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CYCLIC CASCADE CARBOPALLADATION REACTIONS AS A ROUTE TO BENZENE AND FULVENE DERIVATIVES†

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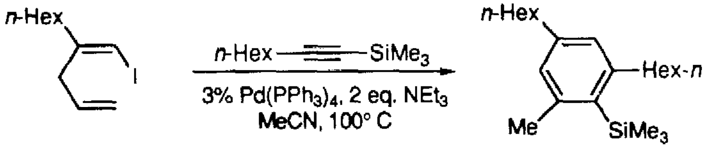
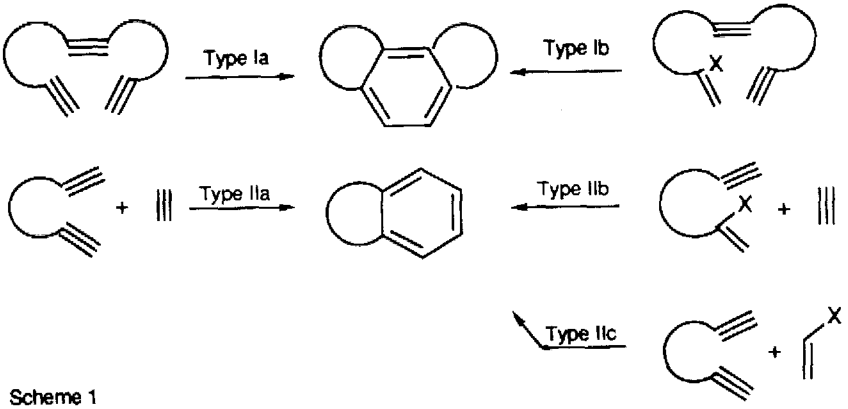
Summary: Palladium-catalyzed cyclization of appropriately structured triynes, haloalkenyldiynes, or haloalkenylalkyne-alkyne mixtures can provide the corresponding benzene derivatives, while the Pd-catalyzed intermolecular reaction of diynes with alkenyl halides can give fulvene derivatives.

Cascade carbopalladation has been implicated in the [2+2+2] cyclotrimerization of alkynes to produce benzene derivatives[1]. The intermolecular version of the reaction, however, does not provide a generally satisfactory route to benzene derivatives with good control of "pair" selectivity and regioselectivity. We recently reported a highly regiocontrolled and partially intramolecular reaction to give a benzene derivative via carbopalladation[2,3] (Eq. 1).



(1)

Pursuing along this line, we sought selective carbopalladation routes to benzene derivatives with varying degrees of intramolecularity[4-6] (Scheme 1).



Scheme 1

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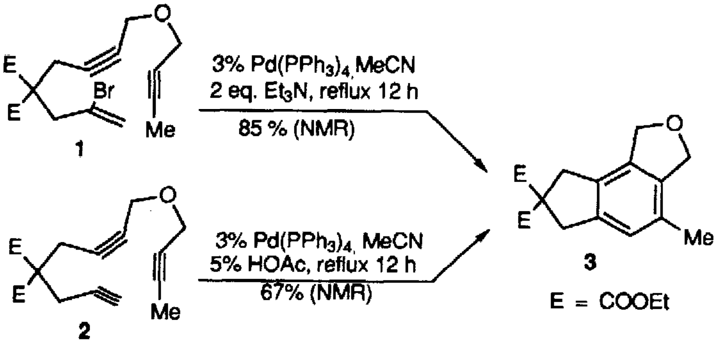
†This paper is dedicated to Professor Herbert C. Brown of Purdue University on the occasion of his 80th birthday.

