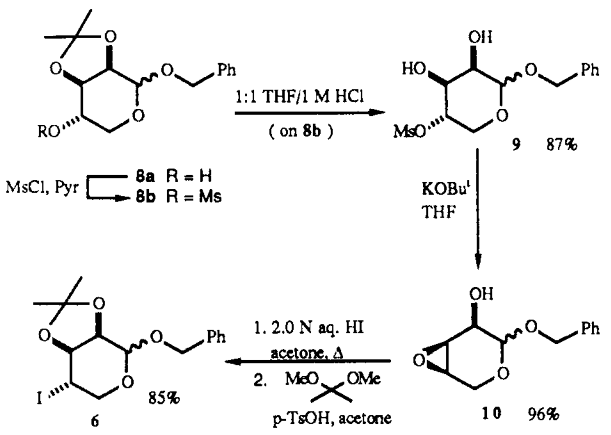
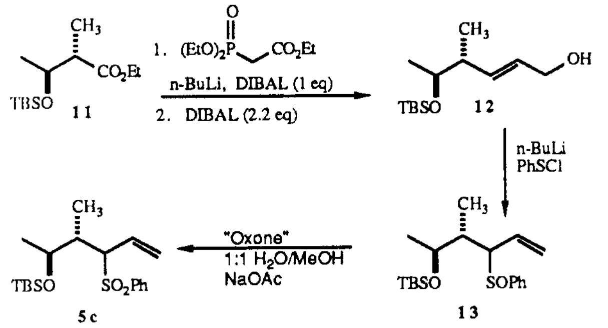
Scheme I



Scheme II



general procedure of Evans,[11] followed by oxidation with Oxone[12] to give the desired sulfone as a ca. 2:1 mixture of epimers.[13]

The desired one-electron union of **5c** and **6** proved much more difficult than anticipated and required scrupulous attention to experimental detail for success. For example, exhaustive investigation using chemical initiation with initiators such as AIBN or ACN[14] at 80–110 °C in the presence of 1.0 equiv of hexabutylditin[6] failed to afford detectable amounts of the desired coupling products. Failure was also encountered using the Hart protocol[15] with initiation from stoichiometric amounts of bis(trimethylstannyl) benzopinacolate.

Better results were obtained using photochemical initiation. For example, when a mixture of 3 equiv of sulfone **5c**, 1 equiv of iodide **6**, and 1.5 equiv of hexabutylditin in toluene was irradiated (450-W Hanovia lamp with Pyrex filter) for 12 h, 20% of the desired addition product was isolated, along with 60% of the product of simple reduction of iodide **6** and allylically transposed sulfone. Finally it was found that slow addition (syringe pump) of a THF solution (0.54 M in **5c**) of 1.0 equiv of sulfone **5c** and 0.5 equiv of hexabutylditin to an irradiated solution of 1.0 equiv of iodide **6** and 0.5 equiv of hexabutylditin (0.54 M in THF) under argon afforded the desired coupling product **7a** in 74% isolated yield (note eq 1).

NMR analysis indicated a 13:1 mixture of trans/cis C_{10}–C_{11} geometric isomers. Reductive cleavage (Li, NH_3 (1), THF) of the benzyl group gave the α-lactol **7b**, which was spectroscopically indistinguishable (^1H NMR, ^{13}C NMR, HRMS) from material previously prepared in our laboratories and subsequently converted to (+)-pseudomonic acid C.[2h] HPLC analysis of the UV-active 1-*O*-benzoyl derivative again revealed a 13:1 mixture of trans/cis C_{10}–C_{11} geometric isomers. Isomeric substances resulting from incomplete facial selectivity in construction of the C_8 stereogenic center were not detected.

The successful realization of a "second generation" total synthesis of (+)-pseudomonic acid C according to the free-radical addition–fragmentation process described herein again demonstrates the power of such reactions in organic synthesis[16] and also suggests that such reactions will find continuing application.

Acknowledgment. Financial support of this research by the NSF (Grant CHE 8312729) is gratefully acknowledged.

Supplementary Material Available: Full experimental details and spectral and physical data for compounds described herein (24 pages). Ordering information is given on any current masthead page.

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(11) Evans, D. A.; Andrews, G. L. *Acc. Chem. Res.* **1974**, 7147.

(12) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(13) The major sulfone (stereochemistry unassigned) could be isolated by column chromatography (3% THF/hexanes; silica gel) for purposes of characterization. For synthetic purposes, the 2:1 mixture was employed.

(14) (a) Overberger, C. G.; Biletch, J.; Finestone, A. B.; Lilker, J.; Herbert, J. *J. Am. Chem. Soc.* **1943**, *75*, 2078. (b) For a discussion of "some properties of radical reactions important in synthesis", note: Walling, C. *Tetrahedron Symp.* **1985**, *41*, 3887.

(15) Hart, D. J.; Seely, L. S. *J. Am. Chem. Soc.* **1988**, *110*, 1631.

(16) For the use of a free radical addition-fragmentation process for the construction of $PGF_{2\alpha}$ see: Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958.

Palladium-Catalyzed Polyene Cyclizations of Trienyl Triflates

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Summary: Spirotricyclic dienones are conveniently prepared by palladium-catalyzed cyclizations of enol triflate derivatives of 2-dienyl-1,3-cyclohexanediones. The use of chiral (nonracemic) ligands allows assembly of these products with moderate enantioselectivity, demonstrating a potentially powerful new method for catalytic asymmetric construction of quaternary carbon stereocenters.

