experimental value, 1.42 kcal/mol,[2b] suggests an anomeric effect of ca. 3.7 kcal/mol.[15]

Seen in this light, it appears that the anomeric effects operative in O-C-P(O) and S-C-P(O) segments are of similar magnitude, close to 3 kcal/mol.[18]

Acknowledgment. We are indebted to Norma González-Rojano for technical assistance, to Guillermo Uribe for recording the ^{13}C and ^{31}P NMR spectra, and to CONACYT for partial financial support.

Registry No. *cis*-**3**, 122700-51-0; *trans*-**3**, 122700-52-1; (±)-*cis*-**4**, 122700-53-2; (±)-*trans*-**4**, 122700-54-3; (±)-*cis*-**5**, 122700-55-4; (±)-*trans*-**5**, 122700-56-5; (±)-$CH_3CH(OH)CH_2CH_2OH$, 18826-95-4; $HOCH_2CH(Bu\text{-}t)CH_2OH$, 2819-05-8; $ClPPh_2$, 1079-66-9; $HC(OCH_3)_3$, 149-73-5; pivaldehyde, 630-19-3.

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[18] The nature of the O-C-P(O) and S-C-P(O) anomeric interactions operative in 1 and 2, respectively, could be different.[3,4,19]

[19] Mikolajczyk, M.; Graczyk, P.; Kabachnik, M. I.; Baranov, A. P. *J. Org. Chem.* **1989**, *54*, 2859-2861.

Catalytic Palladium-Mediated Tetraene Carbocyclizations[1]

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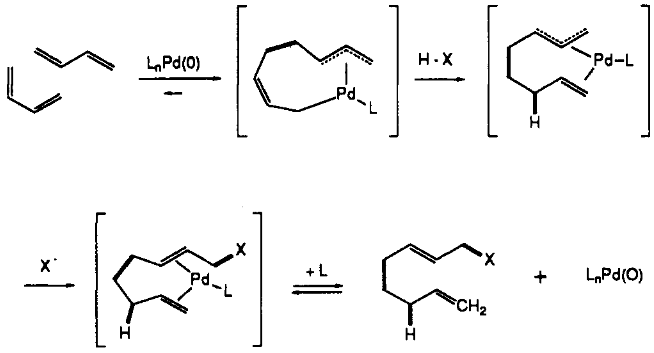
Summary: A new palladium-catalyzed carbocyclization of substrates containing two 1,3-diene moieties leads to the efficient, stereoselective preparation of functionalized cyclopentanes and pyrrolidines. Treatment of tetraenes with 5 mol % of a palladium catalyst and 2-10 equiv of an H-X trapping reagent effects carbocyclization under mild reaction conditions (25-65 °C) in good-to-excellent yields (50-94%) and with good-to-excellent stereoselectivity (5 to >20:1,trans:cis). Of particular note is the exceptional versatility of this methodology; versatility arising from the fact that the tetraene substrate is regioselectively coupled to an H-X (X = C, N, O, S) trapping reagent during the course of the cyclization.

Sir: The palladium-catalyzed linear telomerization of 1,3-butadiene was first reported in 1967 from the groups of Smutny and Hagihara.[2] Since those early reports the methodology has been extended to include the use of other metal catalysts, a few substituted 1,3-dienes, and a wide range of H-X trapping reagents (X = nucleophilic carbon, oxygen, nitrogen, or sulfur). The chemical yield, catalytic efficiency, and isomer selectivity observed in the telomerizations of 1,3-butadiene have typically been quite high. The simple 1,3-butadiene-derived linear dimers have found use as intermediates in synthesis.[3] The field has been independently reviewed by Smutny, Tsuji, Jolly, and Behr.[4] In recent years Jolly has spectroscopically and/or crystallographically characterized intermediates consistent with the proposed catalytic cycle outlined in Scheme I.[5,6]

Scheme I. A Proposed Catalytic Cycle for the Palladium-Catalyzed Telomerization of 1,3-Butadiene and Substituted 1,3-Dienes[5]



To date, the use of telomerization methods as a cyclization strategy for the direct construction of functionalized ring systems has found limited utility.[7] This is perhaps not surprising. Substituted 1,3-dienes typically telomerize with much less facility than 1,3-butadiene, and mixtures of isomeric linear-dimer products are obtained. From our experience with catalytic iron-mediated ene carbocyclizations[8] and from the growing list of other catalytic metal-mediated carbocyclization methods,[9-12] it is apparent

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[1] All new compounds isolated were fully characterized spectroscopically and the elemental composition determined by combustion analysis and/or high-resolution mass spectrometry.