We initially chose $\mathbf{1}^7$ and $\mathbf{2}^7$ as test substrates. Treatment of **1** with $Pd(PPh_3)_4$ (3 mol %) and NEt_3 (2 equiv) in refluxing MeCN for 12 h provided a 54% isolated yield (85% by NMR) of the desired tricyclic product **3**: ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 6H), 2.19 (s, 3H), 3.44 (s, 2H), 3.56 (s, 2H), 4.21 (q, J = 7 Hz, 4H), 5.06 (s, 4H), 6.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.75, 18.44, 38.32, 38.83, 61.62, 72.85, 73.16, 124.01, 130.02, 130.28, 134.38, 137.11, 140.12, 171.75; IR (neat) 2980, 2940, 2900, 1740, 1465, 1370 cm^{-1}. High resolution MS Calcd for $C_{18}H_{22}O_5$: 318.1468. Found: 318.1466. More attractive, however, is the corresponding reaction of **2** under the influence of 3 mol% of $Pd(PPh_3)_4$, and 5 mol % of HOAc[8] in refluxing MeCN for 12 h. This reaction provided **3** in 70% NMR yield (Eq. 2). The use of a catalytic amount of $Pd(PPh_3)_4$ or $\{Cl_2Pd(PPh_3)_2 + 2\ n\text{-BuLi}\}$ in the presence of HOAc was satisfactory. Other potential hydrogen sources, such as PhCOOH, DIBAH and *t*-BuMgCl, used in conjunction with either $Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$ failed to induce the desired conversion of **2** into **3**. Likewise, the use of $Cl_2Pd(PhCN)_2$, employed previously by Maitlis[1] for alkyne cyclotrimerization, did not induce conversion of **2** into **3** in significant yield. Although the mechanisms of these reactions are not very clear at this time, it is likely that **4** is a common intermediate in both reactions (Eq. 2). Conversion of **4** into **3** may proceed either via **5**, i.e., carbopalladation, or via **6**, i.e., electrocyclic reaction, but it is not possible to rule out either pathway at this time. The Type Ia procedure described above was satisfactory also for the conversion of $\mathbf{7}^7$ into $\mathbf{8}^9$ in 63% isolated yield.



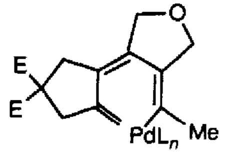
1

2

3

E = COOEt

(2)



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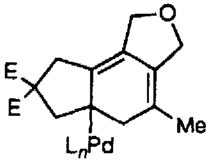

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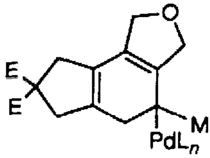

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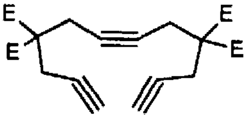

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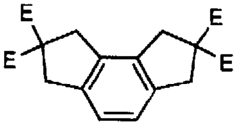

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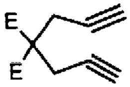
In contrast to the totally intramolecular Type I cyclization, their partially intermolecular versions, i.e., Type IIa-IIc reactions, have proved to be much less predictable. The reaction of **9**[10] with 5 equiv of 3-hexyne in DMF in the presence of 5 mol % of $Pd(PPh_3)_4$ and 5 mol % of HOAc at 65°C overnight produced **10**[9] in 37% NMR yield along with some unidentified byproducts. More disappointing were the reactions of **9** with diphenylacetylene and diethyl acetylenedicarboxylate, neither of which provided the expected products in any significant yield (<5%). A minor product obtained in 15% yield from the latter reaction has been tentatively identified as **11**. To circumvent the conceptually difficult requirement of matching the reactivity of a diyne with that of a monoyne to avoid unwanted self-polymerization of either of these two reactants, we turned our attention to the Type IIb reaction. To our disappointment, however, the reaction of **12**[7] with 3-hexyne in the presence of $Pd(PPh_3)_4$ (5 mol %) and NEt_3 (2 equiv) in DMF produced **10** only in 28% NMR yield. It then occurred to us that, in the Type IIb reaction, a putative intermediate represented by **13**, which may be formed via oxidative addition and cyclic carbopalladation, must react selectively with the monoyne rather than the haloenyne in order to produce the desired benzene derivative. This requires that the monoyne be sufficiently more reactive and/or more abundant than the haloenyne. Indeed, the reaction of **14**[7] with 3-hexyne under comparable conditions provided **15**[9] in 58% NMR yield (40% isolated) (Eq. 3). Although the structural requirements mentioned above are somewhat restrictive, a reasonable level of predictability is expected from the Type IIb reaction.



