Synthesis of allenes *via* palladium catalysed addition of certain activated methynes to conjugated enzynes

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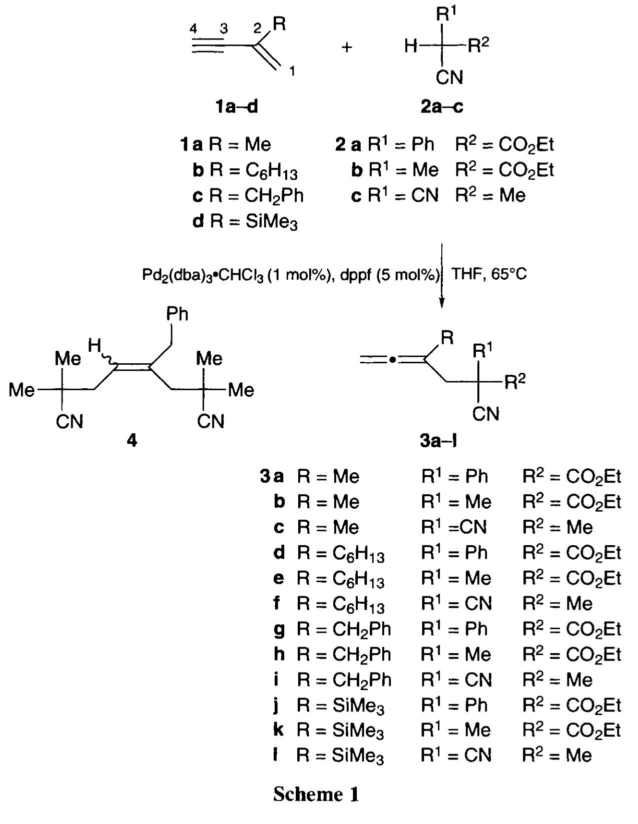
The palladium catalysed reaction of conjugated enzynes 1 with certain activated methynes 2 gives allenes 3 in good to high yields.

It is well known that conjugate dienes react with pronucleophiles in the presence of transition metal catalysts to afford alkenes, as 1 : 1 adducts, in good yields.[1] However, to the best of our knowledge, there have been no reports on the transition metal-catalysed reaction of conjugated enynes with pronucleophiles.[2] We report that the palladium-catalysed reaction of conjugated enynes **1** with certain activated methynes **2** gives allenes **3** in good to high yields (Scheme 1).

The results are summarized in Table 1. The reaction of 2-methylbut-1-en-3-yne **1a** with ethyl 2-phenyl-2-cyanoacetate **2a** in the presence of $Pd_2(dba)_3\cdot CHCl_3$ (1 mol%) and dppf (5 mol%) in THF (1.0 cm^3 for 0.5 mmol scale) gave allene **3a** in quantitative yield (entry 1). We tested other transition metal catalysts and other phosphine ligands, but the above combination gave the best result. The reactions of **1a** with ethyl 2-cyanopropionate **2b** and methylmalononitrile **2c** under similar conditions afforded the corresponding allenes **3b** and **3c**, respectively, in good yields (entries 2 and 3). The reactions of **1b**,[3] bearing a longer alkyl chain than **1a**, with pronucleophiles **2a–c** were more sluggish than those of **1a** giving lower yields of the allenes **3d–f** (entries 4–6). The addition of **1c**,[4] substituted by a benzyl group at the C-2 position, proceeded smoothly when **2a** or **2b** was used as the pronucleophile (entries 7 and 8). We also found that the 1,3-bis adduct **4** could be isolated when an excess of pronucleophile **2** was added to the enynes; for example, enyne **1c** reacted with 1.5 equiv. of pronucleophile **2c** to give the 1,3-bis adduct **4** in 61% yield along with the ordinary mono-adduct **3i** (28% yield) (entry 9). The formation of **4** can be explained in the following way based upon our previous finding.[5] The mono-addition would take place at the beginning, and the resulting allene **3i** would react further with **2c** to give the bis adduct. As long as a small excess (1.5 equiv.) of enynes **1** was added to the pronucleophiles, such a double addition product was not isolated. The reactivity of the trimethylsilyl substituted enzyne **1d** was high, giving the adducts **3j–l** in very high yields (entries 10–12).



