

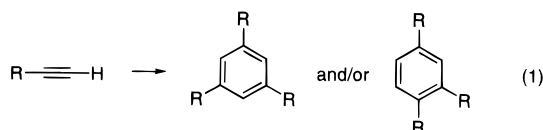
## Regioselective Synthesis of 1,3,5-Unsymmetrically Substituted Benzenes via the Palladium-Catalyzed Cyclotrimerization of 1,3-Diynes

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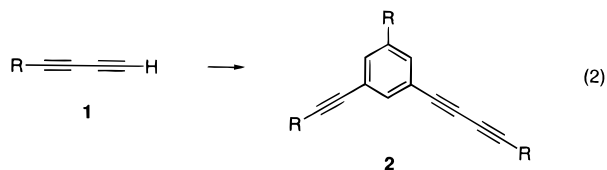
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The transition metal catalyzed homocyclotrimerization of alkynes is well known as a simple method for the synthesis of trisubstituted benzenes (eq 1).<sup>1</sup> However, a mixture of 1,3,5- and 1,2,4-trisubstituted benzenes is obtained in general, and furthermore, the three substituents are restricted to same R group. These drawbacks diminish synthetic usefulness of the



well-known trimerization reaction. We now report the regioselective synthesis of 1,3,5-trisubstituted benzenes **2** via the palladium-catalyzed novel trimerization of 1,3-diynes **1** in which three different substituents can be introduced at the 1-, 3-, and 5-positions (eq 2).



Recently, we reported the palladium-catalyzed addition of pronucleophiles to allenes<sup>2</sup> and conjugated enynes.<sup>3</sup> In order to extend this “hydrocarbonation reaction” of unactivated alkenes, we examined the reaction of pronucleophiles with 1,3-diynes. To our surprise, no addition product was obtained. Instead, the trimerization of 1,3-diynes took place quite readily, and furthermore, the mode of the trimerization was totally different from the well-accepted mode of monoynes.<sup>1</sup> The results are summarized in Table 1. The reaction of 1,3-decadiyne **1a** in the presence of Pd(dba)<sub>2</sub> (5 mol %)/PPh<sub>3</sub> (20 mol %) proceeded smoothly to give **2a** in 64% yield (entry 1). The use of Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol %) catalyst produced **2a** in 62%

**Table 1.** Palladium-Catalyzed Cyclotrimerization of 1,3-Diynes **1a–i**<sup>a</sup>

entry	R	catalyst <sup>b</sup>	product	yield (%) <sup>c</sup>
1	<i>n</i> -hexyl ( <b>1a</b> )	A	<b>2a</b>	64
2	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> ( <b>1b</b> )	A	<b>2b</b>	46
3	Ph(CH <sub>2</sub> ) <sub>2</sub> ( <b>1c</b> )	B	<b>2c</b>	51
4	<i>t</i> -Bu ( <b>1d</b> )	B	<b>2d</b>	21
5	cyclohexenyl ( <b>1e</b> )	B	<b>2e</b>	40
6	<i>p</i> -tolyl ( <b>1f</b> )	A	<b>2f</b>	46
7	TrO(CH <sub>2</sub> ) <sub>2</sub> ( <b>1g</b> )	A	<b>2g</b>	65
8	MOMO(CH <sub>2</sub> ) <sub>4</sub> ( <b>1h</b> )	A	<b>2h</b>	43
9	MOMO(CH <sub>2</sub> ) <sub>2</sub> C ( <b>1i</b> )	A	<b>2i</b>	56

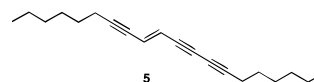
<sup>a</sup> A THF (15 mL) solution of **1** (0.5 mmol) in the presence of Pd catalyst was refluxed overnight under Ar. The products were isolated by silica gel column chromatography using hexane as an eluent. <sup>b</sup> Catalyst A: Pd(dba)<sub>2</sub> (5 mol %) and PPh<sub>3</sub> (20 mol %). Catalyst B: Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol %). <sup>c</sup> Isolated yield. Other products were unidentified polymeric materials.