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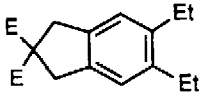

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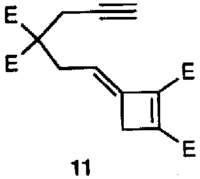

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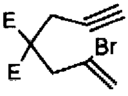

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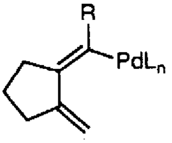
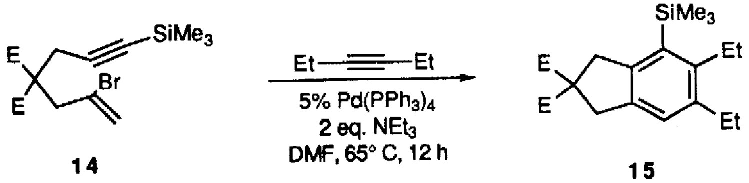
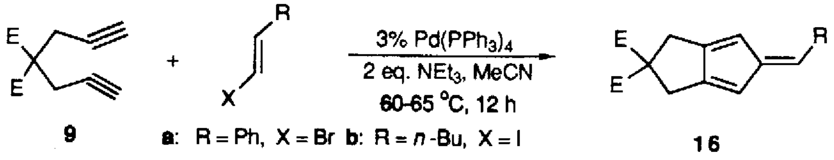


13 R= H, C, or Si group



14 **15** (3)

To explore the synthetic value of the Type IIc approach, we ran the reaction of **9** with (*E*)-β-bromostyrene and (*E*)-1-iodo-1-hexene in the presence of 5 mol % of $Pd(PPh_3)_4$ and 2 equiv of NEt_3 in MeCN at 60-65°C overnight. In these cases, however, the major products were fulvene derivatives **16a** (52%) and **16b** (40%), respectively, obtained in the isolated yields shown in parentheses (Eq. 4). None of the benzene derivatives were detected in these cases. Some examples of the intermolecular version of this reaction were recently reported.[11]



(4)

In summary, the Type Ia, Ib, and IIb reactions provide promising and selective routes to benzene derivatives, while the Type IIc reaction can produce fulvenes. Further delineation of the synthetic scope of these reactions is being conducted.

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(3) For our other papers on cyclic carbopalladation of alkynes, see (a) Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507. (b) Negishi, E.; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393. (c) Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590.

(4) For papers on the Type Ib cyclization published during our study, see (a) Meyer, F. E.; de Meijere, A. *Synlett.* **1991**, 777. (b) Meyer, F. E.; Parsons, P. J.; de Meijere, A. *J. Org. Chem.* **1991**, *56*, 6487.

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(6) For a recent paper on an endiyne cyclization leading to the formation of cyclohexadienes, see Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791.

(7) The compound **1** was prepared by the reaction of diethyl 2-(2-bromo-2-propenyl)malonate with 4-(2-butynyloxy)-2-butynyl mesylate using NaH as a base. The mesylate was prepared via the base-mediated reaction of 2-butynol with propargyl bromide followed by hydroxymethylation with $(CH_2O)_n$ and mesylation. The preparation of **12** and **14** were carried out analogously. The preparation of **2** and **7** was achieved via alkylation of diethyl 2-(2-propynyl)malonate with 4-(2-butynyloxy)-2-butynyl mesylate and 1,4-bis(mesyloxy)-2-butyne, respectively, using NaH as a base.

(8) For the use of HOAc in conjunction with $Pd_2(dba)_3{\cdot}CHCl_3$, tri-*o*-tolylphosphine, and polymethylhydrosiloxane for cyclization of enynes, see Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161.

(9) Satisfactory spectral data including high resolution mass spectral data were obtained.

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