initial experiments on palladium-catalyzed enyne–triyne cross-benzannulation (eq 6). We found that **3c** reacted selectively with terminal triple bond of bis-silyl-triyne **10** producing synthetically useful silylated diyne **11**²¹ as a sole product in excellent chemical yield (eq 4).

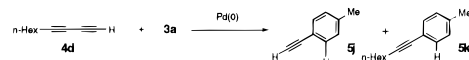


Although further investigation to settle a precise reaction mechanism is needed, the present procedure provides a new regiospecific and synthetically useful route to 1,2,4-trisubstituted benzenes.

Supporting Information Available: Spectroscopic and analytical data for compounds **5a–k** and **11** (21 pages). See any current masthead page for ordering and Internet access instructions.

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(17) The reaction of **3a** with terminal unsymmetric diyne **4d** produced **5j** in 50% yield (NMR) along with a minor product **5k** (28% by NMR). This indicates that both triple bonds of **4d** could act as an enynophile and thus the regioselectivity in this case is not perfect.



(18) π -Propargyl palladium complexes have been recently isolated and fully characterized. See: (a) Ogoshi, S.; Tsutsumi, K.; Kurosawa, H. *J. Organomet. Chem.* **1995**, 493, C19. (b) Ogoshi, S.; Tsutsumi, K.; Ooi, M.; Kurosawa, H. *J. Am. Chem. Soc.* **1995**, 117, 10415.

(19) The coordination of palladium to propargyl group in the intermediate **8** is supported not only by the exclusive formation of a sole regioisomer **5** but also by the fact that simple alkynes, such as acetylene and its alkyl-, aryl-, halo-, and cyanoderivatives, which do not possess such an additional alkynyl group, do not act as enynophiles in the mentioned reaction at all. Accordingly, an alternative explanation of remarkable reactivity of diynes in terms of steric effects was discounted by the observation that acetylene itself did not act as an enynophile in that reaction.

(20) This type of 6-membered strained cyclic cumulene has been recently proposed as an intermediate in the dehydro Diels–Alder cycloadditions. (a) For a review, see: Johnson, R. P. *Chem. Rev.* **1989**, 89, 1111. (b) See also ref 12.

(21) Silyl-substituted aromatic alkynes and diynes are very useful building blocks for assembling of conjugated oligo- and polyarylene ethynyls. For reviews, see: (a) Tour, J. M. *Chem. Rev.* **1996**, 96, 537. (b) Harriman, A.; Ziesse, R. *J. Chem. Soc., Chem. Commun.* **1996**, 1707. See also: (c) Ziesse, R.; Suffert, J. *Tetrahedron Lett.* **1996**, 37, 2011. (d) Kitamura, T.; Lee, C. H.; Taniguchi, Y.; Fujiwara, Y. *J. Am. Chem. Soc.* **1997**, 119, 619.