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Palladium-Catalyzed Regioselective Bis-Alkynylation of Propargylic Carbonates: Synthesis of Enediyne Compounds

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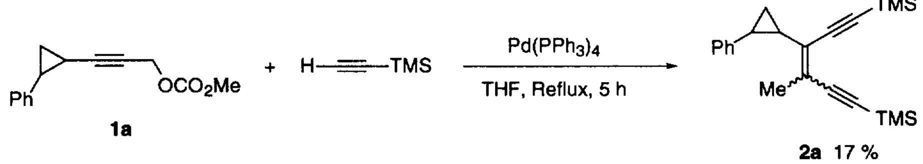
Abstract: Conjugated enediyne compounds were synthesized by the palladium-catalyzed bis-alkynylation reaction of propargylic carbonates with terminal alkynes. An unsymmetric enediyne was also synthesized by successive addition of two different alkynes. © 1997 Elsevier Science Ltd.

Carbon-carbon bond formations between sp and sp^2 carbons have been widely studied,[1] especially in view of the synthetic utility of the conjugated enyne products. These coupling reactions are generally achieved by the reactions of alkenylmetal intermediates with metal acetylides generated *in situ* sometimes[1] through transmetallation. Conjugated enediyne compounds are of importance among the enyne systems since they exist in bioactive compounds such as antitumor agents.[2] The palladium-catalyzed coupling reactions between sp and sp^2 carbons play a central role in the field of enediyne synthesis.[1] Here we report a novel bis-alkynylation of propargylic carbonates that provides a new route to enediyne compounds.

An unexpected product having a conjugated enediyne structure was obtained, in the course of our study on the chemistry of cyclopropanes,[3] by the reaction of carbonate **1a** with an excess amount of trimethylsilylacetylene in the presence of $Pd(PPh_3)_4$ in refluxing THF (Scheme 1). This reaction could be successfully applied to a variety of substrates, since the reaction did not require to have a cyclopropane ring in the substrate. The results after optimization of the reaction conditions are listed in Table 1.[4-5]

Scheme 1



The following exemplifies a successful coupling of propargylic carbonates with alkynes. A mixture of carbonate **1b** (71 mg, 0.5 mmol), phenylacetylene (153 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (29 mg, 5 mol%) in dimethoxyethane (5 ml) was heated under reflux for 7 h, then the catalyst was removed by passage of the reaction mixture through silica gel short column (eluent; 10% ethyl acetate in hexane). Purification by PTLC (hexane) gave each isomer of the corresponding enediyne products.

Alkynes having an alkyl, aryl, silyl, or oxygen-containing substituent at the terminus were applicable for this reaction (Table 1, runs 3-6). This reaction proceeded smoothly when propargylic carbonates with a primary or secondary alkyl substituent on the terminal carbon were used, but substrates with an aryl or silyl substituent led to the formation of a complex mixture, probably due to the preferential formation of a propargylpalladium intermediate rather than an allenylpalladium intermediate.[6] It should be noted that two alkynes were introduced exactly at two sp-carbons of the initial propargylic carbonates in all cases (*vide infra*). Although the E/Z selectivity of the reaction was low, each isomer could be separated by a careful chromatography on silica gel in most of the cases.

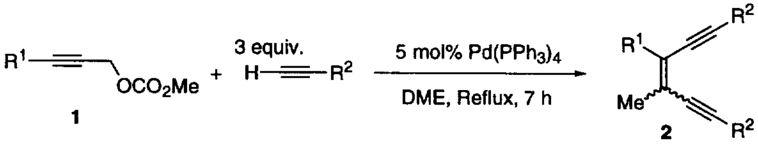
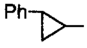


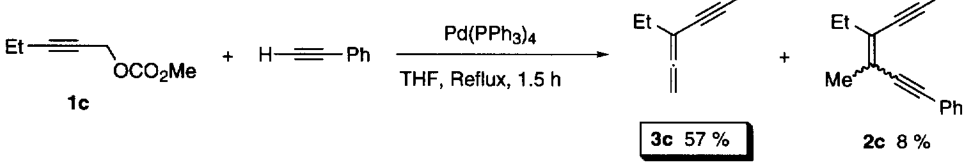
Table 1. Palladium-Catalyzed Bis-Alkynylation of Propargylic Carbonates.

