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LETTERS

Palladium-Catalyzed Bisdiene Carbocyclizations: Cycloisomerizations of Bisdienes Bearing an Ester Substituent

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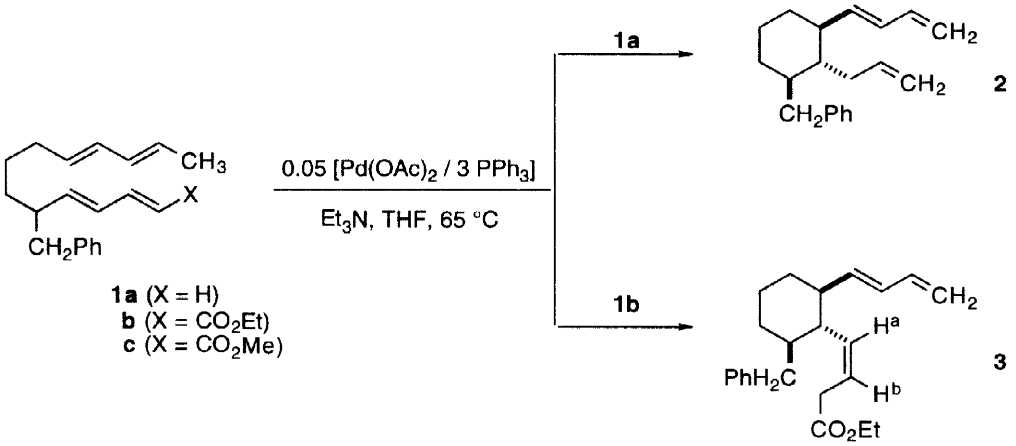
Summary: Bisdienes bearing a terminal ester substituent undergo facile diastereoselective palladium-catalyzed cycloisomerization to afford cyclized enediene products bearing a β,γ-unsaturated ester side chain.

Transition metal catalyzed cyclization reactions have defined a number of new strategies for assembling structurally complex ring systems. Those cyclizations that proceed catalytic in metal are particularly noteworthy and may contribute toward meeting the need for environmentally benign chemical synthesis strategies for pharmaceutical and/or agrochemical products. Palladium catalysis is playing a significant role in this area, and a number of efficient and stereoselective palladium-mediated carbocyclization strategies are under development in laboratories around the world.[1-6]

We have been interested in the cyclization-trapping and cycloisomerization reactions of bisdiene substrates.[7-14] In this regard, we recently reported a novel palladium-catalyzed cycloisomerization of unsymmetric alkyl-substituted bisdienes to cyclized enedienes.[15] For example, bisdiene **1a** (X = H) undergoes palladium-catalyzed cyclization to afford enediene **2**. This transformation is of particular interest to us, since it defines a bond construction that is not readily accessible by classical methods. In addition, the regio- and stereoselectivity of the reaction is quite remarkable, particularly in light of the large number of potential cyclization pathways available to substrates in which the two 1,3-diene subunits are substituted differently. We now report that related bisdienes bearing an ester substituent (e.g., **1b** (X = CO_2Et)) undergo facile cycloisomerization via a complementary reaction pathway. In some cases, two alternative complementary pathways have been observed depending on the reaction conditions.[16]



