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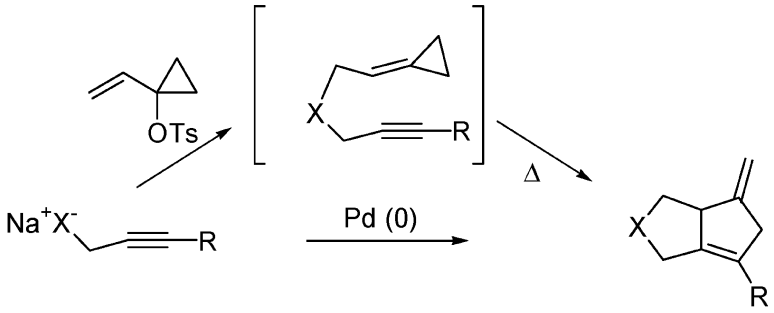

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Palladium-Catalyzed [3+2] Intramolecular Cycloaddition of Alk-5-ynylidenecyclopropanes: A Rapid, Practical Approach to Bicyclo[3.3.0]octenes

Alejandro Delgado, J. Ramón Rodríguez, Luis Castedo, and José L. Mascareñas*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Universidad de Santiago de Compostela, 15782, Santiago de Compostela, Spain

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The prominent occurrence of polycyclic natural products containing cyclopentanoid rings continues to encourage the development of new strategies for their rapid and efficient synthesis.[1] Among the different approaches described, the intramolecular cycloaddition of methylenecyclopropanes (MCPs) to alkenes or alkynes is particularly attractive.[2−4] It has been shown that palladium complexes can catalyze the intramolecular cycloaddition of alkyne-tethered MCPs such as **1** to give cyclopentene derivatives such as **2**.[3,4] Despite the relevance of the transformation, its synthetic utility is somewhat limited by the lack of general and practical routes to the precursors, and by the apparent restriction of its success to alkynes bearing electron-withdrawing substituents at the terminal position (Z = CO_2Me, COMe, CH_2OR).[3,4] The hypothesized mechanism of the reaction involves initial oxidative addition at the distal position of the cyclopropyl alkene to give palladacyclobutane **A** followed by carbometalation to **B** and final reductive elimination (path I, Scheme 1).[4b]

In view of regiochemical results obtained in previous intermolecular Ni-catalyzed reactions[5] and of recent mechanistic calculations on MCP-alkene cycloadditions,[6] we envisaged that alkylidenecyclopropanes such as **3** might also participate in a metal-catalyzed [3+2] cycloaddition process.[7] These achiral precursors (**3**) are particularly attractive because they should be easily assembled by palladium-catalyzed coupling of appropriate nucleophiles to a sulfonic ester derivative of 1-ethenylcyclopropanol.[8] The hypothetical reaction might be initiated by formation of the palladacycle **C**, which could evolve to **B** directly[6] or following rearrangement to **A** (path II).

The viability of the approach was tested on substrate **3a**,[9] which bears a silyloxymethyl group at the alkyne terminus, because this substituent performs very well with methylenecyclopropyl substrates of type **1**.[4b] Heating a toluene solution of **3a** with 6 mol % of $Pd_2(dba)_3$ and 20% of PPh_3 in toluene at 110 °C for 2 h did provide the desired cycloadduct **4a**, albeit in rather low yield (<30%).[10] Gratifyingly, the use of $P(O^iPr)_3$ as ligand instead of PPh_3 considerably increased the efficiency of the reaction, which now, after 1 h of refluxing in toluene, afforded an 86% isolated yield of the cycloadduct. A GC screening of the influence of different parameters on the progress of the reaction confirmed $P(O^iPr)_3$ as the best choice of ligand (Table 1). Lowering the temperature to 80 °C aborted the reaction in toluene, but not in dioxane (entry 7).[11] Performing the reaction in dioxane at 100 °C gave a 100% conversion (88% isolated yield) in 30 min (entry 8). Other phosphine-to-Pd ratios gave poorer results (entries 9−11), and the use of $Pd(PPh_3)_4$ (10 mol %) instead of $Pd_2(dba)_3$/L as catalyst led to 35% conversion after 2 h at 100 °C in dioxane. In the absence of catalyst, heating **3a** in dioxane at 100 °C for 48 h did not give any cycloadduct, and most of the starting material remained unaltered.