Run	R^1	R^2	Products	%Yield[a] (E/Z Ratio)[b]
1		TMS[c]	**2a**	54 (82/18)[d]
2	Me	Ph	**2b**	57 (54/48)
3	Et	Ph	**2c**	79 (56/44)
4	Et	Bu	**2d**	74 (53/47)
5	Et	TMS[c]	**2e**	48 (58/42)
6	Et	CH_2OTHP	**2f**	42 (40/60)

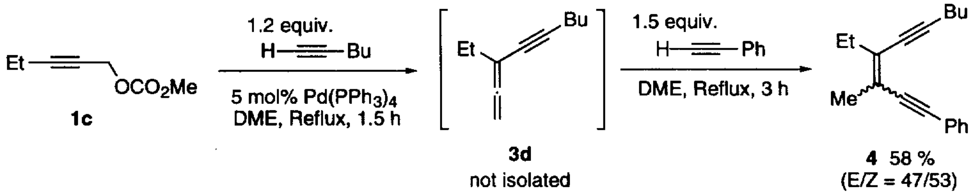
a) Isolated yields. b) Unless otherwise noted, the ratio was recorded by weight of the isomers. c) 5 equivalents of the alkyne were used. d) The ratio was determined by ^1H NMR because two isomers could not be separated.

Mono-alkynylated intermediate, i.e., the allenyne **3c** was not only detected by GCMS during the reaction, but also isolated as a major product[7] when the reaction of run 3 in Table 1 was quenched after 1.5 h (Scheme 2). In addition, the sequential coupling reaction of **1c** with two different alkynes gave the corresponding unsymmetrical enediyne **4** (Scheme 3). These facts clearly show that the present reaction proceeds in two steps; the formation of the allenyne intermediate and the addition of the other alkyne to the intermediate, as depicted in Scheme 4.

Scheme 2

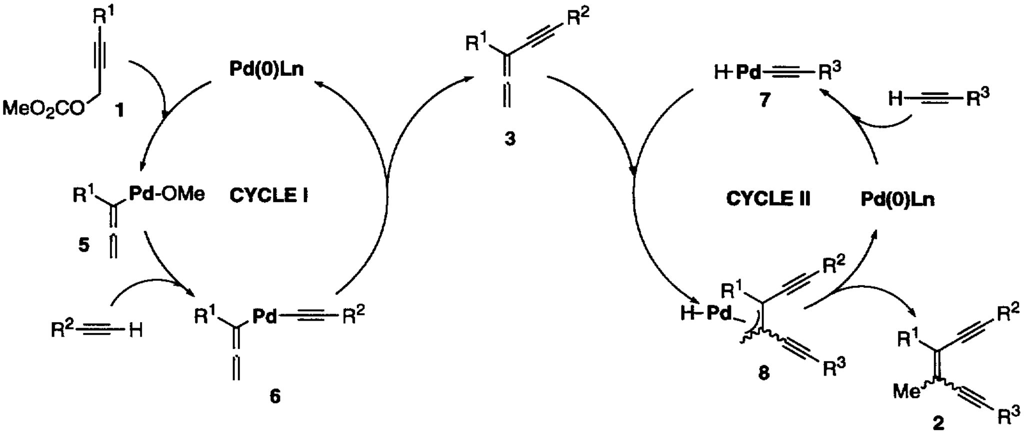


Scheme 3



The palladium-catalyzed reactions giving allenynes from propargyl compounds and alkynes are usually performed in the presence of a copper salt, which accelerates the formation of allenylalkynylpalladium intermediates **6** through transmetallation.[7-9] However, addition of cuprous iodide to the present reaction

Scheme 4



caused inhibition of the bis-alkynylation, probably because the transmetallation of the copper acetylide, formed *in situ*, to the Pd(0) compound could not occur in CYCLE II (Scheme 4). Noteworthy is that the allenyne was produced in the absence of a copper co-catalyst in our case[4,9] thus, the latter step proceeded smoothly probably via oxidative insertion of the terminal alkyne into Pd(0) to form the alkynylpalladium hydride intermediate **7**, which underwent the following carbopalladation with the allenyne intermediate **3**. The regioselectivity of the latter reaction indicates that carbopalladation of the allenyne **3** occurs predominantly at the central carbon of the allenyl moiety[10-12] to form π-allylpalladium intermediate **8** under thermodynamic control.[10] The steric hindrance between the alkynyl moiety and the R^1 group in the π-allylpalladium intermediate **8** could be negligibly small, since only little E/Z selectivity was induced.

The present reaction provides a new entry into the methods for the synthesis of enediyne compounds from easily preparable propargylic carbonates and a variety of terminal alkynes. The bis-alkynylation consists of the stepwise substitution and addition of terminal alkynes to propargylic carbonates, thus an unsymmetrical enediyne compound could be synthesized in one pot.

