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Catalytic Palladium-Mediated Tetraene Carbocyclizations: 1,2- and 1,4-Stereochemical Control in a Polycyclization Reaction

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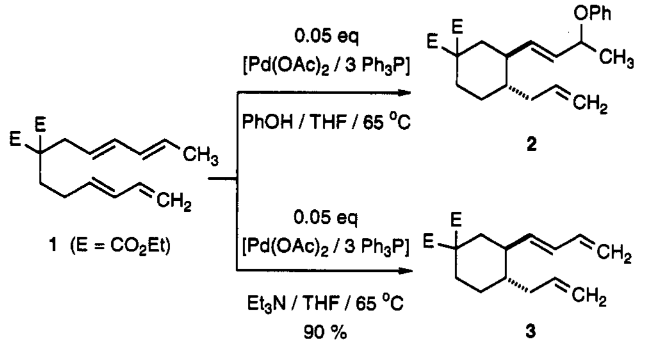
Summary: The palladium-mediated intramolecular diene-to-diene coupling with intramolecular trapping provides a novel route for the stereoselective construction of two new rings via the net 1,4-addition of carbon and oxygen across an internal diene subunit.

We recently began a study of the palladium-mediated reactions of certain tetraene compounds, substrates that contain within their structures two 1,3-diene subunits.[1-4] Our interest in the cyclization/trapping of these substrates derives from the extensive literature describing efficient palladium-mediated dimerization/trapping reactions of 1,3-butadiene, a process referred to as butadiene telomerization.[5-7] Our studies are directed toward developing this cyclization strategy for applications in natural product total synthesis, and toward that goal, we are exploring solutions to the problem of controlling reaction mode selectivity and/or group selectivity in the cyclizations of unsymmetric tetraenes. The attempted cyclization/trapping of the unsymmetric tetraene **1** illustrates the problem. Treating **1** with 0.05 equiv of a [Pd(OAc)$_2$/3Ph$_3$P] mixture and 2.2 equiv of phenol affords some of the cyclized and phenol-trapped product. The phenoxy moiety adds selectively to the more substituted 1,3-diene group in tetraene **1**, affording phenol-trapped product **2**, but **2** is the minor product (<10%) isolated from the reaction mixture. The major product, triene **3**, arises from a competing reaction mode involving palladium-mediated cycloisomerization. Optimized conditions for the tetraene-to-triene cycloisomerization omit the trapping reagent (*i.e.*, phenol in the case under discussion) and include triethylamine (5–10 equiv) as a promoter. Under these latter conditions tetraene **1** affords triene **3** in 90% yield.[4]



The optimized tetraene-to-triene cycloisomerization conditions provide one solution to the problem of controlling mode and group selectivity in the cyclization of unsymmetric tetraene substrates. To optimize the trapping reaction we reasoned that we should be able to exploit the classical strategy of rendering the desired reaction mode intramolecular. A variety of weak oxygen, nitrogen, sulfur, and carbon nucleophiles are useful intermolecular trapping reagents in palladium-mediated tetraene cyclizations.[1,2] Herein, we report some promising results concerning the efficiency and stereoselectivity of palla-

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

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

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

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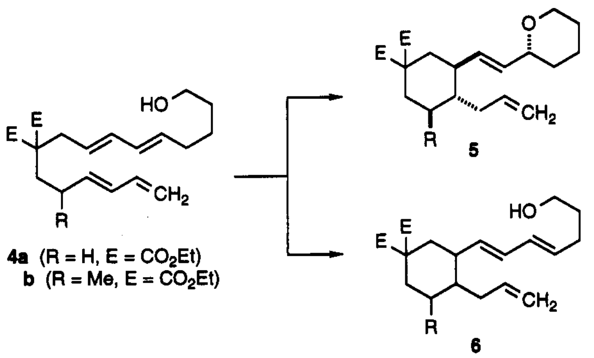
dium-mediated intramolecular diene-to-diene coupling with intramolecular trapping by a tethered hydroxyl group.

Tetraene **4a** is prepared by standard methods and treatment with 0.05 equiv of a [Pd(OAc)$_2$/3PPh$_3$] mixture in THF (65 °C, 24 h) affords the cyclized and intramolecularly trapped diene **5a** in good chemical yield (82%) and with good diastereoselectivity (9:1 mixture of two diastereomers). In contrast to the intermolecular trapping of **1**, only a small amount (ca. 10%) of the product arising from competing tetraene-to-triene cycloisomerization (*i.e.*, **6a**) is formed. Cyclization of the racemic tetraene **4b**, employing 0.05 equiv of a [Pd(OTFA)$_2$/3Ph$_3$P] mixture, gives comparable results. The cyclized product **5b** is obtained in 73% yield with 15–20% of the cycloisomerization product **6b**. Cyclization of **4b** also proceeds using the standard [Pd(OAc)$_2$/3PPh$_3$] mixture, but a relatively large amount (ca. 30%) of the cycloisomerization product **6b** is formed. It is possible that the less basic trifluoroacetate counter ion suppresses the competing cycloisomerization pathway. The stereocenter in tetraene **4b** resides adjacent to the lower diene subunit. The cyclization proceeds with a high level of 1,2-stereoinduction (>20:1) relative to that resident stereocenter.[8]