[2] (a) Smutny, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 6793. (b) Takahashi, S.; Shibano, T.; Hagihara, N. *Tetrahedron Lett.* **1967**, 2451.

[3] Behr, A. *Industrial Application of Homogeneous Catalysis*; Mortreux, A., Petit, F., Eds.; Reidel: Dordrecht, Netherlands, 1988; pp 141-75.

[4] (a) Behr, A. *Aspects Homogeneous Catal.* **1984**, *5*, 3-73. (b) Jolly, P. W. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 283-295. (c) Tsuji, J. *Adv. Organomet. Chem.* **1979**, *17*, 141-193. (d) Smutny, E. J. *Ann. N. Y. Acad. Sci.* **1973**, *214*, 125.

[5] (a) Jolly, P. W.; Mynott, R.; Raspel, B.; Schick, K.-P. *Organometallics* **1986**, *5*, 473-81. (b) Benn, R.; Jolly, P. W.; Joswig, T.; Mynott, R.; Schick, K.-P. *Z. Naturforsch.* **1986**, *41b*, 680-91. (c) Benn, R.; Jolly, P. W.; Mynott, R.; Raspel, B.; Schenker, G.; Schick, K.-P.; Schroth, G. *Organometallics* **1985**, *4*, 1945-53.

[6] For an alternative mechanistic proposal, see: Behr, A.; Ilsemann, G. v.; Keim, W.; Kruger, C.; Tsay, Y.-H. *Organometallics* **1986**, *5*, 514-8.

[7] To date, the applications of telomerization methods to the construction of functionalized rings usually involve the sequential capture of the butadiene linear dimer by trapping reagents (X = Y) containing double or triple bonds. For representative examples, see: (a) Braunstein, P.; Matt, D.; Nobel, D. *J. Am. Chem. Soc.* **1988**, *110*, 3207-12. (b) Ohno, K.; Tsuji, J. *J. Chem. Soc. Chem. Commun.* **1971**, 247-8. (c) Ohno, K.; Mitsuyasu, T.; Tsuji, J. *Tetrahedron* **1972**, *28*, 3705-20. (d) Benn, R.; Gabor, G.; Jolly, P. W.; Mynott, R.; Raspel, B. *J. Organomet. Chem.* **1985**, *296*, 443-7. (e) Reference 4.

[8] (a) Takacs, J. M.; Anderson, L. G.; Creswell, M. W.; Takacs, B. E. *Tetrahedron Lett.* **1987**, *28*, 5627-30. (b) Takacs, J. M.; Anderson, L. G. *J. Am. Chem. Soc.* **1987**, *109*, 2200-02.

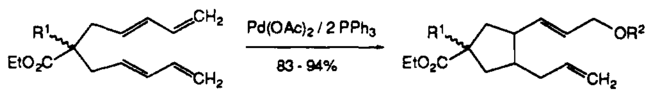
[9] (a) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904-6. (b) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221-4. (c) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678-9. (d) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 5231-33. (e) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268-70.

[10] (a) Trost, B. M.; Luengo, J. I. *J. Am. Chem. Soc.* **1988**, *110*, 8239-41. (b) Trost, B. M.; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 213-5. (c) Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2271-4. (d) Trost, B. M.; Matsuda, K. *J. Am. Chem. Soc.* **1988**, *110*, 5233-5. (e) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255-8. (e) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636-8.

0022-3263/89/1954-5193$01.50/0

that for appropriate ring sizes the effect of intramolecularity can greatly facilitate an otherwise unfavorable intermolecular metal-mediated reaction. On this basis we set out to explore the utility of the palladium-catalyzed telomerization of 1,3-dienes as a method for the catalytic palladium-mediated carbocyclization of tetraenes.

A large number of palladium catalysts and catalyst-precursors have been employed for the telomerization of 1,3-butadiene. In the experiments reported herein, we have evaluated only the $Pd(OAc)_2/2\ PPh_3$ catalyst system. Since oxygen nucleophiles have been the most widely investigated class of H–X trapping reagents, we began our investigations with cyclizations in the presence of alcohol trapping reagents. Tetraenes **1** and **2** were prepared by standard methods and subjected to 5 mol % of the Pd catalyst in an excess of benzyl alcohol (neat, 25 °C). Carbocyclization and trapping by benzyl alcohol proceeded smoothly to give cyclopentanes **3a** and **4a**, in 88% and 83% yields, respectively. Similarly, **1** and **2** reacted with phenol to give **3b** and **4b** (THF, 65 °C) in 94% and 88% yield. In each cyclic product the regioselective formation of the terminal double bond, the stereoselective formation of the trans internal double bond, and the regioselective incorporation of the alkoxy group (X^-) at the allylic terminus are consistent with results observed in the linear dimerization of simple 1,3-dienes.