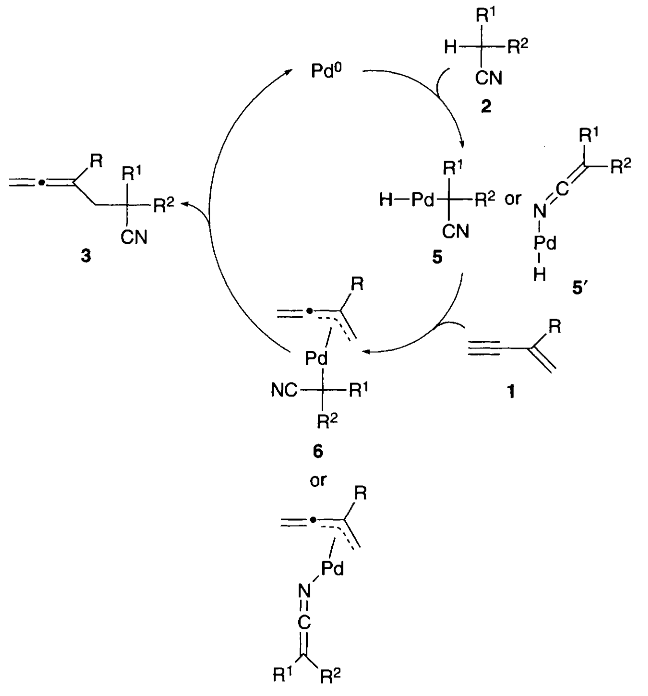
Scheme 1

There are several interesting and noticeable points on the above reaction. Firstly, the addition of the pronucleophiles (HNu) to the enynes proceeds regioselectively; the Nu portion adds to the terminal carbon of the double bond. Secondly, the pronucleophiles are limited to those having at least one CN substituent; other pronucleophiles such as diethyl methylmalonate; acetylmalononitrile, and 2,2,5-trimethyl-1,3-dioxane-4,6-dione (methyl Meldrum's acid) did not react at all under the conditions shown above, and activated methylenes did not react even if they were substituted with CN group. Thirdly, if there is a substituent at either terminal carbon of the enynes, the addition reaction is quite sluggish, and does not proceed at all in some cases. Fourthly, most reactions of the pronucleophiles with enynes proceeded only under the neutral conditions, Pd^0–ligand–HNu (our original conditions on the reaction of pronucleophiles[5]); the reaction did not proceed under basic conditions Pd^{II}–ligand–KOBu^t–HNu (Trost condition[1a,6]). Finally, the addition of pronucleophiles to enynes takes place more readily than the addition to allenes, and therefore it is expected that the addition of two different pronucleophiles

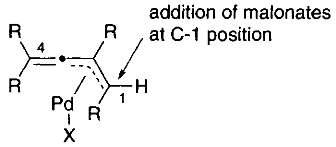
Table 1 Palladium-catalysed 1,4-addition of pronucleophiles **2** to conjugated enynes **1**[a]

Entry	Enyne	Pronucleophile	Product	*t*/h	Yield (%)
1	**1a**	**2a**	**3a**	63	100
2		**2b**	**3b**	65	60
3		**2c**	**3c**	63	75
4	**1b**	**2a**	**3d**	65	50
5		**2b**	**3e**	80	49
6		**2c**	**3f**	65	49
7	**1c**	**2a**	**3g**	72	95
8		**2b**	**3h**	36	65
9		**2c**[b]	**3i**	72	28[c]
10	**1d**	**2a**	**3j**	72	100
11		**2b**	**3k**	43	90
12		**2c**	**3l**	72	100

[a] A mixture of 0.75 mmol of enyne **1** and 0.5 mmol of pronucleophile **2** is refluxed in THF in the presence of $Pd_2(dba)_3\cdot CHCl_3$ (1 mol%) and dppf (5 mol%), except where otherwise indicated. [b] A mixture of 0.5 mmol of **1c** and 0.75 mmol of **2c** was treated with Pd catalyst in THF. [c] 1,3-Bis adduct **4** was isolated as a major product in 61% yield.



Scheme 2 Hydropalladation mechanism



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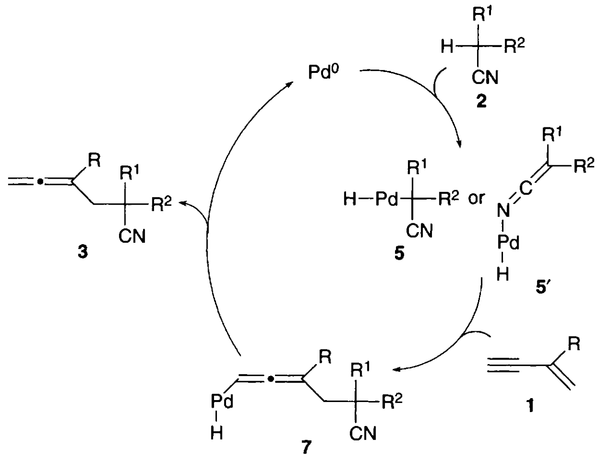
X = OAc, OPO(OEt)$_2$

successively to an enyne *in situ* would give a 1,3-bis adduct with two different substituents in one step.

A plausible mechanism of this reaction is shown in Scheme 2, although it is speculative. Oxidative insertion of Pd^0 into the C–H bond of pronucleophiles **2** would produce the Pd^{II} species **5** (or its imino enolate analogue **5′**). Hydropalladation of **1** with **5** or **5′** would afford the *exo*-methylene π-allylpalladium intermediate **6** or **6′**, respectively. Reductive elimination would lead to the formation of **3** and Pd^0 catalytic species. Although the *exo*-methylene π-allylpalladium structure is highly strained, a related intermediate has been proposed previously.[7] If the carbopalladation mechanism were involved in the palladium-catalysed allene formation, strained allenylpalladium intermediate **7** must be considered (Scheme 3). Furthermore, Cazes *et al.* have reported that the Pd-catalysed reaction of esters of α-allenic alcohols with anions of malonates proceeded regioselectively at the C-1 position of the intermediate **8**.[8] Taken together, most probably the present reaction proceeds through hydropalladation mechanism shown in Scheme 2.



Scheme 3 Carbopalladation mechanism

Although further investigation is needed to clarify the mechanism, the present reaction provides a new efficient method for the synthesis of substituted allenes from enynes. This type of the transformation *via* catalytic process has not been known previously, and thus the present development provides a further example of transition metal-catalysed addition of the C–H bond of pronucleophiles to unsaturated C–C bonds.

M. M. S. and S. S. gratefully acknowledge fellowships from the Japan Society for the Promotion of Science for Young Scientists.

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Received, 12th September 1995; Com. 5/06016H