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A Route to *Z*-Enediynes via Pd Catalyzed Alkyne Additions

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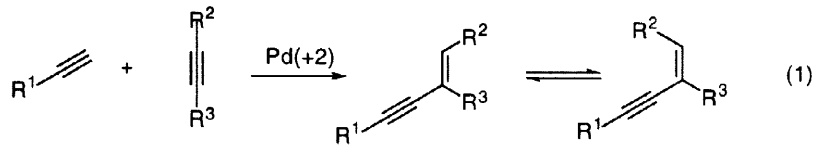
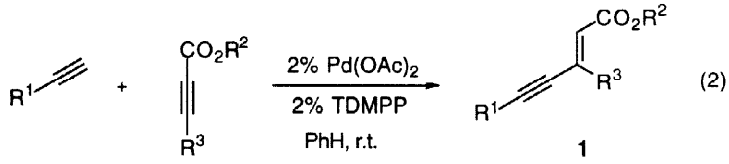
Summary: The combination of a Pd catalyzed mixed addition of a terminal alkyne with an internal alkyne and radical catalyzed ***E-Z*** isomerization provides an atom economical route to ***Z***-enediynes.

The discovery of the enediyne antitumor agents represented by the kedarcidin[1] and the related epoxide neocarzinostatin[2] chromophores has stimulated much activity in developing synthetic routes to ***Z***-enediynes.[3] A very successful approach has been based upon cross-coupling reactions of appropriately functionalized vinyl systems.[4] Our development of the palladium catalyzed addition of terminal alkynes[5] with a suitable acceptor alkyne suggested a more atom economical approach to enynes as illustrated in eq. 1. R^2 could be chosen such



(1)

that it easily could be converted into an alkyne; however, only access to the ***E***-isomers is available from the Pd catalyzed addition. If isomerization to the ***Z***-isomers could be performed, access to the requisite ***Z***-enediynes would then occur. Keeping our goal to have this be performed as efficiently as possible, we sought to effect the isomerization catalytically. Under such circumstances, we would be effecting an equilibration in which the ***E-Z*** equilibrium constant will be defined largely by R^2 and R^3 (eq. 1). In this paper, we report our studies of the synthesis of the requisite ***E***-enynes and their equilibration to the ***Z***-isomers.



(2)

The requisite ***E***-enynes[6] were prepared by the mixed addition reaction as illustrated in eq. 2 and Table 1 wherein an approximately 1:1 mixture of the two alkynes were stirred with a catalyst generated from mixing palladium acetate and tris(2,6-dimethoxyphenyl)phosphine (TDMPP) in benzene or THF at room temperature. In each case, only a single geometric isomer was obtained as shown. In the case of entry 8, two regioisomeric products were obtained as outlined in eq. 3. This is the first indication that addition α (to give **2h**) rather than β (to give **1b**) to the activating ester moiety could occur. It appears to be significantly a steric issue as revealed by the fact that decreasing the steric size of the substituent on the oxygen by going to p-methoxybenzyl increases