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4. In the course of optimization of the reaction conditions, an obvious solvent effect was observed. Solvents with relatively high polarity tended to accelerate the reaction, giving the allenyne. Dimethoxyethane (DME) was the solvent of choice, and THF could be used even though the yield was slightly lower. In polar solvents such as DMSO and acetonitrile, the formation of the allenyne completed very fast even at rt, but the enediyne product was formed in lower yield even at 80 °C.
5. ^{1}H NMR data (270 MHz, CDCl$_3$) for the products: **2a** (*E*): δ 0.12 (s, 9 H), 0.21 (s, 9 H), 1.15–1.23 (m, 1 H), 1.40–1.50 (m, 1 H), 2.05 (s, 3 H), 2.14–2.28 (m, 1 H), 2.45–2.52 (m, 1 H), 7.04–7.30 (m, 5 H); **2b** (*E*): δ 2.21 (s, 6 H), 7.25–7.52 (m, 10 H); **2b (Z)**: δ 2.02 (s, 6 H), 7.25–7.52 (m, 10 H); **2c** (*E*): δ 1.23 (t, J = 7.5 Hz, 3 H), 2.22 (s, 3 H), 2.61 (q, J = 7.5 Hz, 2 H), 7.28–7.55 (m, 10 H); **2c (Z)**: δ 1.20 (t, J = 7.5 Hz, 3 H), 2.03 (s, 3 H), 2.36 (q, J = 7.5 Hz, 2 H), 7.18–7.56 (m, 10 H); **2d** (*E*): δ 0.92 (t, J = 7.2 Hz, 6 H), 1.07 (t, J = 7.5 Hz, 3 H), 1.37–1.65 (m, 8 H), 1.98 (s, 3 H), 2.30–2.48 (m, 6 H); **2d (Z)**: δ 0.92 (t, J = 6.9 Hz, 6 H), 1.06 (t, J = 7.5 Hz, 3 H), 1.39–1.62 (m, 8 H), 1.85 (s, 3 H), 2.17 (q, J = 7.5 Hz, 2 H), 2.35–2.44 (m, 4 H); **2e** (*E*): δ 0.19 (s, 9 H), 0.20 (s, 9 H), 1.09 (t, J = 7.5 Hz, 3 H), 2.01 (s, 3 H), 2.40 (q, J = 7.5 Hz, 2 H); **2e (Z)**: δ 0.21 (s, 18 H), 1.08 (t, J = 7.5 Hz, 3 H), 1.87 (s, 3 H), 2.19 (q, J = 7.5 Hz, 2 H); **2f** (*E*): δ 1.08 (t, J = 7.5 Hz, 3 H), 1.45–1.95 (m, 12 H), 2.02 (s, 3 H), 2.40 (q, J = 7.5 Hz, 2 H), 3.48–3.62 (m, 2 H), 3.80–3.93 (m, 2 H), 4.45 (s, 2 H), 4.48 (s, 2 H), 4.80–4.92 (m, 2 H); **2f (Z)**: δ 1.08 (t, J = 7.5 Hz, 3 H), 1.45–1.85 (m, 12 H), 1.88 (s, 3 H), 2.22 (q, J = 7.5 Hz, 2 H), 3.48–3.62 (m, 2 H), 3.77–3.93 (m, 2 H), 4.45 (s, 2 H), 4.47 (s, 2 H), 4.88–4.95 (m, 2 H); **3c**: δ 1.74 (quintet, J = 7.5 Hz, 2 H), 2.10 (dq, J = 3.5, 7.5 Hz, 2 H), 3.51 (t, J = 6.4 Hz, 2 H), 4.51 (s, 2 H), 4.66 (dt, J = 3.5, 6.4 Hz, 2 H), 5.11 (quintet, J = 6.7 Hz, 1 H), 7.22–7.38 (m, 5 H); **4** (*E*): δ 0.94 (t, J = 6.5 Hz, 3 H), 1.14 (t, J = 8.2 Hz, 3 H), 1.35–1.65 (m, 4 H), 2.10 (s, 3 H), 2.30–2.56 (m, 4 H), 7.17–7.50 (m, 5 H); **4 (Z)**: δ 0.86 (t, J = 6.9 Hz, 3 H), 1.11 (t, J = 7.5 Hz, 3 H), 1.38–1.64 (m, 4 H), 1.96 (s, 3 H), 2.24 (q, J = 7.5 Hz, 2 H), 2.43 (t, J = 6.9 Hz, 2 H), 7.15–7.60 (m, 5 H). All products gave the corresponding molecular ion peaks in their mass spectra.
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