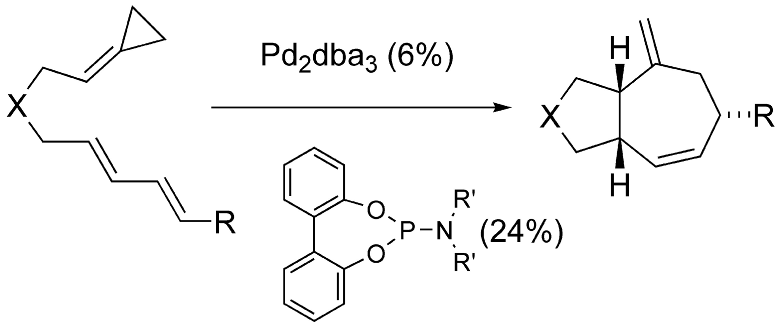
Communication

Palladium-Catalyzed [4 + 3] Intramolecular Cycloaddition of Alkylidenecyclopropanes and Dienes

Moiss Gulas, Juan Durn, Fernando Lpez, Luis Castedo, and Jose L. Mascareas

J. Am. Chem. Soc., **2007**, 129 (36), 11026-11027• DOI: 10.1021/ja0756467 • Publication Date (Web): 21 August 2007



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Palladium-Catalyzed [4 + 3] Intramolecular Cycloaddition of Alkylidenecyclopropanes and Dienes

Moisés Gulías, Juan Durán, Fernando López, Luis Castedo, and Jose L. Mascareñas*

*Departamento de Química Orgánica, Universidad de Santiago de Compostela,
15782 Santiago de Compostela, Spain*

Received July 28, 2007; E-mail: qojoselm@usc.es

Transition-metal-catalyzed cycloadditions are among the most practical and efficient methods to construct cyclic products from relatively simple, acyclic starting materials.[1,2] We recently reported that readily accessible alkynylidenecyclopropanes, as well as related alkenylidene derivatives of type **1a**, undergo efficient [3 + 2] intramolecular cycloadditions under appropriate Pd catalysis.[3] The reaction probably involves the formation of a palladacyclohexane intermediate **2a**, which yields the final carbocyclic product by reductive elimination. We envisaged that the presence of a conjugated diene instead of an alkene in the precursor, as in **1b**, might enable the formation of a seven-membered cycloadduct by way of a π-allylic rearrangement of **2b** to palladacyclooctane **3** (Scheme 1). Overall, the process would constitute a new type of [4C + 3C] cycloaddition reaction.[4]

Herein we report several examples that demonstrate the feasibility of the approach. Previous reports on metal-catalyzed [4C + 3C] cycloadditions are essentially limited to those published by Trost in the 1980s, on the intermolecular addition of 2-(trimethylsilylmethyl)-3-acetoxy-1-propene to activated dienes.[5] However, the success of these cycloadditions is restricted to dienes blocked in a cisoid conformation and activated by the presence of electron-withdrawing substituents.

The annelation was first examined on substrate **4a**,[6] in which the diene is activated by the presence of an ester substituent at the terminal double bond. Treatment of precursor **4a** with 10 mol % of Pd_2dba_3 and 40 mol % of $P(O^iPr)_3$ in refluxing dioxane (6 h) led to the desired 5,7-bicarbocyclic product as a single diastereoisomer (**5a**, 37%), together with the five-membered adduct **6a** (24%). The selectivity of the reaction (seven- versus five-membered adduct) seems to be highly influenced by the nature of the ligand; for example, the use of P(*o*-tolyl)$_3$ favored the formation of the [4 + 3] adduct (entry 2, Table 1), which was isolated in 43% yield, while the use of (2-biphenyl)dicyclohexylphosphine (**L1**) led to a reversal in the selectivity, with the five-membered adduct becoming predominant (entry 3). Phosphite **L2**, which has been shown to accelerate the cycloaddition of alkylidenecyclopropanes to alkynes,[3b] led to a significant increase in the reaction rate and provided the seven-membered adduct as the major product. In the presence of this ligand, the reaction can be accomplished using lower catalyst loadings (entry 4). The use as ligand of phosphoramidite **L3** resulted in a further increase in the yield of the desired seven-membered adduct (entry 5).[7] Interestingly, the reaction also took place in presence of chiral ligand **L4**, providing the cycloadduct **5a** in 73% isolated yield and 47% ee.[8] This result represents the first example of an enantioselective transition metal-catalyzed [4C + 3C] cycloaddition. The high diastereoselectivity of the cycloaddition process, which generates three stereocenters in a completely diastereoselective manner, should be noted.[9]