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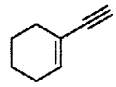
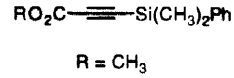
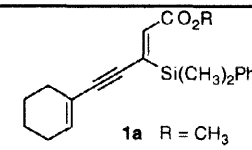
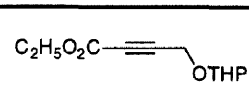
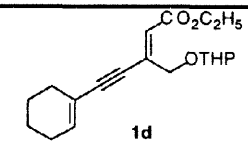
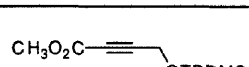
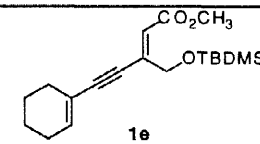
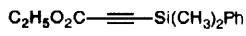
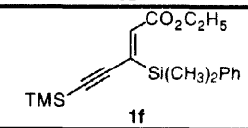
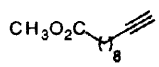
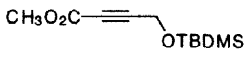
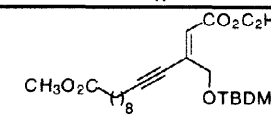
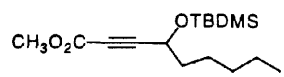
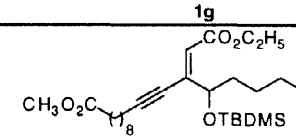
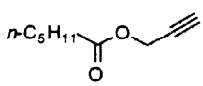
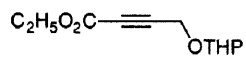
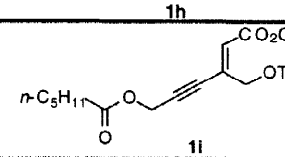
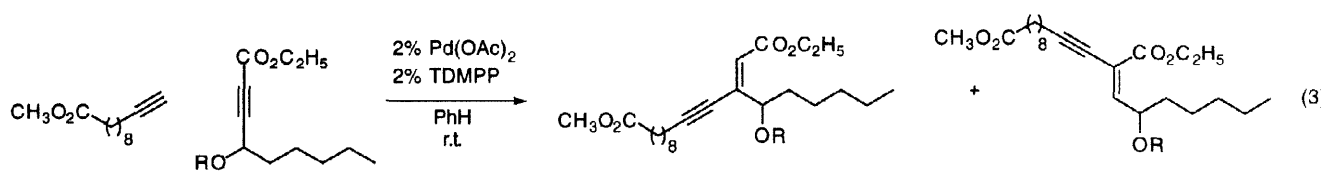
Table 1. Pd Catalyzed Mixed Addition[a]

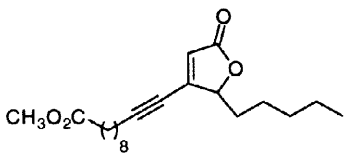
Entry	Donor Alkyne	Acceptor Alkyne	Product	Yield
1		 R = CH_3	 **1a** R = CH_3	89%
2		R = CH_3CH_2	**1b** R = CH_3CH_2	99%
3		R = *t*-C_4H_9	**1c** R = *t*-C_4H_9	65%
4			 **1d**	85%
5			 **1e**	88%
6			 **1f**	70%
7[b]			 **1g**	88%
8			 **1h**	See text
9[c]			 **1i**	85%

a) Reactions performed at 0.5-1.0M with 1:1 to 1:1.2 ratio of alkynes for approximately 24h as outlined in eq. 2 unless otherwise indicated. b) Performed with 4% $Pd(OAc)_2$ and 4% TDMPP. c) Reaction performed in THF.

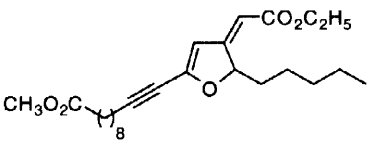


(3)

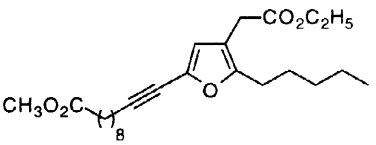
the "normal" attack β to the ester (**1i**). In the case of R = H, the isolated products were all secondary ones derived from the initial adduct **1j** by cyclization of the free hydroxyl group onto the ester leading to the lactone **3** and onto the triple bond leading to furan derivatives **4a** and **4b**.[7] Thus, it appears that steric and electronic effects are surprisingly more nearly balanced, indicating that polar effects driving the reaction towards conjugate addition products may be overwhelmed by sufficient steric hindrance.



