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A NOVEL CYCLOALKYLATION OF 1,6- AND 1,7-ENYNES WITH STABILIZED PRONUCLEOPHILES

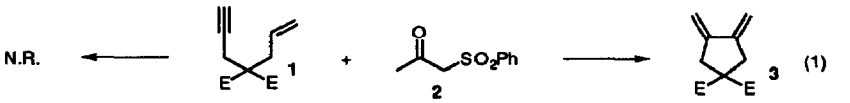
Barry M. Trost, Lin Zhi and Katsuharu Imi
Department of Chemistry
Stanford University
Stanford, CA 94305-5080

Summary. Formation of five and six membered rings simultaneously with addition of a functionalized side chain for further elaboration occurred upon exposing a 1:1 mixture of an enyne and a pronucleophile to a palladium catalyst derived from $Pd(OAc)_2$ and a bidentate ligand.

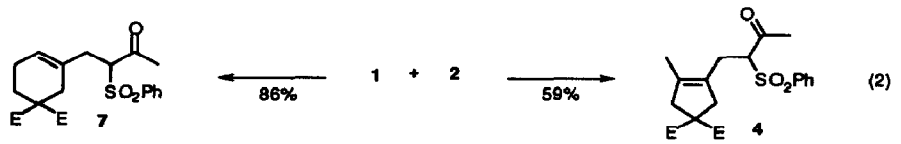
Increasing our repertoire of simple addition reactions is important in providing enhanced synthetic efficiency.[1] Our recent development of a palladium catalyzed addition of a pronucleophile to a diene[2-4] suggested that a direct cyclization-alkylation of α,ω-enynes may be possible (eq. 1). Several obstacles were apparent. The palladium catalyst for cycloisomerization of enynes to 1,3-dienes[5] requires palladium

carboxylates[6] (chloride ion inhibited the reaction!) which is quite different from the preferred source for the addition to dienes (π-allylpalladium chloride dimer.)[2] Furthermore, bidentate ligands, required for the latter reaction, appeared to shut down the former.[6a] In spite of these inconsistencies, we believe that enough opportunities to modify the catalyst existed so that we could find a good compromise catalyst. We wish to record our initial success in reaching this goal.

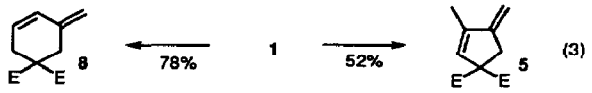
We chose as our model reaction the addition of enyne **1** to phenylsulfonyl-2-propanone (**2**). As summarized in eq.1, subjecting a 1:1 mixture in benzene to the standard conditions for the enyne cyclization [5% $Pd(OAc)_2$, 10% Ph_3P, THF][6a] gave only the 1,3-diene **3** in 71% yield; whereas, the standard conditions



for the addition of pronucleophiles to dienes [2.5% (π-allyl $PdCl)_2$, 5% dppp, PhH or THF][2] gave only recovered starting material. On the other hand, a mixed catalyst system [5% $Pd(OAc)_2$, 5% dppp, THF, 70°] gave the desired product **4**[7] in 50-59% yields (eq. 2). That the reaction likely proceeded through the