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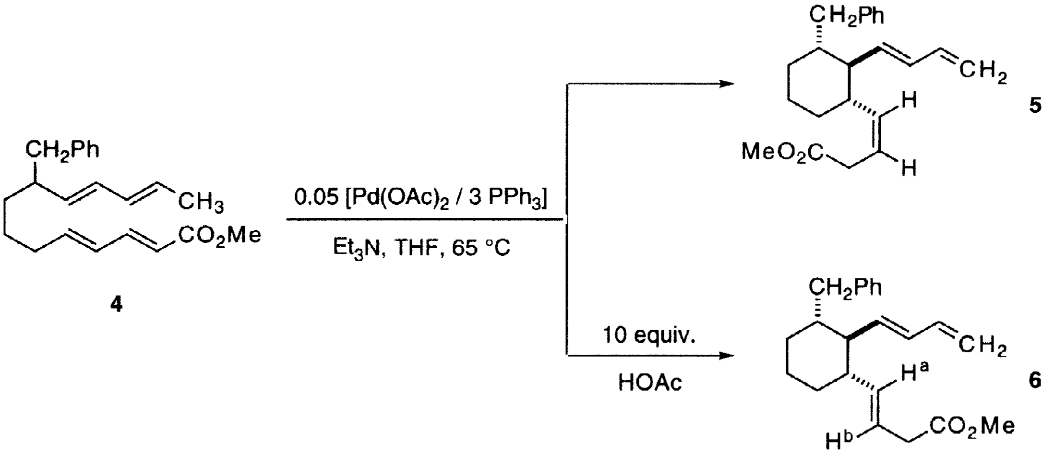
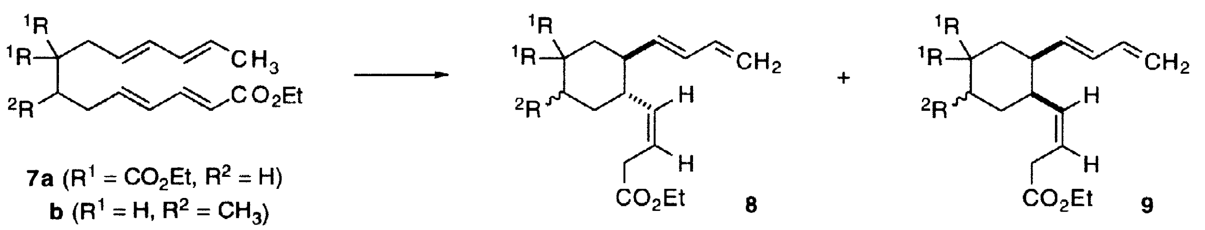
Bisdiene **1b** was prepared via standard methods. Palladium-catalyzed cyclization (0.05 equiv. $[Pd(OAc)_2$ / 3 $PPh_3]$, 5 equiv. Et_3N, THF, 65 °C, 12 h) affords product **3** in high yield (>90 %) and good diastereomeric purity (>90 %).[17] As in the case of **2**, the trisubstituted cyclohexane core within product **3** possesses predominantly the trans,trans relationship, and the butadiene side chain is formed with the E geometry. The difference between **2** and **3** lies in the presence of the β,γ-unsaturated ester moiety in **3**, which is formed selectively with the Z-double bond. Formation of the deconjugated ester is somewhat reminiscent of the kinetic protonation of an extended enolate. Brun and co-workers reported that the palladium-catalyzed reaction of methyl 2,4-pentadienoate affords the tail-to-tail dimer as a mixture of α,β- and β,γ-unsaturated isomers.[18] The Z double bond geometry is assigned on the basis of an 11 Hz $J_{a,b}$ coupling constant and a 9.4 % nOe observed between the cis hydrogens.[19] Formation of the Z double bond geometry is consistent with the catalytic cycle we previously proposed for the cyclization of **1a** to **2**.[15]

Having found the facile cyclization and good levels of stereoinduction with the benzyl-substituted bisdiene **1b**, we next examined the reaction of bisdiene **4**. Bisdiene **4** bears a complementary substitution pattern; that is, the benzyl substituent resides adjacent to the methyl bearing 1,3-diene moiety. Bisdiene **4** also cyclizes smoothly under the conditions employed for **1b** and affords compound **5** in high yield (95 %) and good diastereoselectivity (>90 % diastereomeric purity).



We had previously found that alcohol and alcohol-THF solvent mixtures are particularly good reaction media for carrying out the palladium-catalyzed cycloisomerizations of bisdienes analogous to **1a**.[15] We were therefore surprised to find that a rather severe mixture of diastereomers is formed when the cyclization of **4** is carried out in a methanol-THF solvent mixture. Since methanol obviously dramatically changes the diastereoselectivity, we decided to add a stronger protic acid, acetic acid, to the reaction mixture. Under conditions otherwise identical to those that led to the formation of the (*Z*) β,γ-unsaturated ester **5**, except for the addition of 10 equivalents of acetic acid (i.e., 0.05 equiv. $[Pd(OAc)_2$ / 3 $PPh_3]$, 5 equiv. Et_3N, 10 equiv. HOAc, THF, 65 °C, 12 h), bisdiene **4** affords the (*E*) β,γ-unsaturated ester **6** in high yield (93 % yield) and good selectivity (>90 % diastereomeric purity).[20] The reason for the change in double geometry is not clear at this point in our investigations. Furthermore, bisdiene **1c** (X = CO_2Me) does not exhibit the corresponding reversal of double bond geometry in the presence of acetic acid. Nonetheless, the ability to selectively form either **5** or **6** extends the potential utility of this cyclization, and may ultimately offer insight into the mechanistic pathway(s) available to this class of palladium-catalyzed reactions.

The achiral parent bisdiene **7a** also undergoes facile palladium-catalyzed cyclization (0.05 equiv. [Pd(OAc)$_2$ / 2 PPh$_3$], 5 equiv. Et$_3$N, THF, 65 °C, 12 h, 87 %). The product consists of a 5:1 mixture of trans and cis substituted cyclohexanes (i.e., **8a** and **9a**), and it seems likely that the cis substituted products may account for the minor diastereomers found in the cyclizations discussed above. The trans:cis product ratio is somewhat sensitive to the choice of ligand and catalyst precursor. For example, it can be improved to about 8:1 by substituting tri(o-tolyl)phosphine for triphenylphosphine. Palladium-catalyzed cyclization of bisdiene **7b** proceeds smoothly (0.05 equiv. [Pd(OAc)$_2$ / 2 PPh$_3$], 5 equiv. Et$_3$N, THF, 65 °C, 12 h, 93 %), but affords a relatively complicated mixture of diastereomers. We are not able to unambiguously assign each of the products, but hydrogenation affords a 64:13:3:2 mixture of products as discerned by capillary GC analysis. This ratio suggests that cyclization proceeds with both incomplete simple diastereoselection and incomplete stereoinduction; that is, **8b** and **9b** are each formed as a mixture of epimers at the methyl bearing stereocenter.