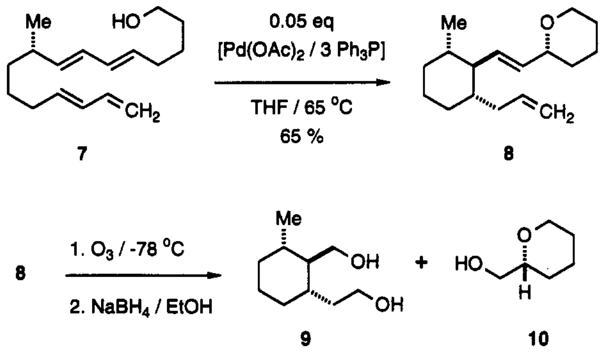
4a (R = H, E = CO$_2$Et)
b (R = Me, E = CO$_2$Et)

5

6

The polycyclization of unsaturated substrates via palladium-mediated tandem or cascade reactions has attracted considerable interest in recent years.[9-15] The conversion of **4** to **5** is unique among these polycyclizations in constructing two new six-membered rings via the net 1,4-addition of the elements carbon and oxygen across a diene subunit. In addition to the issue of 1,2-stereoinduction relevant to the cyclization of **4b**, three stereochemical elements are controlled in the cyclization of **4** to **5**. Two of these elements, the *E* double-bond stereochemistry and the trans relative stereochemistry between substituents on the newly formed cyclohexane ring, are easily established on the basis spectral data and their control is consistent with results we obtain in other palladium-catalyzed tetraene cyclizations.[1,2,4] The third element, the relative stereochemical relationship between the newly formed carbon–carbon and carbon–oxygen bonds, could arise either via the net *anti* 1,4-addition (as depicted in **5**) or the net *syn* 1,4-addition of carbon and oxygen across the internal diene moiety. To establish the sense of 1,4-stereochemical control, we investigated the palladium-mediated cyclization of the chiral tetraene **7**.

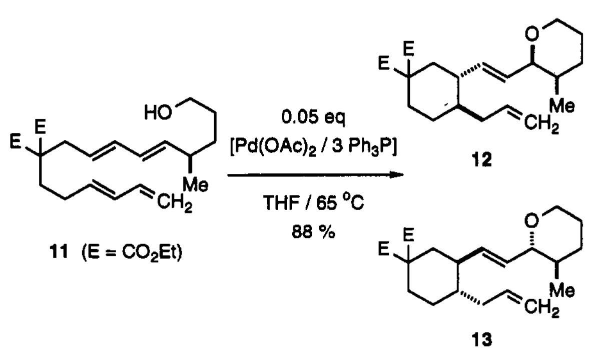
Palladium-mediated cyclization of scalemic (*S*)-**7** (0.05 equiv of [Pd(OAc)$_2$/3PPh$_3$], THF, 65 °C, 24 h) proceeds with a high level of 1,2-stereoinduction (>20:1) from the resident methyl-bearing stereocenter. Scalemic **8** is the only cyclized product isolated (65% yield), although under these conditions 35% of unreacted starting material is recovered. We see no evidence for competing tetraene-to-triene cycloisomerization. Bäckvall and co-workers[16] examined the palladium(II)-catalyzed 1,4-dioxidation of 1,3-dienes and found that either net *syn-* or net *anti-*addition products could be obtained. Product **8** is used to establish the net *anti* sense of 1,4-stereocontrol during the palladium-mediated cyclization. Ozonolysis of **8** (CH$_2$Cl$_2$/EtOH, −78 °C) followed by treatment with NaBH$_4$ (EtOH/CH$_2$Cl$_2$, 25 °C) yields **9** and scalemic tetrahydropyran-2-methanol (**10**). The relative stereochemistry of **9** is established by spectroscopic analysis. The sign of the optical rotation exhibited by scalemic **10**[17] correlates with the *R* absolute configuration.[18]



7 **8**

9 **10**

Substrates **4b** and **7** establish the stereochemical influence of a methyl substituent positioned adjacent to the newly forming carbon–carbon bond. To complete the study of 1,2-stereoinduction, we examined the cyclization of **11**, a tetraene in which the stereogenic center resides adjacent to the site of C–O bond formation. Palladium-mediated cyclization of **11** proceeds in good yield (88%), affords little of the triene byproduct, but gives a 1:1.6 mixture of diastereomers **12** and **13**.



11 (E = CO$_2$Et)

12

13

All of the results observed to date are consistent with the working model for the catalytic cycle illustrated in Scheme I. The cycle in Scheme I is adapted from that proposed by Jolly and co-workers[19] for the dimerization

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[8] Cyclized product **5b** is accompanied by two minor diastereomeric side products, each comprising 3–4% of the cyclization product mixture. One diastereomer possesses a *cis* rather than a *trans* double bond. The other is tentatively assigned as arising from the opposite sense of stereoinduction from the resident methyl-bearing stereocenter.