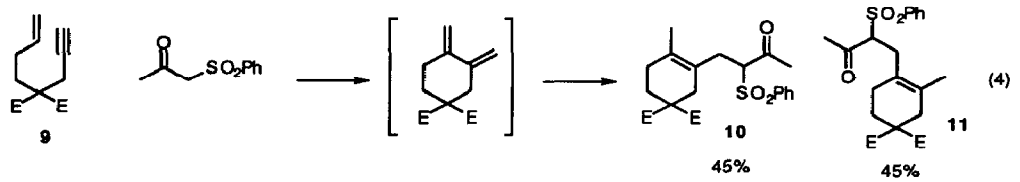


intermediacy of **3** was suggested by the conversion of the latter to the cycloalkylated product **4** under the same conditions. The key to the success of this reaction in light of our earlier observations on the role of bidentate ligands in the initial cycloisomerization was the ratio of ligand to palladium. Whereas, a 1:1 ratio allowed the reaction to proceed smoothly, increasing that ratio to 2:1 dramatically decelerated the reaction. In order to ascertain that cycloisomerization indeed proceeds under these conditions, the enyne **1** was exposed to the same reaction conditions in the absence of a pronucleophile. In this case, the cycloisomer **5**[7], presumably arising from isomerization of the thermodynamically less stable dimethylenecyclopentane **3** which should be the kinetic product, formed in good yields (eq. 3). Such isomerizations have been previously noted. The beneficial role of



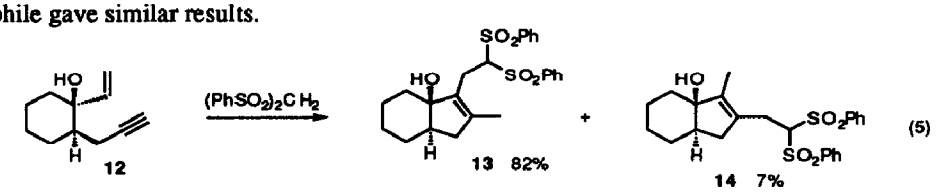
bis(di-2-methoxyphenylphosphino)propane (**6**)[8] as a ligand in additions of pronucleophiles to dienes led to its exploration in this reaction with startling results. Smooth cycloalkylation occurred but only 6% of the expected product **4** was detected. The major product, isolated in 86% yield, was the six membered ring **7**[7] (eq. 2). That the cycloisomerization indeed changed course by this ligand was demonstrated by subjecting enyne **1** to 5% $Pd(OAc)_2$ and 5% ligand **6** in THF at 60° whereby methylenecyclohexene formed in 78% yield (eq. 3). Resubjecting **8** to the reaction conditions in the presence of ligand **6** produced the cycloalkylated product **7**. Interestingly, the same reaction in the presence of dppp as ligand led only to recovered starting material!

Extension to formation of a six membered ring was explored with 1,7-enyne **9** [4% $Pd(OAc)_2$, 4% **6**, THF, 75°C]. Because of the unsymmetrical nature of the purported diene intermediate, alkylation produced a 1:1 mixture of the two cycloalkylated products **10**[7] and **11**[7].

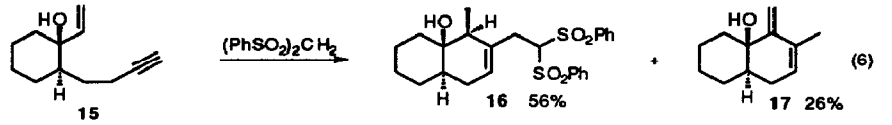


With bicyclic systems, good regioselectivity was observed with unsymmetrical substrates. Cycloalkylation of enyne **12** with bis(phenylsulfonyl)methane [5% $Pd(OAc)_2$, 5% dppp, THF, 70°] gave an

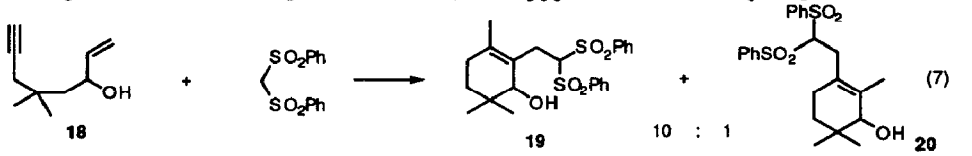
82% yield of bicycle **13**[7] with only 7% of its regioisomer **14**[7] (eq. 5). Use of phenylsulfonylpropan-2-one as the pronucleophile gave similar results.