3 (28%)

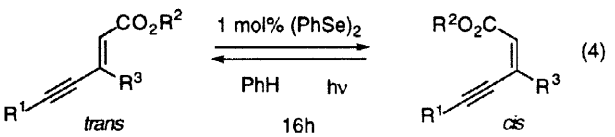


4a (45%)



4b (3%)

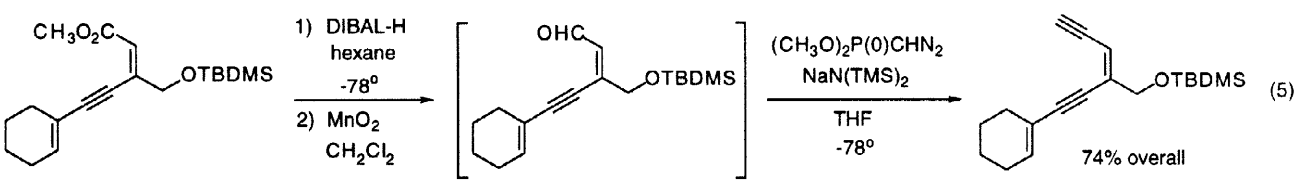
With the availability of the *trans*-enynes, we explored their equilibration with the **Z**-enynes[6] by phenylselenenyl radical generated by the photolytic dissociation of diphenyldiselenide in benzene at room temperature.[8] Table 2 and eq. 4 summarizes the results with the reaction being run for a standard period of 16 h. In several cases, reaction times were extended but led to no change in the *cis/trans* ratio—an observation suggesting the stated values represent thermodynamics. An exception was entry 8. Under the standard conditions, a 95% yield of a *cis/trans* ratio of 0.94 was observed. Performing the reaction at reflux with 10 mol% of diphenyldiselenide at reflux improved the ratio to 3.3 (98% yield). The best result, entry 8 of Table 2, involved increasing the amount of diphenyldiselenide to 10 mol% for an extended period. Even so, it is not clear that the reaction has reached equilibrium.



(4)

As shown in table 2, simple steric consideration normally accounts for the observed trends. Neither the choice of ester (entries 1-3) nor the choice of ether protecting group (entries 4 and 5) has any discernible effect on the equilibrium.

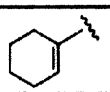
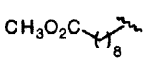
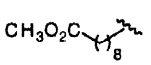
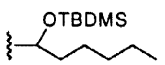
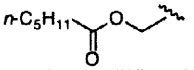
Having a simple access to the *cis*-enynes, we examined the conversion to an enediyne as shown in eq. 5. The ester was converted to an aldehyde in a two-step protocol since direct reduction to the aldehyde was problematic. The difficulty may stem from the instability of the aldehyde. Thus, the aldehyde was allowed to react directly with the diazoalkane[9] to give the desired enediyne in 74% overall yield for the three steps and 62% overall yield from the starting alkyne. Thus, *cis*-enediynes are available from simple building blocks in a



(5)

total of five steps with a great flexibility and demonstrates the utility of the atom economical Pd catalyzed addition of terminal donor alkynes with acceptor alkynes. The potential of this methodology for creation of facile strategies for the synthesis of the fascinating families of biologically important systems is a future goal.

Table 2. Thermodynamic Equilibration of Enediynes[a]

Entry	R^1	R^2	R^3	Yield	*cis/trans*
1		CH_3	$Si(CH_3)_2Ph$	71%	20.7
2		C_2H_5	$Si(CH_3)_2Ph$	91%	19.8
3		t-C_4H_9	$Si(CH_3)_2Ph$	79%	20.9
4		C_2H_5	CH_2OTHP	94%	7.4
5		CH_3	$CH_2OTBDMS$	95%	8.3
6	TMS	C_2H_5	$Si(CH_3)_2Ph$	86%	23.5
7		CH_3	$CH_2OTBDMS$	91%	9.1
8		C_2H_5		80%	5.2[b]
9		C_2H_5	CH_2OTHP	62%	6.8

a) Performed as described in eq. 4 unless otherwise noted. b) Performed with 10% $(PhSe)_2$ in benzene at room temperature for 48 h.

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6. This compound has been fully characterized spectroscopically and the elemental composition established by high resolution mass spectrometry or combustion analysis.
7. Trost, B.M.; McIntosh, M.C. *J. Am. Chem. Soc.* **1995**, *117*, 7255.
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9. Yaw, E.K.; Coward, K. *J. Org. Chem.* **1990**, *55*, 3147.