[9] Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791–2.

[10] Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323–34.

[11] Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813–1819.

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[13] Larock, R. C. *Pure Appl. Chem.* **1990**, *62*, 653–60.

[14] Grigg, R.; Dorrity, M. J.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1990**, *31*, 1343–6.

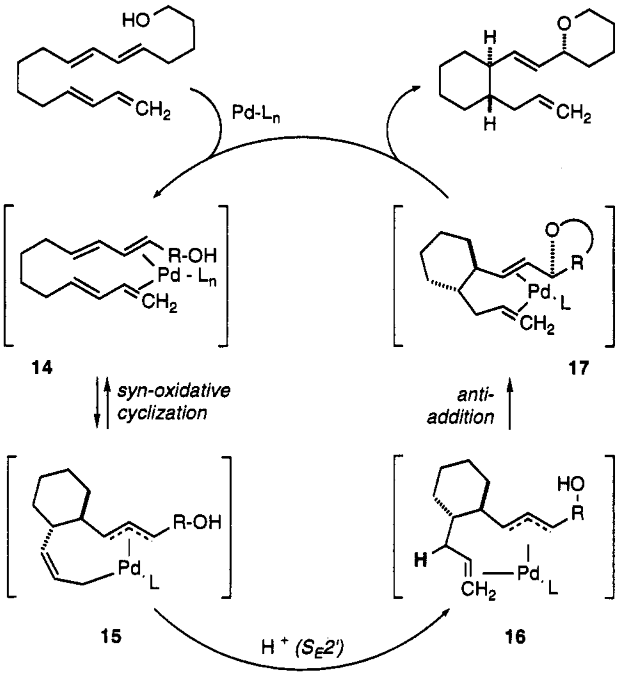
[15] Grigg, R.; Sridharan, V.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1139–42.

[16] Backvall, J. E. *Pure Appl. Chem.* **1992**, *64*, 429–37.

[17] Scalemic **10**: $[\alpha]_D$ −6.0° (1.12, water), 44% ee by GC analysis of the corresponding Mosher esters.

[18] (*S*)-**10**, $[\alpha]_D$ +22° (1, water). See: Lemieux, R. U.; Martin, J. C. *Carbohydr. Res.* **1970**, *13*, 139.

Scheme I. Working Model for the Catalytic Cycle Accounting for the Stereochemical Features of the Palladium-Catalyzed Cyclization with Intramolecular Trapping



of 1,3-butadiene with intermolecular trapping. In our model the tetraene templates about a reduced palladium center (*e.g.*, **14**) and undergoes oxidative cyclization (coupling) via the *syn* addition of carbon and palladium across the diene to afford the intermediate palladacycle **15**. Protonation of the η^1-allyl in an S_E2' fashion leads to the alkene complex **16**, and stereospecific *anti* addition of the oxygen nucleophile to the (η^3-allyl)palladium moiety completes the catalytic cycle. To account for the net *anti* 1,4-addition of carbon and oxygen across the diene, the addition of the oxygen nucleophile to the η^3-allyl in **16** must be fast relative to the rearrangement of palladium between the diastereomeric faces of the η^3-allyl. We speculate that the alkene complexed to palladium in intermediate **16** plays a crucial role in slowing the rate of isomerization.[20]

The extent of 1,2-stereoinduction observed in the cyclizations of tetraenes **4b**, **7**, and **11** can also be rationalized by this working model. In the model C–C bond formation precedes C–O bond formation, and for substrates such as those discussed here C–O bond formation is assumed to be irreversible under the reaction conditions. A stereogenic center residing within the developing cyclohexane ring (*i.e.*, as in **4b** and **7**) would reasonably influence the stereochemical course of the carbon–carbon bond construction. However, a stereocenter residing within the developing tetrahydropyran ring (*i.e.*, as in tetraene **11**) should exert minimal influence over the initial carbon–carbon bond formation, the event that sets the stereochemical course of carbon–oxygen bond construction. Consequently, tetraenes **4b** and **7** cyclize with a high level of 1,2-stereoinduction, but tetraene **11** affords nearly an equimolar mixture of diastereomers.

The palladium-mediated intramolecular diene-to-diene coupling with intramolecular trapping provides a novel route for the construction of two new rings via the net 1,4-addition of carbon and oxygen across an internal diene subunit. The cyclizations proceed with efficient 1,4-stereochemical control via the net *anti* addition across the diene and with good levels of 1,2-stereoinduction when the substituent is positioned adjacent to the newly forming carbon–carbon bond. Further studies are in progress.

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Supplementary Material Available: Experimental procedures, characterization data, and copies of 2D NMR spectra of **5a**, **5b**, **8**, **12**, and **13** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(19) Jolly, P. W.; Mynott, R.; Raspel, B.; Schick, K. P. *Organometallics* **1986**, *5*, 473–81.

(20) Jolly found that the alkene remained complexed to palladium upon protonation and subsequent intermolecular trapping of the palladacycle derived from butadiene. See ref 19.