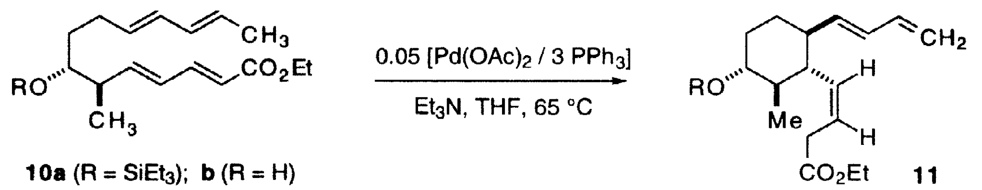


7a (R^1 = CO$_2$Et, R^2 = H)
b (R^1 = H, R^2 = CH$_3$)

8

9

The silyl ether **10a** cyclizes under the conditions described below to afford **11a** in 88 % yield as a 4:1 mixture of diastereomers.[21] In contrast, the corresponding alcohol **10b** cyclizes only slowly in THF (27 % yield after 14 h at reflux). Cyclization proceeds better in refluxing isopropanol, but still fails to go to completion under the conditions employed (14 h at reflux). **11b** is isolated in 67 % yield (4:1 mixture of diastereomers[21]), and 23 % of the starting bisdiene is recovered.



10a (R = SiEt$_3$); **b** (R = H)

11

In summary, bisdienes bearing an ester substituent undergo facile palladium-catalyzed cycloisomerization via a pathway that complements that found for substrates without the ester substituent and defines a new bond construction that is inaccessible by classical methods. The cyclization proceeds with good-to-excellent levels of stereoinduction relative to a resident asymmetric center in the bisdiene substrate. In one case, either the E or the Z β,γ-double bond geometry can be obtained selectively by the inclusion or absence of acetic acid in the reaction milieu. Further studies are in progress.

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References and Notes

(1) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1-16.

(2) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Thangavelanthum, R.; Thorton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803-11826.

(3) Negishi, E.-i.; Coperet, C.; Ma, S. *Chem. Rev.* **1996**, *96(1)*, 365-93.

(4) Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975-1015.

(5) Larock, R. C. *Adv. Met. Org. Chem.* **1994**, *3*, 97-224.

(6) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423-30.

(7) Takacs, J. M.; Zhu, J. *J. Org. Chem.* **1989**, *54*, 5193-5.

(8) Takacs, J. M.; Zhu, J. *Tetrahedron Lett.* **1990**, *31*, 1117-20.

(9) Takacs, J. M.; Chandramouli, S. V. *Organometallics* **1990**, *9*, 2877-2880.

(10) Takacs, J. M.; Zhu, J.; Chandramouli, S. *J. Am. Chem. Soc.* **1992**, *114*, 773-774.

(11) Takacs, J. M.; Chandramouli, S. *J. Org. Chem.* **1993**, *58*, 7315-7.

(12) Takacs, J. M.; Lawson, E. C. *Organometallics* **1994**, *13*, 4787-93.

(13) Takacs, J. M.; Chandramouli, S. V.; Shoemaker, R. *Tetrahedron Lett.* **1994**, *35*, 9161-4.

(14) Takacs, J. M.; Chandramouli, S. V. *Tetrahedron Lett.* **1994**, *35*, 9165-8.

(15) Takacs, J. M.; Clement, F.; Zhu, J.; Chandramouli, S. V.; Gong, X. *J. Am. Chem. Soc.* **1997**, *119*, 5804-17.

(16) For another example wherein an acyl substituent strongly influences the course of a catalytic palladium-mediated carbocyclization, see: Trost, B. M.; Grese, T. A. *J. Org. Chem.* **1992**, *57*, 686-97.

(17) The diastereomeric purity of the cyclized product (>90 %) seems to depend, at least in part, on the E:Z isomeric purity of the starting bisdiene.

(18) Tenaglia, A.; Brun, P.; Waegell, B. *Tetrahedron Lett.* **1985**, *26*, 3571-4.

(19) In comparison, the trans vinyl hydrogens within the butadienyl side chain of **3** exhibit a 15 Hz coupling constant and an approximate 0.5 % nOe.

(20) For compound **6**, $J_{a,b}$ = 15.9 Hz.

(21) The minor component is tentatively assigned as the diastereomer that is epimeric at the 4-position of the cyclohexanol core in **11**.