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Palladium-Catalyzed [3 + 2] Intramolecular Cycloaddition of Alk-5-enylidenecyclopropanes

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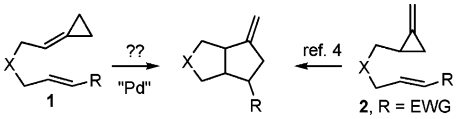
Small, strained cyclic systems that are capable of undergoing metal-triggered ring-opening processes are attractive fragments for use in metal-catalyzed cycloadditions. In particular, alkylidenecyclopropanes (ACPs) have been shown to participate as three-carbon components in several intermolecular palladium- or nickel-catalyzed [3 + 2] cycloadditions to unsaturated bonds.[1] We recently demonstrated that alk-5-ynylidenecyclopropanes undergo a mild intramolecular [3 + 2] cycloaddition under palladium catalysis to give interesting bicyclo[3.3.0]octenes.[2] A challenging and mechanistically interesting extension of this research concerns the feasibility of using alkenes as two-carbon components in the cycloaddition, a process that could generate bicyclic systems containing up to three stereogenic centers (Scheme 1). To the best of our knowledge, this type of annulation has not been previously examined—except for an isolated study published in 1989, which described how the cycloaddition can be achieved with peculiar cyclooctanic substrates bearing exocyclopropylidene and methylene units at relative positions 1 and 5, but fails with more common precursors, such as (*E*)-ethyl-7-cyclopropylidene-5,5-dimethylhept-2-enoate.[3] Studies by Motherwell and by Lautens indicate that isomeric methylenecyclopropane precursors of type **2** undergo the cycloaddition, although its success is restricted to activated alkenes (conjugated to EWG groups) and is fairly dependent on the substrate structure and reaction conditions.[4]

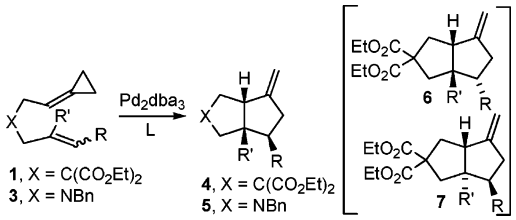
Scheme 1



Herein we demonstrate that alk-5-enylidenecyclopropanes of type **1**, which can be readily assembled from allylcyclopropyltosylate,[5] do undergo a mild and stereoselective [3 + 2] intramolecular cycloaddition upon treatment with appropriate palladium catalysts. We also present a putative mechanistic scenario formulated on the basis of preliminary theoretical studies carried out on a model system.

The viability of the reaction was first tested on substrate **1a**,[6] which bears a conjugated ester group at the *trans*-terminal position of the alkene. When a solution of (*E*)-**1a** with 6 mol % of $Pd_2(dba)_3$ and 20% of $P(O^iPr)_3$ was heated in refluxing dioxane for 6 h, the desired [3 + 2] cycloadduct (**4a**) was obtained in 74% yield. The stereochemistry of the adduct was assigned on the basis of NOE experiments as well as by analysis of NMR spectra (including NOEs) of the product resulting from acid-induced isomerization[7] and of the ketone resulting from ozonolysis of the exomethylene moiety (see the Supporting Information). The formation of the *cis*-fused stereoisomer is consistent with the results observed in previous related cycloadditions of Pd−trimethylenemethane (Pd−TMM) species generated from bifunctional conjuctive reagents.[7,8] The cycloaddition can be achieved using other ligands, with tris(2,4-di-*tert*-butylphenyl)phosphite (**8**) being particularly efficient and with PPh_3 or $P(OPh)_3$ significantly less productive.

Table 1. Palladium-Catalyzed Cycloaddition[a]