Scheme 1. Mechanistic Basis for a [4C + 3C] Cycloaddition of Dienylidenecyclopropanes

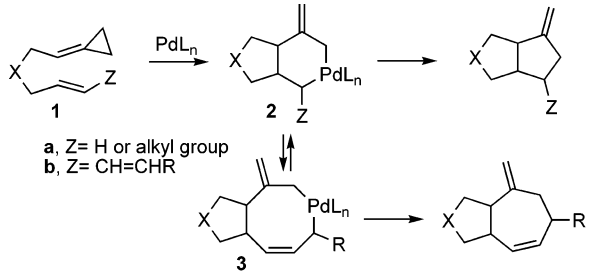
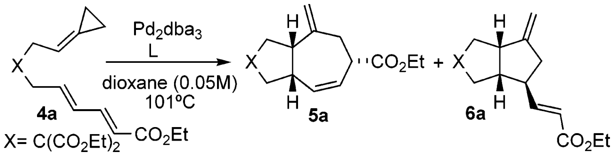
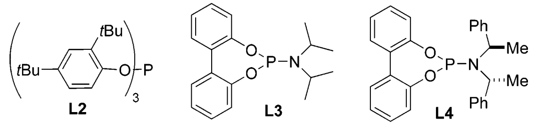


Table 1. Effect of Different Ligands on the Cycloaddition of **4a**



entry	Pd_2dba_3	L (mol %)	time (h)	**5a** (%)[a]	**6a** (%)[a]
1	10%	$P(O^iPr)_3$ (40)	6	37	24
2	10%	P(*o*-tolyl)$_3$ (40)	6	43	13
3	10%	**L1** (40)[b]	6	10	47
4	1%	**L2** (2.5)	3	51	25
5	6%	**L3** (24)	3	65	8
6	6%	**L4** (24)	2	73	7

[a] Isolated yields. [b] **L1**: (2-Biphenyl)dicyclohexylphosphine.

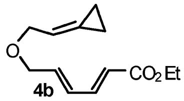
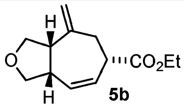
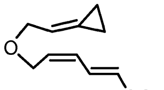
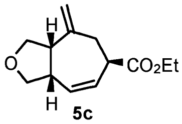
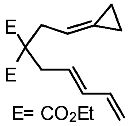
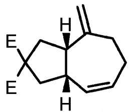
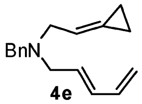
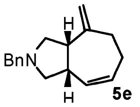
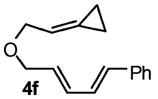
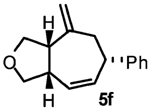
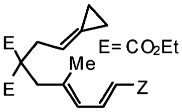
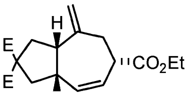
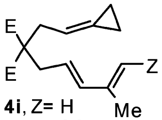
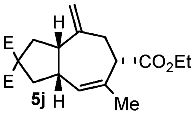