yield.<sup>4</sup> The structure of **2a** was determined by NMR analysis (Figure 1).<sup>5</sup> Judging from the chemical shifts ( $\delta$  2.35 and 2.38), H<sub>b</sub> and H<sub>c</sub> were assigned to the propargylic methylene protons. A triplet at  $\delta$  2.51 was assigned to the benzylic methylene proton H<sub>a</sub>. The chemical shifts ( $\delta$  7.17, 7.19, and 7.32) and the coupling pattern (triplet,  $J = 1.5$  Hz) of aromatic protons H<sub>d</sub>–H<sub>f</sub> agreed well with the 1,3,5-substituted aromatic system of **2a**. The reaction of other simple aliphatic diynes **1b** and **1c** proceeded smoothly to give the corresponding trimerization products **2b** and **2c**, respectively, in good and allowable yields (entries 2 and 3). However, the reaction of **1d** having a bulky substituent (*t*-Bu) gave **2d** only in 21% yield (entry 4); **2d** was the only isolable compound, and the others were polymeric materials. The conjugated diynes **1e** and **1f** afforded the corresponding 1,3,5-unsymmetrically substituted benzenes **2e** and **2f**, respectively, in moderate yields (entries 5 and 6) along with polymeric compounds. Highly reactive **1e** and **1f** polymerized readily in the absence of the catalysts at room temperature when the solvent was evaporated. The reaction of triphenylmethoxy-(TrO) (**1g**) and methoxymethoxy-(MOMO) substituted diynes (**1h** and **1i**) afforded the desired products **2g**, **h**, and **i**, respectively, in good and moderate yields (entries 8, 9, and 10). Accordingly, oxygen-containing functional groups such as TrO and MOMO can be introduced at the 1-, 3-, and 5-position side chains.

To the best of our knowledge, the regioselective *intermolecular* mixed cyclotrimerization of alkynes is not known, although the *intramolecular* cyclization of three acetylenic functionalities has been demonstrated.<sup>1</sup> We examined the reaction of **1a** (0.5 mmol) with phenylacetylene **3** (1.0 mmol) (eq 3). The mixed coupling product **4** was obtained in 21% yield along with 24% of the homocoupling product **2a**. When 0.5 equiv (0.25 mmol) of **3** was used, only **2a** was produced and none of **4** was obtained. Accordingly, even mixed coupling between a diyne and monoynone may be possible under certain conditions.

A plausible mechanism for this unprecedented cyclotrimerization is illustrated in Scheme 1. The initial step would be

(4) With transition complexes such as PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Co<sub>2</sub>(CO)<sub>8</sub>, CpCo(CO)<sub>2</sub>, and Ni(PPh<sub>3</sub>)<sub>2</sub>(CO)<sub>2</sub>, no reaction took place and the starting diyne was recovered. The head-to-head dimerization of **1a**, leading to enyne **5**, took place with RhH(CO)(PPh<sub>3</sub>)<sub>3</sub> and RhCl(PPh<sub>3</sub>)<sub>3</sub> catalyst. See: Ohshita, J.; Furumori, K.; Matsuguti, A.; Ishikawa, M. *J. Org. Chem.* **1990**, *55*, 3277–3280.



(5) For detailed data on chemical shifts, see Supporting Information.

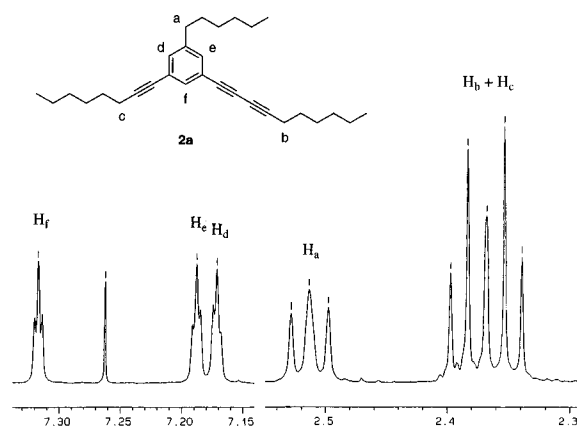
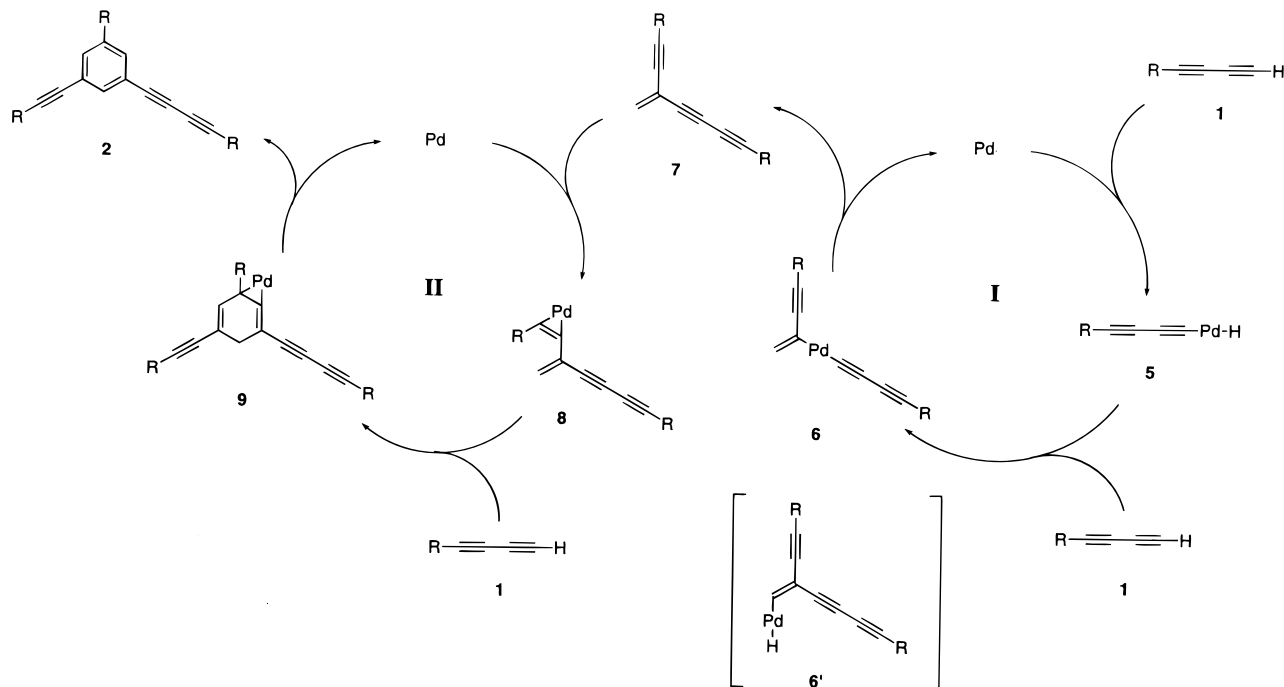
<sup>†</sup> Institute for Chemical Reaction Science.