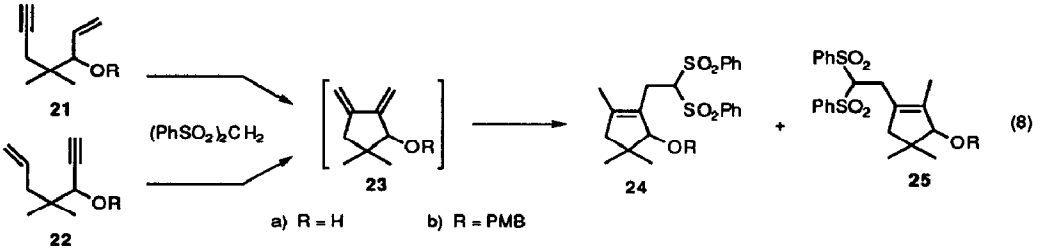
On the other hand, cycloalkylation of enyne **15** [8% $Pd(OAc)_2$, 8.8% **6**, THF, 65°] gave dramatically different results wherein the cycloalkylation product **16**[7] was isolated in 56% yield along with 26% of cyclized non-alkylated product **17**[7] (eq. 6). This product differs from that obtained in eq. 5 in both the position of the



double bond and the regioselectivity of the alkylation (distal to the hydroxyl group). That these two differences are related is suggested by the fact that cycloalkylation of all other substrates bearing an oxygen substituent normally alkylate proximal to that substituent (cf eq. 7). The proximal (**19**)[7] to distal (**20**)[7] cycloalkylation ratio is 10:1 in forming a six membered ring [4% $Pd(OAc)_2$, 4% dppp, THF, 65°, 29% yield].



Since these experiments raised questions regarding the mechanism of this reaction with substrates bearing allylic oxygen substituents, we examined the two regioisomeric enynes **21** and **22** which should yield the same product mixture if the reaction proceeds through diene **23** (eq. 8). Using the standard conditions with



dppp as ligand substrates, **21a** and **22a** gave a 2.3:1 ratio of the proximal (i.e., **24a**[7]) and distal (i.e., **25a**[7]) products.[9] Regiochemistry was readily established by Eu(+3) shift studies. For example, the vinyl methyl group of **24a** showed a $\Delta\delta$ of 9 Hz whereas that of **25a** showed a $\Delta\delta$ of 36 Hz in the presence of 10 mol% $Eu(thd)_3$. Synthetically, better yields and regioselectivity are obtained with the p-methoxybenzyl ether whereby

22b gave a 52% yield of **24b**[7] under identical conditions.

Thus, cycloalkylations of enynes with stabilized pronucleophiles provide opportunities to perform ring constructions simultaneously with regioselective elaboration of side chains functionalized to provide an opportunity for further structural elaboration. The major pathway appears to involve a two stage process whereby a palladium catalyst induces cycloisomerization of an enyne to a 1,3-diene followed by addition of the pronucleophile. A palladium hydride complex formed by deprotonation of the pronucleophile by a ligated Pd(0) may be the active species in both stages. Two variations stand out -- the divergence of the initial cyclization to a 6-endo product when the ligand is changed to bis-phosphine **6** (eq. 2) and of the regioselectivity in the alkylation in the case of a bicyclo [4.4.0] ring system (eq. 6). Since the speculative nature of any discussion of these "abnormal" products precludes treatment at this time, it appears that in both cases the products derive from a thermodynamically more stable π-allylpalladium intermediate. Thus, the role of ligand **6** in both cases appears to be to promote equilibration of the organopalladium intermediates -- a suggestion that merits further investigation. The fact that this structural elaboration arises by a simple addition of the two building blocks imparts particular efficiency to this strategy.

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7. This compound has been characterized spectroscopically and elemental composition established by combustion analysis and/or high resolution mass spectrometry.
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9. In this reaction, **23a** was isolated in 33% yield in addition to a 28% yield of **24a** and 12% yield of **25a**.

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