Scheme 1

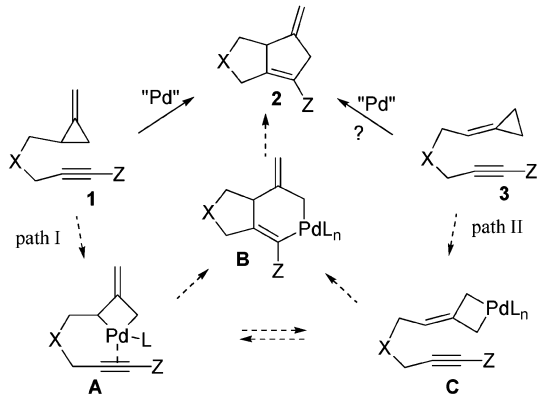
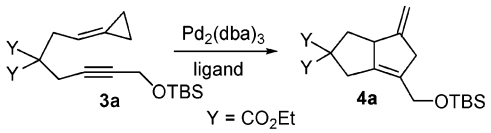


Table 1. Palladium-Catalyzed Cycloaddition of **3a**[a]



entry	solvent (T[a])	ligand (%)	time	conversion[b]
1	toluene (110 °C)	PPh_3 (20)	2 h	30%
2	toluene (110 °C)	$P(O^iPr)_3$ (20)	1 h	94%
3	toluene (110 °C)	$P(OEt)_3$ (20)	1 h	0%
4	toluene (110 °C)	$P(Bu)_3$ (20)	1 h	19%
5	toluene (110 °C)	dppe (20)	1 h	2%
6	toluene (80 °C)	$P(O^iPr)_3$ (20)	2 h	<5%
7	dioxane (80 °C)	$P(O^iPr)_3$ (20)	2.5 h	78%
8	dioxane (100 °C)	$P(O^iPr)_3$ (20)	0.5 h	100%
9	dioxane (100 °C)	$P(O^iPr)_3$ (0)	2 h	0%
10	dioxane (100 °C)	$P(O^iPr)_3$ (12)	1 h	73%
11	dioxane (100 °C)	$P(O^iPr)_3$ (48)	1 h	5%

[a] Reactions were carried out by adding the palladium catalyst (6 mol %) and the phosphine to a 0.05 M solution of **3a** in the solvent. [b] Calculated by GC, by considering the relative areas of the peaks corresponding to the starting material and the product. Significant amounts of other products were not detected in any experiment.

Having optimized the reaction conditions, we next investigated the effect of the substituent at the acetylenic carbon on the efficiency of the cycloaddition. To this end, we prepared substrates **3c**−**e** by Pd-catalyzed coupling of the diester sodium salts **6** to the cyclopropylvinyltosylate **5** (Scheme 2).[8] All of these reactions, which proceed via a Pd π-1,1-ethyleneallyl complex, took place rapidly and in good yield at room temperature.

As illustrated in Table 2, the cycloaddition of alkynes **3b**−**e** proceeded efficiently under the conditions optimized for **3a**. These results are in sharp contrast with those obtained with alkynylmethylenecyclopropanes **1**, which react very sluggishly when the

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Scheme 2

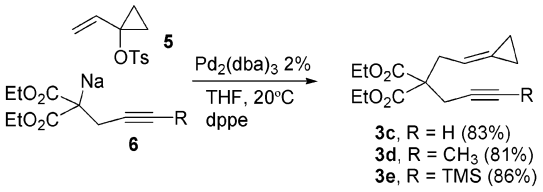
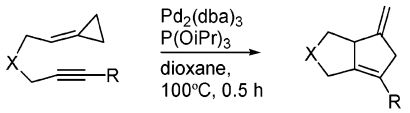


Table 2. Effect of the Alkyne Substituent on the Cycloaddition



entry	substrate	X	R	product	yield (%)[a]
1	**3a**	$C(CO_2Et)_2$	CH_2OTBS	**4a**	88%
2	**3b**	$C(CO_2Et)_2$	CH_2OH	**4b**	82%[b]
3	**3c**	$C(CO_2Et)_2$	H	**4c**	65%
4	**3d**	$C(CO_2Et)_2$	CH_3	**4d**	96%
5	**3e**	$C(CO_2Et)_2$	TMS	**4e**	95%[d]
6	**3f**[c]	$C(CO_2Et)_2$	CO_2Bn		
7	**7**[e]	O	CH_2OTBS	**8**	67%

