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Palladium(0)-Catalyzed Cross-Benzannulation between Conjugated Enynes. Reactivity-Controlled Synthesis of Multifunctionalized Benzenes

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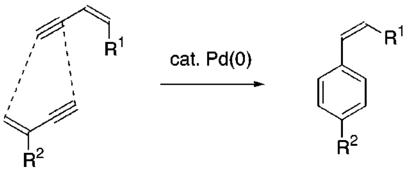
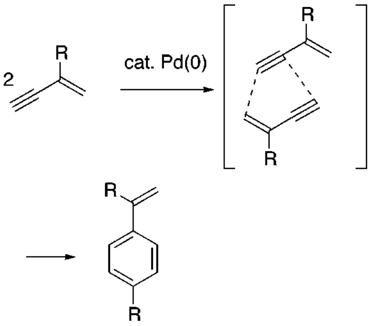
ABSTRACT



The synthesis of multifunctionalizbenzenes such as polysubstituted alkoxycarbonyl- or cyanostyrenes was carried out by the regioselective cross-benzannulation between conjugated enynes in the presence of Pd(PPh_3)$_4$.

Transition metal-catalyzed cyclooligomerization of unsaturated hydrocarbons is a powerful synthetic method for the regioselective synthesis of the benzene ring.[1] For example, the cyclotrimerization of alkynes has been studied extensively, and the synthesis of natural products as well as theoretically interesting molecules has been accomplished by this method.[2] Recently, we developed homo-benzannulation of conjugated enynes[3] (eq 1), and this chemistry was further expanded to the cross-benzannulation of conjugated enynes with diynes.[4] These reactions are useful for the regioselective construction of styrenes and ethynylbenzenes.[5] However, the scope of the homo-benzannulation of conjugated enynes has been somewhat limited by the fact that the same substituents were introduced to the benzene ring and/or the olefinic moiety of the product. In principle, it would be possible to carry out the cross-coupling between two different enynes. However, the attempted cross-coupling between two different enynes did not give satisfactory results, yielding a mixture of isomeric compounds.[6]



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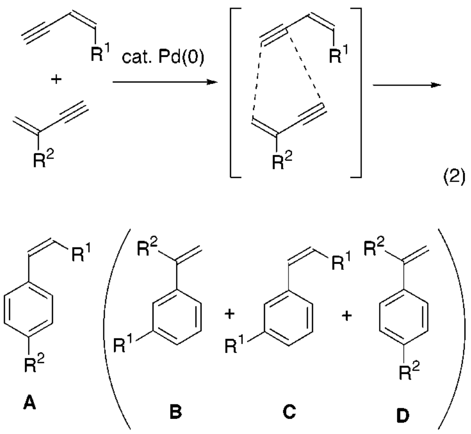
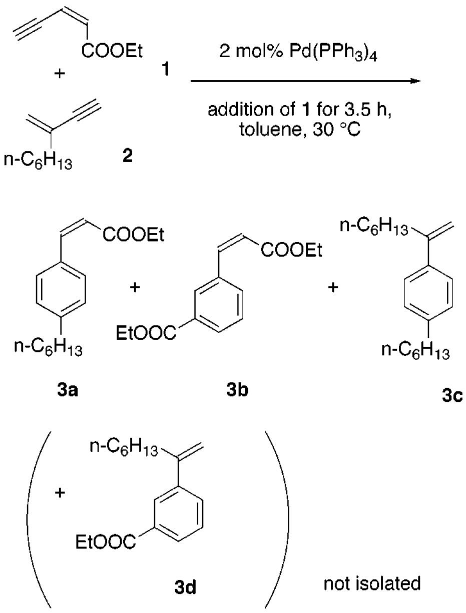
Recently, we reported that the reactivity of the conjugated enynes was enhanced by the introduction of an electron-withdrawing group.[7] This finding prompted us to examine the possibility of the selective cross-coupling reaction between two different enynes, controlled by the difference of the reactivity of enynes. In the benzannulation reaction between two different enynes which are equally reactive, a statistical mixture of homo- and cross-benzannulation products (**A**−**D**) will be isolated (eq 2). However, by carefully controlling the reaction conditions, it will be possible to carry out the cross-benzannulation between a highly reactive enyne and a less reactive enyne and obtain the cross-coupled product such as **A** in a regio- and chemoselective manner (eq 2). In this paper we report the highly selective cross-benzannulation between two different enynes.



The palladium-catalyzed cross-benzannulation of 1-ethoxycarbonyl-1-butene-3-yne (**1**) with 2-hexyl-1-butene-3-yne (**2**) was investigated, and the results are summarized in Table 1. When a mixture of **1** and **2** was heated at 30 °C, a small amount of the cross-coupled product **3a**, together with the homo-dimerized product **3b**, was isolated (entry 1). The slow addition of the more reactive enyne **1** to a solution of **2** was effective for carrying out the cross-benzannulation efficiently, and the yield of **3a** increased to 61% (entry 2). The best result was obtained when a solution of 1 (1 equiv) was added to a solution of **2** (1.5 equiv) for 3.5 h, and **3a** was obtained in 75% yield (entry 4).[8] It is noteworthy that only one isomer (**3a**) of the possible two isomers of the cross-coupled products was isolated and the other isomer (**3d**) was not isolated in this reaction.