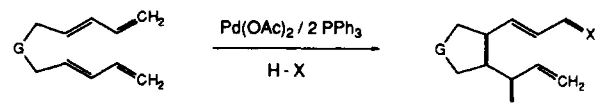


1 ($R^1 = CO_2Et$)
2 ($R^1 = CN$)

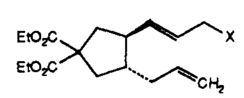
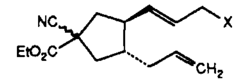
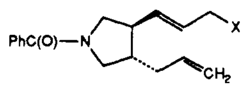
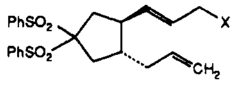
3 ($R^1 = CO_2Et$), a $R^2 = CH_2Ph$, b $R^2 = Ph$
4 ($R^1 = CN$), a $R^2 = CH_2Ph$, b $R^2 = Ph$

In part the synthetic potential of this new cyclization reaction lies in the wide range of functionalities (X) that can be incorporated into the carbocyclic product simply by varying the H–X trapping reagent. The results obtained from the reactions of other oxygen nucleophiles, as well as nitrogen, sulfur, and carbon nucleophiles, and from other tetraene substrates are summarized in Table I. In addition to the reactions of tetraenes **1** and **2**, amide **6** and bis-sulfone substrate **7** cyclized with the incorporation of phenol in good chemical yields (entries 8, 10). A carboxylic acid trapping agent was also employed to introduce allylic oxygen functionality into the cyclic product. For example, bis-sulfone substrate **7** cyclized in the presence of acetic acid to give the corresponding allylic acetate in 80% yield (entry 11). Allylic amine functionality can be introduced by cyclization in the presence of an amine. The cyclization of diester **1** with diethylamine gave the allylic amine in 76% yield (entry 3). Cyclization in the presence of *p*-toluenesulfinic acid gave the allylic sulfone functionalized product, albeit in a modest 50% yield (entry 4). Perhaps the greatest synthetic potential of this bond construction lies in the capability to form a second carbon–carbon bond subsequent to the cyclization. This can be accomplished in several ways. Diester **1** cyclized with incorporation of nitromethane in 79% yield (entry 5). Amide **6** and bis-sulfone **7** each were cyclized in the presence of diethyl malonate to yield product in 73% yield (entries 9, 12).

Table I. The Catalytic Palladium-Mediated Carbocyclizations of Tetraenes 1, 2, 6, and 7 with Carbon-, Oxygen-, Nitrogen-, and Sulfur-Containing Trapping Reagents[13]



6 G = NC(O)Ph
7 G = $C(SO_2Ph)_2$

Tetraene	H-X (solvent temp)	Major Cyclized Product	yield (*trans* : *cis*)
1	$PhCH_2OH$ (neat 25°)	 **8** (X = OCH_2Ph)	88% (7 : 1)
1	PhOH (THF 65°)	**8** (X = OPh)	94% (15 : 1)
1	$(C_2H_5)_2NH$ (THF 65°)	**8** (X = $N(C_2H_5)_2$)	76% (>20 : 1)
1	*p*-$CH_3C_6H_4SO_2H$ (PhH 70°)	**8** (X = SO_2Ar)	50% (13 : 1)
1	CH_3NO_2 (neat 60°)	**8** (X = CH_2NO_2)	79% (9 : 1)
2	$PhCH_2OH$ (neat 25°)	 **9** (X = CH_2OPh)	83% (7 : 1)
2	PhOH (THF 65°)	**9** (X = OPh)	88% (15 : 1)
6	PhOH (THF 65°)	 **10** (X = OPh)	73% (>20 : 1)
6	$CH_2(CO_2Et)_2$ (THF 65°)	**10** (X = $CH(CO_2Et)_2$)	73% (>20 : 1)
7	PhOH (THF/65°)	 **11** (X = OPh)	77% (18 : 1)
7	$(Et_3NH)^{+}\ ^{-}OAc$ (HOAc/THF/65°)	**11** (X = OAc)	80% (5 : 1)
7	$CH_2(CO_2Et)_2$ (THF/65°)	**11** (X = $CH(CO_2Et)_2$)	73% (>20 : 1)