entry	1	R	R′	L	product	yield
1	(*E*)-**1a**	CO_2Et (*E*)	H	$P(O^iPr)_3$	**4a**	74%
2	(*E*)-**1a**	CO_2Et (*E*)	H	PPh_3	**4a**	30%
3	(*E*)-**1a**	CO_2Et (*E*)	H	$P(OPh)_3$	**4a**	25%
4	(*E*)-**1a**	CO_2Et (*E*)	H	**8**[b]	**4a**	82%
5	(*Z*)-**1a**	CO_2Et (*Z*)	H	$P(O^iPr)_3$	**4a**	72%
6	(*Z*)-**1a**	CO_2Et (*Z*)	H	**8**[b]	**6a**+**7a**[d]	87% (5.3:1)
7	(*Z*)-**1b**	COMe (*Z*)	H	$P(O^iPr)_3$	**4b**	78%
8	**1c**[c]	CN	H	$P(O^iPr)_3$	**1c**	
9	**1c**[c]	CN	H	**8**[b]	**4c**+**6c**	96% (3.5:1)
10	(*Z*)-**1d**	CO_2Et (*Z*)	Me	$P(O^iPr)_3$	**4d**+**6d**	83% (5:1)
11	**1e**	H	H	$P(OiPr)_3$	*e*	
12	**1e**	H	H	**8**[b]	**4e**+**7e**	83% (1:1.6)
13	(*E*)-**1f**	Ph	H	**8**[b]	**4f**	70%
14	**3e**	H	H	**8**[b]	**5e**	82%
15	(*E*)-**3g**[f]	CH_3	H	**8**[b]	**5**g	57%

[a] Reactions were carried out in refluxing dioxane (50 mM), using $Pd_2(dba)_3$ (6%) and L (20%). [b] Tris(2,4-di-*tert*-butylphenyl)phosphite (**8**). [c] Substrate prepared as a ~3.5:1 mixture of *E*:*Z* stereoisomers. [d] These compounds can be readily separated by chromatography. [e] This reaction leads to cycloisomerization products, but cycloadducts were not observed. [f] This substrate contains a small amount (<10%) of the *Z*-isomer.

Remarkably, when the *cis*-alkene (*Z*)-**1a** was subjected to the reaction conditions, we obtained the same diastereoisomeric product as formed from the *trans* isomer.[9] When the reaction was run to partial conversion, the recovered starting material maintained the original alkene stereochemistry. This provides firm evidence that isomer **6a** does not epimerize to **4a** under the reaction conditions, meaning that the stereochemistry of the product must be a reflection of the reaction mechanism. The epimeric product **6a** was surprisingly obtained as the major product when the reaction of (*Z*)-**1a** was carried out in the presence of the bulky phosphite **8** rather than $P(OiPr)_3$ (entry 6, Table 1).

The behavior of ketone **1b** is similar to that of the ester. However, nitrile **1c** is reluctant to react under standard conditions,[10] but does react if **8** is used as ligand (entry 9). The cycloaddition is also feasible with substrate **1d**, in which the alkene bears a β-methyl substituent, leading to a relevant bicyclic skeleton with a quaternary methyl group at the fusion position.

Not unexpectedly, substrate **1e**, in which the alkene is not activated, failed to undergo the cycloaddition under standard

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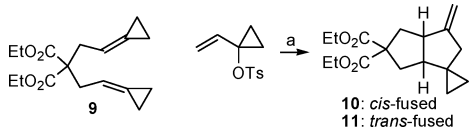
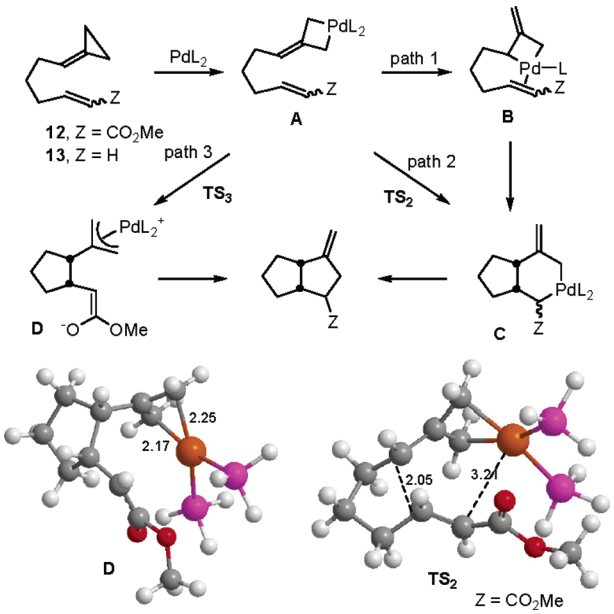
Scheme 2. Tandem Coupling Cycloaddition



[a] Conditions: (a) $Na^+CH(CO_2Et)_2^-$, Pd_2dba_3, $P(O^iPr)_3$, dioxane, rt to reflux.