Table 1. Cross-Benzannulation between **1** and **2**

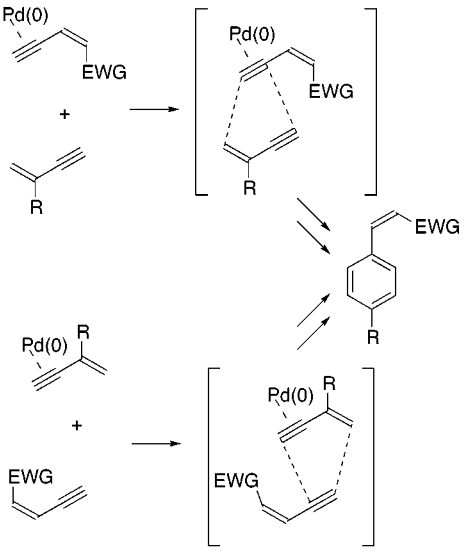


entry	**1** (equiv)	yield (%)		
		3a	**3b**	**3c**
1	1[a]	11	36	
2	1	61	10	3
3	1.3	69	11	4
4	1.5	75	5	10

[a] A mixture of **1** and **2** was heated for 3 h.

The cross-benzannulation between other conjugated enynes was carried out, and the results were summarized in Table 2. The cross-benzannulation of a less reactive (*E*)-enyne **4** with 2-hexyl-1-butene-3-yne (**2**) proceeded at elevated temperature (65 °C), and the disubstituted benzene **9** was isolated in 64% yield (entry 2). The reaction of **1** with functionalized 2-substituted enynes such as **5** and **6** proceeded smoothly,

Scheme 1



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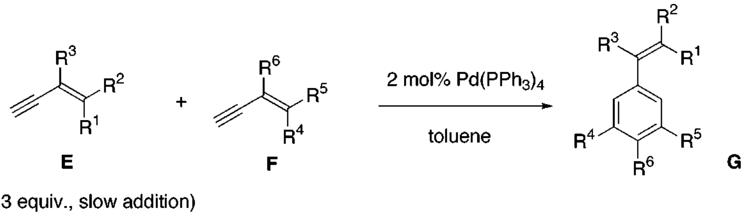
(8) **Representative procedure**: To a solution of **2** (68 mg, 0.5 mmol) and Pd(PPh$_3$)$_4$ (12 mg, 0.01 mmol) in dry toluene (1 mL) was slowly (3.5 h) added a solution of **1** (93 mg, 0.75 mmol) in dry toluene (1 mL) at 30 °C under Ar by a syringe pump. The solution was stirred for 10 min after the addition completed, and the mixture was passed through a short alumina column. The solvent was removed by evaporation, and the products were isolated by column chromatography (hexane, then hexane:ethyl acetate = 20:1), giving **3a** (98 mg, 75%), **3b**[7] (6 mg, 5%), and **3c**[3] (13 mg, 10%). See Supporting Information for the analytical and spectral data of **3a** and **9**−**14**.

Table 2. Cross-Benzannulation between Conjugated Enynes



	E				F							G
entry	enyne	R^1	R^2	R^3	enyne	R^4	R^5	R^6	addition time (min)	temp (°C)		yield (%)
1	**1**[a]	CO_2Et	H	H	**2**	H	H	n-C_6H_{13}	150	30	**3a**	75
2	**4**	H	CO_2Et	H	**2**	H	H	n-C_6H_{13}	60	65	**9**	64
3	**1**	CO_2Et	H	H	**5**	H	H	$(CH_2)_2C(CH_3)_2OH$	180	50	**10**	58
4	**1**	CO_2Et	H	H	**6**	H	H	$(CH_2)_9OCH(OEt)CH_3$	210	30	**11**	48
5	**1**[b]	CO_2Et	H	H	**7**	H	CN	n-C_5H_{11}	15	55	**12**	46
6	**7**	H	CN	n-C_5H_{11}	**2**	H	H	n-C_6H_{13}	60	65	**13**	40
7	**8**	CN	H	n-C_5H_{11}	**2**	H	H	n-C_6H_{13}	20	65	**14**	51

[a] One and half equiv of enyne **1** was used. [b] One equiv of enyne **1** was used.

and the products were isolated in moderate yields (entries 3−4). The cross-benzannulation of **1** with a 1-cyanoenyne **7** also proceeded, and trisubstituted benzene **12** was isolated (entry 5). The cyanoenynes **7** and **8** were also used as the reactive component, and the cross-benzannulation proceeded with the less reactive enyne **2** (entries 6−7). In these reactions the acetylenic moiety of the more reactive enynes reacted as the C2 unit in the benzannulation reactions, and in most cases single isomers were isolated as the cross-coupled products.

Currently we assume that the observed high chemoselectivity would be explained in terms of the high reactivity of the electron-deficient enyne as the C2 component (Scheme 1). The electron-deficient enynes might be activated by coordination with the Pd(0) species, or the electron-rich enyne might be activated as the C4 unit by interaction with the Pd complex. Since the increased nucleophilicity of the corresponding alkyne−Pt(0) complexes[9] and enyne−Pt(0) complexes[10] has been observed, the activation of the electron-rich enyne might be more important for this reaction to proceed.

In summary, we succeeded in the cross-benzannulation between conjugated enynes in the presence of a Pd(0) catalyst. The reaction proceeded in a highly regio- and chemoselective manner. Now we are in a position to prepare multifunctionalized benzenes efficiently by this annulation methodology.

Supporting Information Available: Analytical and spectral data for compounds **3a** and **9−14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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