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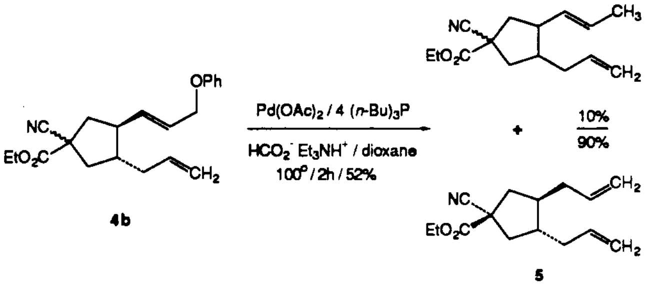
(11) (a) Oppolozer, W. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 38–52. (b) Negishi, E.; Iyer, S.; Rousset, C. J. *Tetrahedron Lett.* **1989**, *30*, 291–4.

(12) (a) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454–6. (b) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047–50. (c) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328–9.

(13) The following experimental procedure is representative. **Palladium-Catalyzed Carbocyclization Reaction of Tetraene 1 with Nitromethane.** To a nitrogen-blanketed solution of palladium(II) acetate (12.0 mg, 0.05 mmol) and triphenylphosphine (26.0 mg, 0.10 mmol) in nitromethane (2.0 mL) was added diethyl 2,2-di-2,4-pentadienylmalonate (1, 292 mg, 1.0 mmol). The resulting solution was warmed (60 °C, 12 h) and then cooled, and the excess nitromethane removed in vacuo. Chromatography on silica gel (10:1 hexane–ethyl acetate) gave 280 mg (79%) of nitro compound 8 (X = CH_2NO_2) as a clear liquid: IR (neat) 1730 (s, C=O), 1640 (m, C=C), 1554 (s, NO_2), and 1379 cm^{-1} (m, NO_2); ^1H NMR (360 MHz, $CDCl_3$) δ 5.78–5.66 (m, 1 H, $CH{=}CH_2$), 5.44–5.34 (m, 2 H, $CH{=}CH$), 5.02–4.94 (m, 2 H, $CH{=}CH_2$), 4.38 (t, J = 7.0 Hz, 2 H, CH_2NO_2), 4.15 (q, J = 7.0 Hz, 4 H, $CO_2CH_2CH_3$), 2.68 (dt, J = 5.8, 7 Hz, 2 H, $CH_2CH_2NO_2$), 2.53–2.40 (m, 2 H, CH, CH'), 2.28–2.10 (m, 2 H, $CH_2CH{=}CH_2$), 1.98–1.61 (m, 4 H), and 1.22 ppm (t, J = 7.0 Hz, 6 H, $CO_2CH_2CH_3$); ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.47 (C=O), 172.42 (C=O), 136.61 (C(H)=C), 136.53 (C(H)=C), 124.48 (C(H)=C), 115.25 (C=CH_2), 75.21 (CH_2NO_2), 61.37 (CO_2CH_2), 58.25 ($(EtO_2C)_2C$), 48.40 (CH, trans diastereomer), 44.91 (CH, minor cis diastereomer), 44.70 (CH, trans diastereomer), 42.50 (CH, minor cis diastereomer), 40.46 (CH_2), 39.43 (CH_2), 36.89 (CH_2), 30.39 (CH_2), and 13.98 ppm (CH_3); HRMS (FAB, $C_{18}H_{28}NO_6$ 354.1917) found m/z 354.1926.

With respect to the stereochemistry of cyclization, the reaction of tetraene **2** with benzyl alcohol or phenol afforded as the major products a 1:1 mixture of stereoisomeric cyclopentanes **4**. Only minor amounts of other diastereomers were detected. As expected, the diastereomeric cyclopentanes **4** were stereoisomeric at the resident quaternary stereocenter. Assignment of the trans relative stereochemistry to the side chains is based upon reduction of the stereoisomeric mixture of allyl phenyl ethers **4b** by the method of Tsuji[14] to give predominantly the (*d,l*)-*trans*-diene **5** rather than the corresponding cis-diastereomers.[15] In the five-membered ring carbocyclizations investigated to date, the level of trans/cis simple diastereoselectivity varied from 5:1 (entry 11) to >20:1 (entries 3, 8, 9, 12), as determined by capillary gas chromatography, HPLC, and/or high-field ^{1}H/^{13}C NMR analysis. The origin of the stereoselectivity is at this point unclear. Certain literature data, obtained for the telomerizations of isoprene[5a] and piperylene,[16] suggest that the oxidative cyclization of the tetraene substrate to the intermediate fused-bicyclic palladacycle (the stereochemical-determining step in the proposed mechanism) should be reversible under the cyclization conditions. Consequently, the relative stabilities of the diastereomeric trans/cis metallacycles[17] and/or their relative rates of trapping by H–X may determine the diastereoselectivity of the cyclization. We find that the trans/cis ratio of cyclized products is sensitive to the nature of the tetraene substrate (e.g. **1** vs **6** entries 2, 8), the nature of the trapping reagent (e.g. PhOH vs $PhCH_2OH$, entries 1, 2, or PhOH vs AcOH, entries 10, 11), and also the reaction temperature. Palladium-catalyzed cyclization of tetraene **1** with benzyl alcohol at 65 °C gave a 3:1 trans/cis ratio as compared to the 7:1 ratio observed when the reaction was carried out at ambient temperature.