We next explored the reactivity of other substrates.[6] The ether derivative **4b**, which lacks the geminal diester group present in **4a**, generated the desired 5,7-cycloadduct **5b** as a single diastereoisomer (Table 2, entry 1). With the chiral ligand **L4** (conditions B), **5b** was obtained in slightly better yield and 45% ee. Substrate **4c**, which is isomeric to **4b** in the stereochemistry of the internal double bond of the diene, also underwent the cycloaddition, although this led to a poorer selectivity of the seven- over the five-membered cycloadduct (entry 2). The use of ligand **L4** instead of **L3** produced a marked increase in the cycloaddition yield. The observation that the resulting cycloadduct (**5c**) is epimeric to that obtained from **4b** is consistent with a concerted cycloaddition mechanism involving the formation of a palladacyclooctane intermediate of type **3** (Scheme 1).[10]

Remarkably, nonactivated dienylidenecyclopropanes **4d** and **4e** also underwent the cycloaddition reaction when heated in dioxane in the presence of the standard catalytic complex (Pd_2dba_3, **L3**). The selectivity ratio (seven- versus five-membered ring) was better using ligand **L4** (conditions B). The terminally phenyl-substituted

10.1021/ja0756467 CCC: $37.00 © 2007 American Chemical Society

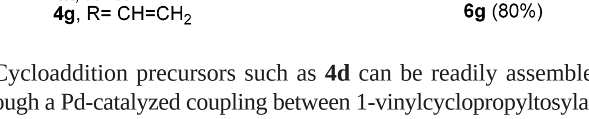
Table 2. Palladium-Catalyzed [4 + 3] Cycloaddition

entry	substrate	[4+3] cycloadduct	5/6 ratio[a]	yield of 5[d]
1	 **4b**	 **5b**	A:[b] 10:1 B:[c] 10:1	70%[e] 74%[e]
2	 **4c**	 **5c**	A: 1.4:1 B: 2.1:1	32% 56%
3	 E= CO2Et **4d**	 **5d**	A: 2.8:1 B: 15:1	37% 58%
4	 **4e**	 **5e**	A: 1.6:1 B: 4:1	38% 60%
5	 **4f**	 **5f**	A: >8:1	40%
6	 **4g**, Z= H **4h**, Z= CO2Et	 **5h**	A: 3.3:1 B: 3.5:1	56% 59%
7	 **4i**, Z= H **4j**, Z= CO2Et	 **5j**	B: 4:1	61%[e]

[a] Ratio of 5,7- and 5,5-cycloadducts determined by NMR and/or GC of crude reaction mixtures. The 5,5-cycloadducts are obtained as single diastereoisomers. [b] Conditions A: dioxane, 101 °C (50 mM), for 2−3 h, using 6% of Pd_2dba_3 and 24% of phosphoramidite **L3**. [c] Conditions B: **L4** used as the ligand. [d] Isolated yields. [e] The yield refers to the **5**/**6** mixture of cycloadducts, as **6** could not be removed by chromatography.

substrate **4f** also underwent the cycloaddition providing the adduct **5f** in 40% isolated yield.

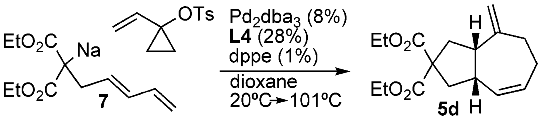
Nonactivated, methyl-substituted substrates **4g** and **4i** failed to undergo the cycloaddition reaction, providing a relatively complex mixture of products. However, their [4 + 3] cycloaddition reactivity can be recovered upon activation with an ester substituent (substrates **4h** and **4j**). Using conditions B, **5h** was obtained in 64% ee and 59% yield.[11] Interestingly, substrate **4g** underwent a clean and stereoselective [3 + 2] cycloaddition when the reaction was carried out in presence of phosphite **L2** (eq 1). This result is remarkable as the homologous enylidenecyclopropane **4k** provides mixtures of products when heated under the same conditions.[12] Isomer **4i** also experienced an efficient and diastereoselective [3 + 2] process (see the Supporting Information).