(1) 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.

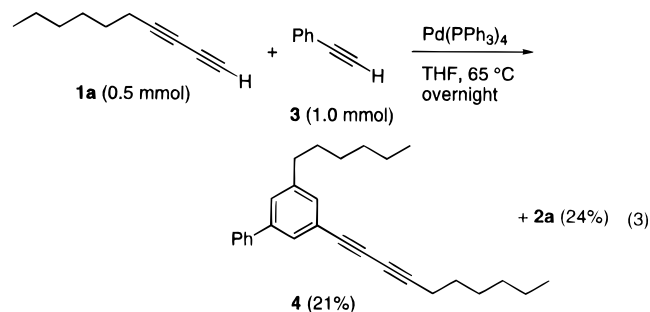
(2) (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019–6020. (b) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N.; Asao, N. *Tetrahedron Lett.* **1995**, *36*, 2811–2814. (c) Yamamoto, Y.; Al-Masum, M. *Synlett* **1995**, 969–970. (d) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N. *J. Chem. Soc., Chem. Commun.* **1996**, 381–382.

(3) Salter, M. M.; Gevorgyan, V.; Saito, S.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 17–18.

## Scheme 1



**Figure 1.** 500 MHz  $^1\text{H}$  NMR spectra for the propargylic ( $\text{H}_b$  and  $\text{H}_c$ ), benzylic ( $\text{H}_a$ ), and aromatic protons ( $\text{H}_d$ – $\text{H}_f$ ) of **2a**.



oxidative addition of Pd(0) species to a diyne **1** to produce **5** (catalytic cycle I). Hydropalladation of **5** to a diyne **1** followed by reductive elimination of Pd(0) would produce an enyne **7**. This process is well accepted as a catalytic dimerization of alkynes.<sup>6</sup> Also, carbopalladation mechanism is conceivable: **7** is produced via **6'**.<sup>7</sup> Catalytic cycle II is very similar to that of

the benzannulation of conjugated enynes, reported recently from our laboratory.<sup>8</sup> The Pd(0) species would produce a  $\pi$ -complex (**8**), which would act as a nucleophilic diene and undergo formal Diels–Alder type reaction with **1** to give **2** via **9**. Other mechanism such as those via a palladacyclopentadiene intermediate are conceivable in addition to the Diels–Alder type mechanism, as mentioned previously.<sup>8</sup> The mixed coupling shown in eq 3 could take place by participation of **3** in the catalytic cycle II; the Diels–Alder type reaction between **8** and **3**, instead of **1**, produces **4**.

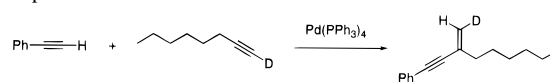
Although further investigation is needed to settle the precise mechanism, we are now in a position to synthesize novel aromatic compounds which are not readily available via the previously known methodologies.

**Supporting Information Available:** Spectroscopic and analytical data for compounds **2a**–**i** and **4** (13 pages). See any current masthead page for ordering and Internet access instructions.

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(7) To confirm the stereoselectivity on the initial step, we examined the cross coupling of phenylacetylene and 1-deuterio-1-octyne in the presence of palladium catalyst.  $^1\text{H}$  NMR analysis and NOE experiments of the product indicated the cis relationship between the hydrogen and phenylethynyl group. It is clear that the dimerization proceeded via cis hydro- or carbopalladation. Similar selectivities on the transition metal catalyzed dimerization of alkynes were reported.<sup>4c,e,f</sup>



(8) Saito, S.; Salter, M. M.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, **118**, 3870–3971.