This catalytic palladium-mediated tetraene carbocyclization method provides a versatile new strategy for the stereoselective preparation of functionalized ring systems. The observed bond construction complements the palladium-catalyzed cyclization-via-isomerizations,[10] palladium–ene cyclizations,[11] and other palladium-mediated carbocyclizations[12] and under development elsewhere. The requisite tetraene substrates are easily prepared, and such substrates have been previously employed for other cyclization reactions, including Ni(0)-catalyzed [4 + 4]-cycloaddition[9a–c] and acid-catalyzed [4 + 2]-cycloaddition[18] reactions. Further studies on the stereoselectivities of other trapping reagents and on the application of this methodology to the stereo- and regioselective construction of other ring systems are in progress.

Acknowledgment. Financial support of this work by the University of Nebraska-Lincoln and the National Institutes of Health (Grant GM34927) is gratefully acknowledged. High-resolution mass spectral analyses were performed by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant No. 8620177).

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[14] Tsuji, J.; Shimizu, I.; Minami, I. *Chem. Lett.* **1984**, 1017–9.

[15] The trans stereochemical assignment of the other vicinally substituted five-membered ring compounds was made by analogy to **4b** and is consistent with the close correlation of ^{13}C NMR ($CDCl_3$) chemical shifts observed for the two methine carbons (δ 48.0 ± 0.5 and 44.5 ± 0.5 ppm) in each cyclized product reported in Table I. In cases where the cis diastereomers could be detected by ^{13}C NMR, the corresponding methine carbon resonances were at approximately δ 44.9 ± 0.3 and 42.4 ± 0.3 ppm.

[16] (a) Beger, J.; Duschek, C.; Reichel, H. *J. Prakt. Chem.* **1973**, *315*, 1077. (b) Hata, G.; Takahashi, K.; Miyake, A. *J. Org. Chem.* **1971**, *36*, 2116.

[17] Preliminary molecular modeling studies of the postulated cis- and trans-fused bicyclic palladacyclic intermediates suggest that five-membered ring carbocyclizations leading to a trans diastereomer should be particularly facile. Modeling studies were performed using MODEL (v 2.93), PCMODEL (v 1.1), and Gilbert and Gajewski's MMX88 minimization program. The metallcyclic intermediates were constructed starting from the crystal coordinates reported for the related palladacycle described in ref 4b. The atoms directly bonded to palladium were restricted to the crystal positions during all minimizations.

[18] Gassman, P. G.; Singleton, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 6085.

High Stereoselectivity in the 1,2-Nucleophilic Additions to a Hindered 2-Alkylidenecyclohexanone: An Example of Predominant Axial Attack by Sterically Demanding Nucleophiles

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Summary: 1,2-Additions of various nucleophiles including sterically demanding carbanions have been shown to take place preferentially from an axial direction to a highly hindered 2-alkylidenecyclohexanone, thus providing an interesting example where the continuous orbital overlap between a newly forming bond and the C=C π-system appears to play a significaant role in controlling the stereochemical outcome in these 1,2-additions.

Sir: The stereochemistry of nucleophilic addition to cyclohexanones[1] and conjugated cyclohexenones has been the subject of increasing attention.[2] The enhanced axial selectivity for 1,2-addition to cyclohexenones over their corresponding saturated ketones is now amply documented for sterically undemanding[2] as well as moderately bulky nucleophiles.[2d,3] A number of theories have been advanced that attempt to rationalize the origin of this enhanced preference for axial addition.[4] The most recent computational model for the transition state by Wu, Houk, and Trost[4c] postulates the thesis that the torsional strain can be employed as the principal determinant to account for the observed selectivity. Here we report a remarkable

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