Scheme 3. Plausible Cycloaddition Mechanisms and Calculated Structures of **D** and **TS$_2$**



conditions ($Pd/P(OiPr)_3$), but it does react in the presence of the bulky phosphite **8** (entry 12), as does the phenyl-substituted alkene **1f** (entry 13). Substrate **3e**, which bears a nitrogen atom instead of the geminal diester in the tether, cyclizes to give **5e** as the only product (entry 14). Quite remarkably, the cycloaddition also occurs with the methyl-substituted derivative **3g** (entry 15), although this reaction produces dienyl cycloisomerization side products (~25% yield). It is noteworthy that using as ligand the bulky phosphite **8** the cycloaddition of all substrates can be carried out with similar efficiency using only 2−3% of the Pd source.

Dicyclopropylidene derivative **9**, in which the alkene is activated by strain, undergoes an efficient cycloaddition even in the presence of the standard ligand ($P(OiPr)_3$) to produce a mixture of *cis*- and *trans*-fused cycloadducts (**10**:**11**, approximately 1:0.8). Interestingly, the cycloaddition of **9** can be combined with its assembly, meaning that the whole process (coupling and cycloaddition) can be achieved from diethyl malonate in a straightforward, one-step procedure (79% yield, Scheme 2).

The cycloaddition mechanism may involve initial insertion of the metal at the distal position of the cyclopropane to give palladacyclobutane **A**, followed by isomerization to **B** through a TMM-like transition state and carbometalation to **C**. Reductive elimination of **C** provides the final adduct (path 1, Scheme 3). However, preliminary DFT calculations on the model system **12**, using PH_3 as the ligand (L), suggest alternative and even less costly pathways that consist of either a concerted pallada-ene reaction from **A** to **C** (path 2) or a stepwise process involving the zwitterionic intermediate **D** (path 3).[11] This latter pathway, which recalls that proposed for the cycloadditions of TMM−Pd species derived from bifunctional reagents,[8] is particularly relevant in terms of explaining the lack of stereospecificity observed in the cycloaddition of (*Z*)-**1a** (entry 5, Table 1). In the case of unsubstituted alkenes (model **13**), the zwitterionic path can be discarded, and the reaction must proceed either via path 1 or 2 (see theoretical data in the Supporting Information).

In conclusion, we have described the first examples of a metal-catalyzed intramolecular cycloaddition of alk-5-enylidenecyclopropanes. Theoretical evidence has unveiled new, previously unsuspected mechanistic pathways based on a metalla-ene rearrangement or a stepwise process involving a zwitterionic intermediate. The reaction is highly diastereoselective and—given the ease of assembling the required precursors—offers a particularly rapid and practical entry to bicyclo[3.3.0]octane systems containing three stereocenters.

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Supporting Information Available: Experimental and computational details, including characterization data for new compounds, and reaction coordinates for paths 1, 2, and 3, as well as Cartesian coordinates of calculated structures. This material is available free of charge via the Internet http://pubs.acs.org.

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(6) The synthesis of substrates **1**, described in the Supporting Information, was accomplished by Pd-catalyzed alkylation of allylcyclopropyltosylate with the sodium salt of diethyl malonate, followed by alkylation with appropriate allylic bromides.

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(9) Partial loss of stereospecificity has previously been observed in cycloadditions between activated *cis*-alkenes and Pd−TMM species generated from bifunctional reagents: Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315−2325. See also ref 4b.

(10) The lack of reactivity seems to be associated with the substrate structure rather than to the presence of a CN group because the cycloaddition of **1a** is inhibited by the presence of 1 equiv of **1c** but not by the addition of excess of valeronitrile.

(11) The calculations were carried out with the Gaussian 98 set of programs using the B3LYP hybrid functional to perform vibrational analysis, characterize stationary points, and determine zero-point energies (ZPE). Whereas the transition state corresponding to the carbometalation step in path 1 for model system **12** is 28.7 kcal/mol above palladacyclobutane **A**, **TS2** for the *E*-alkene is only 16.4 kcal/mol higher in energy than **A**. On the other hand, the activation energy required to convert **A** (with a *Z*-alkene geometry) into **D** through **TS3** is 14.5 kcal/mol. Further computational details are described in the Supporting Information, and full details will be reported in due course.

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