[a] Isolated yield. [b] Yield of the reaction in toluene; in dioxane, the yield is lower (45%). [c] Obtained by carboxyalkylation of **3c** (see Supporting Information). [d] Using a 0.5 M concentration of **3e**, we obtained the product in 88% yield, which suggests that the cycloaddition is tolerant to higher substrate concentrations. [e] Obtained by Pd-catalyzed coupling of **5** with the corresponding alkoxide.

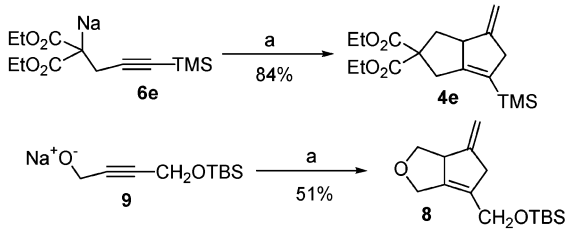
alkyne bears a TMS substituent[4b] and fail to give any cycloadduct when this substituent is methyl[4b] or hydrogen.[3b] Curiously, the presence of a strong electron-withdrawing group at the alkyne terminus is detrimental to the cycloaddition. For example, heating the ester **3f** under the usual conditions did not produce the expected adduct but a mixture of other products.[12] As shown in entry 7, the cycloaddition is also viable with oxygen tethered systems.

The fact that the cycloaddition reaction proceeds with unactivated alkynes and is relatively insensitive to the steric characteristics of the substituent on this group suggests that coordination of the alkyne to the metal is not rate-determining. This situation is consistent with the working mechanistic hypothesis shown in Scheme 1 (path II). The anomalous result obtained with **3f** can be explained by assuming that in this case the reaction proceeds through competitive secondary pathways, presumably opened by an initial alkene-alkyne cyclometalation.

Given that the preparation of the substrates and their cycloadditions are both carried out using the same Pd source, it was of interest to ascertain whether the two processes could be combined in a one-pot tandem sequence, using only temperature to control the reactivity. As hoped, we found that treatment at room temperature of a solution of **6e** (3 equiv) and **5** in dioxane with the catalytic mixture optimized for the cycloaddition afforded the coupling product **3e**, which then isomerized to the cycloadduct **4e** upon heating at 100 °C for 30 min (84% yield, Scheme 3). This tandem process can be extended to other nucleophiles, such as the alkoxide **9**. A significant increase in relevant molecular complexity can therefore be achieved in a single step from readily available and inexpensive precursors.

In summary, we have developed the first transition-metal-catalyzed intramolecular [3+2] alkylidenecyclopropane-alkyne cycloaddition. Patent advantages with respect to cycloaddition of the isomeric 2-alk-4-ynyl-1-methylenecyclopropanes are the greater simplicity and versatility of precursor preparation and the efficiency of the reaction with nonactivated alkynes. The feasibility of carrying out the precursor assembly and the cycloaddition in a tandem, one-step process provides one of the simplest, most practical approaches to bicyclo[3.3.0]octenes yet described. Work to further study the scope and limitations of the method and to elucidate mechanistic details is underway.

Scheme 3 [a]



[a] **5**, $Pd_2(dba)_3$ (8 mol%), $P(OiPr)_3$, (27 mol%), dioxane, 20 °C, 10 min, then 100 °C.

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Supporting Information Available: Experimental procedures, including the preparation of the cycloaddition precursors, and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) This compound was prepared by base-promoted coupling of the diethylester of 2-(2-cyclopropylideneethyl)malonic acid to a protected derivative of 4-tosyloxy-but-2-yn-1-ol (see Supporting Information).
(10) Because the chromatographic Rfs of **3a** and **4a** are very similar, the yield was estimated by integration of NMR signals of the mixture.
(11) Other solvents such as DMF or CH_3CN led to much lower yields.
(12) The alkynyl ester **3f** disappears rather rapidly even when the reaction is carried out at 50 °C, leading to products other than the expected cycloadduct, albeit they could not yet be identified.

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