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The First Chemo- and Regiospecific Palladium-Catalyzed Enyne-Diyne [4+2] Intermolecular *Cross*-Benzannulation: An Effective Route to Polysubstituted Benzenes

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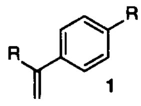
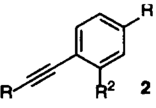
Abstract: Series of di- and trisubstituted conjugated enynes **3** in the presence of $Pd(PPh_3)_4$ catalyst underwent [4+2] *cross*- benzannulation reaction with conjugated diynes **4** affording polysubstituted benzenes **5** in reasonable to excellent chemical yields. In all cases the cycloaddition reaction proceeded in *regio*- and *chemospecific* manner.

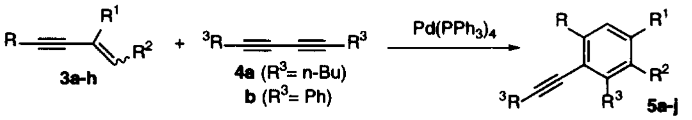
We have recently reported two novel methods for construction of benzene skeleton under the palladium catalysis: the formation 1,4-disubstituted benzene **1**[1] *via* the [4+2]*homo*-benzannulation of conjugated enynes, and synthesis of 1,2,4-trisubstituted benzene **2**[2] *via* an enyne-yne *cross*-benzannulation protocol. Both methods are *regiospecific* in character, affording the products **1** and **2** as sole regioisomers.[1,2] Although the palladium-catalyzed enyne-diyne [4+2] *cross*-benzannulation is a powerful and *regiospecific* approach to synthetically useful trisubstituted benzenes **2**,[2] in some cases the reaction proceeded with moderate degrees of *chemoselectivity*. Accordingly, the reaction mixtures were contaminated with trace to notable amounts of dimer **1**,[2] which arose from the competitive [4+2] *homo*-dimerization of conjugated enyne.[1]



1



2



eq 1

Herein we report the first example for not only *regiospecific*, but also *chemospecific* intermolecular[3] palladium-catalyzed enyne-diyne [4+2] *cross*-benzannulation reaction, leading to tetra-, and pentasubstituted benzenes **5** in moderate to excellent chemical yields (eq 1, Table 1).

Control experiments indicated that neither disubstituted enynes **3a-e** nor trisubstituted enynes **3f-h** were able to undergo *homo*-dimerization[1] reaction in the presence of palladium catalyst even under prolong heating at 120°C. Encouraged by this fact we submitted differently substituted enynes **3a-h** to the *cross*-benzannulation reaction with diynes **4a,b** (eq 1, Table 1). We found that in all cases the benzannulation reaction proceeded with perfect *regiocontrol* (no any other regioisomers of **5** were detected by GC-MS analysis of the crude reaction mixtures) and perfect *chemocontrol* (no traces of *homo*-dimer **1**[1] were formed). 2,4-Disubstituted enynes **3a-c** were found to be the most reactive towards diynes **4** among the all enynes tested. Accordingly, the tetrasubstituted benzenes **5a-f** were obtained in high to excellent chemical yields (entries 1-6). In contrast, the reaction of 1,4-disubstituted enynes **3d,e** with diyne **4a** even under more elevated temperature (120°C) was rather sluggish and afforded the desired aromatic products with trace to unsatisfactory low yields. The main

Table 1. Palladium-catalyzed *cross*-benzannulation of conjugated enynes **3** with diynes **4**[a]

entry	R	R^1	R^2	Diyne	Reacn cond time(days)/temp(°C)	Product (yield, %)[b,c]
1 **3a**	n-Hex	Me	H	**4a**	3/100	**5a** (95)
2 **3a**	n-Hex	Me	H	**4b**	//	**5b** (84)
3 **3b**	Ph	Me	H	**4a**	//	**5c** (79)
4 **3b**	Ph	Me	H	**4b**	//	**5d**(80)
5 **3c**	*c*-hexenyl	Me	H	**4a**	//	**5e** (89)
6 **3c**	*c*-hexenyl	Me	H	**4b**	//	**5f** (68)
7 **3d** (88%-Z)[d]	n-Hex	H	Me	**4a**	5/120	**5g** (45)[e,f]
8 **3e** (84%-Z)[d]	Ph	H	Me	**4a**	//	**5h** (>95)[e]
9 **3f** (Z)[d]	Ph	Me	Me	**4a**	//	**5i** (43)[e,g]
10 **3g** (Z)	Ph	Me	CO_2Me	**4a**	2/120	**5j** (88)
11 **3h** (E)	Ph	Me	CO_2Me	**4a**	//	**5j** (42)[h]

[a] All reactions were carried out in the Wheaton microreactors with equimolar amounts of **3** and **4** (0.5mmol) in toluene or in THF (0.5 M) in the presence of $Pd(PPh_3)_4$ (5 mol%) under reaction conditions indicated in the Table 1. [b] Yield determined by ^{1}H NMR. [c] All structures of new products **5** are in satisfactory agreement with spectroscopic and analytical data. [d] Reactions employing E-enynes produced trace amounts of aromatic products. [e] (TDMPP, 20 mol%) was used as an additive. [f] The recovery of **3d** was 39%. [g] The recovery of **3f** was 38%. [h] The recovery of **3h** was 53%.

reason of last would be the low stability of the palladium catalyst under the prolong heating. This problem was solved by addition of tris(2,6-dimethoxyphenyl)phosphine (TDMPP) to the reaction mixture (4 equiv. *vs* Pd).[6] Accordingly, tetrasubstituted benzenes **5g** and **5h** were obtained in 45 and >95% yields, respectively (entries 7 and 8, Table 1). Benzannulation of trisubstituted **3f** gave pentasubstituted benzene **5i** in rather moderate yield (entry 9), whereas reaction of its carbomethoxy analogue **3g** produced polysubstituted benzoate **5j** in 88% yield (entry 10). It was surprising for us that ester-containing E-enyne **3h**, in contrast to its alkyl- and phenyl analogues (entries 7-9, note d), enabled to undergo benzannulation reaction, even though yield of **5j** in this case was moderate (entry 11). At this stage the reasons for low reactivity of E-enynes in this benzannulation reaction are not clearly understood, therefore, more deep investigation of this reaction is now underway in our laboratory.

Although, further investigation to settle mechanism for enyne-diyne [4+2]*cross*-benzannulation reaction is needed, we are now in a position to synthesize tetra- and pentasubstituted benzenes in moderate to high yields in one step from easily available conjugated enynes and diynes.

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