4k, R= H
4g, R= CH=CH2
6g (80%)

Cycloaddition precursors such as **4d** can be readily assembled through a Pd-catalyzed coupling between 1-vinylcyclopropyltosylate and the sodium salt of diethyl 2-[(*E*)-penta-2,4-dienyl]malonate.

Scheme 2. Tandem, One-Pot Process



7
5d

We thus investigated whether this reaction can be combined with the cycloaddition so that both processes can be carried out in a one-pot process (Scheme 2). Indeed, treatment of sodium carbanion **7** with such a tosylate in presence of Pd_2dba_3, **L4**, and dppe gave the bicyclic adduct **5d** (56% yield).

In summary, we have unveiled a new type of metal-catalyzed cycloaddition that allows the synthesis of appealing, stereochemically rich 5,7-fused bicyclic systems from readily accessible dienylidenecyclopropanes.[13] To the best of our knowledge, this work represents the first report on a metal-catalyzed [4 + 3] intramolecular cycloaddition reaction and provides the first examples of an enantioselective variant. Further studies to broaden the scope and chemoselectivity of the method and to develop efficient asymmetric versions are underway.

Acknowledgment. This work was supported by the Spanish MEC (SAF2004-01044) and Consolider Ingenio 2010 (CSD2007-00006), and the Xunta de Galicia (GRC2006/132). M.G. and J.D. thank the Xunta de Galicia and MEC for predoctoral fellowships. F.L. thanks the Spanish MEC for a Ramón y Cajal contract. We also thank Johnson-Matthey for the gift of Pd_2dba_3.

Note Added after ASAP Publication. After this paper was published ASAP on August 21, 2007, an error was corrected in the last sentence of the fifth paragraph (the correct substrate is **4f**). The corrected version was published ASAP on August 22, 2007.

Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet http://pubs.acs.org.

References

(1) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92.

(2) For recent work, see: (a) Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 5354−5355. (b) Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 6530−6531.

(3) (a) Delgado, A.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9282−9283. (b) Durán, J.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2005**, *7*, 5693−5696. (c) Gulías, M.; García, R.; Delgado, A.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 384−385.

(4) An intermolecular Pd-catalyzed [4 + 3] cycloaddition of methylenecyclopropane and dimethyl muconate is cited as unpublished results in the review: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77−152. For a recent report on Ni-promoted reactions of ethylcyclopropylidene acetate, see: (b) Saito, S.; Takeuchi, K. *Tetrahedron Lett.* **2007**, *48*, 595−598.

(5) (a) Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483−3484. (b) Trost, B. M. *Pure Appl. Chem.* **1988**, *60*, 1615−1626.

(6) For the synthesis of the precursors, see the Supporting Information.

(7) The reaction can be carried out with 4% of the Pd source and 13% of ligand with similar efficiencies, but use of lower loadings leads to a slower reaction and poorer conversions.

(8) The enantiomeric excess was determined by HPLC, on the α,β-unsaturated ester isomer (see the Supporting Information).

(9) The assignment of the structure and stereochemistry of the cycloadducts is discussed in the Supporting Information.

(10) An alternative stepwise process involving zwitterionic intermediates similar to those proposed for the reactions from the Pd-TMM complexes (see ref 4) is less consistent with the observed stereospecificity.

(11) This type of methylated bicyclic frames is an important structural motif in a large variety of natural products: (a) Rigby, J. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers B. V.: Amsterdam, 1988; Vol. 12, p 233. (b) Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, *2*, 2323−2326.

(12) A related beneficial effect of the conjugated double bond has been observed on a Rh-catalyzed Pauson−Khand processes: Wender, P. A.; Deschamps, N. M.; Gamber, G. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1853−1857.

(13) For the synthesis of related compounds by cycloaddition methods, see: (a) Wender, P. A.; Glorius, F.; Husfed, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348−5349. (b) Giguere, R. J.; TAssely, S. M.; Rose, M. I. *Tetrahedron Lett.* **1990**, *31*, 4577−4580.

JA0756467