Sir: Our laboratory recently initiated a program aimed at developing a polyene cyclization chemistry mediated by transition metals.[1,2] A generalized spirocyclic example of

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(1) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328.

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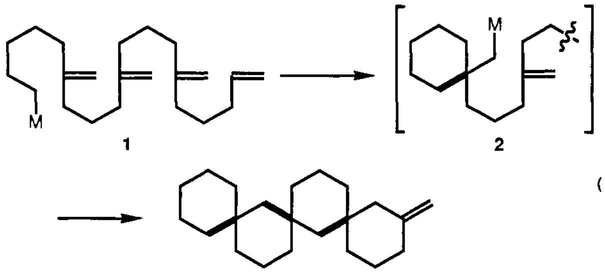
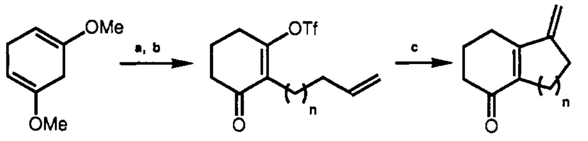
such a transformation, which occurs with the formation of new quaternary carbon centers,[3] is shown in eq 1. A



1 2 3 (1)

fundamental attraction of this chemistry is that its domain of applicability is expected to be quite different from that of the more common polyene cyclization reactions of carbocations and free radicals. Polycyclizations of electron-deficient intermediates (carbenium ions and radicals) have an inherent regiochemical bias for substrates that allow propagation of this intermediate at the more substituted terminus of a participating π-bond.[4] In contrast, a cyclization resulting from sequential intramolecular insertions of transition-metal alkyls is expected with many metals[5] to be most effective when the transition-metal propagates at the least substituted termini of the participating alkene units, e.g. 1 → 2.[6] An enol triflate of a 1,3-diketone is an attractive functionality for initiating transition-metal-catalyzed polyene cyclizations, since the cyclic product would retain the synthetically versatile enone functional group.[7] In this paper we report that spirotricyclic enones containing five- and six-membered rings can be efficiently assembled in this way. We moreover demonstrate, in one case, the use of chiral (nonracemic) ligands to allow catalytic asymmetric construction of the new quaternary carbon center.[8]

To confirm that intramolecular alkene insertions could be initiated with enol triflates derived from cyclohexane-1,3-diones, we initially examined the simple substrates **5** and **6**. These enol triflates were readily assembled in three steps and in 70–75% overall yield from 1,3-dimethoxybenzene by using the method of Piers[9] to prepare the requisite 2-substituted 1,3-cyclohexanediones (eq 2). Enol triflates **5** and **6**[10] underwent cyclization in refluxing acetonitrile in the presence of 10 mol % of $Pd(OAc)_2$, 40 mol % of Ph_3P, and 2 equiv of Et_3N to afford bicyclic dienones **7** and **8** in 88% and 80% yields, respectively.[11,12] Although these products were prepared as a prelude to our polyene cyclization studies, they are of some interest themselves since the dienone functionality offers a number of op-

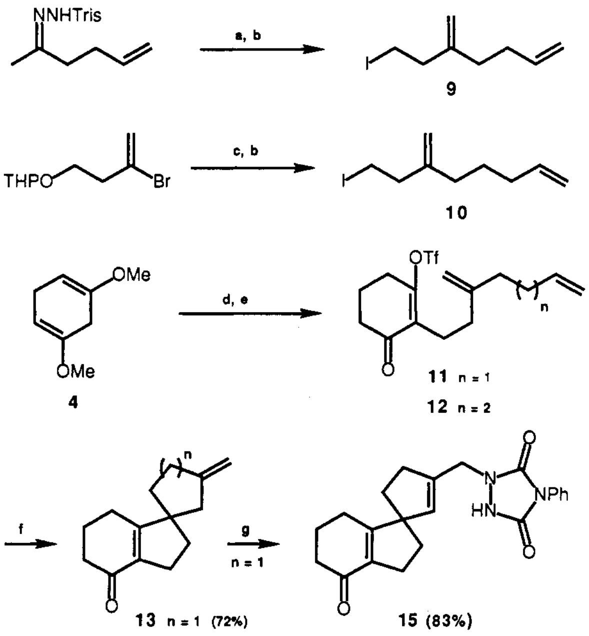


(2)

4 5 n = 1 6 n = 2 7 n = 1 (88%) 8 n = 2 (80%)

(a) t-BuLi, THF, −78 °C; $Br(CH_2)_nCH_2CH{=}CH_2$, −78 °C → room temperature; 1 N HCl; (b) NaH, THF, 0 °C → room temperature; $PhNTf_2$, room temperature → 60 °C; (c) 0.1 equiv of $Pd(OAc)_2$, 0.4 equiv of Ph_3P, 2 equiv of Et_3N, CH_3CN, 70 °C. (Tf = SO_2CF_3)

Scheme I[a]



9 10 4 11 n = 1 12 n = 2 13 n = 1 (72%) 14 n = 2 (70%) 15 (83%)

[a] (a) *n*-BuLi, TMEDA-hex, −78 → 0 °C; ethylene oxide; (b) *p*-TsCl, $CHCl_3$, py, 0 °C → room temperature; NaI, MeCOMe, K_2CO_3, 56 °C; (c) s-BuLi, THF, −78 °C; 5-bromo-1-pentene, −78 °C → 0 °C; HCl, MeOH; (d) t-BuLi, THF, −78 °C; **9** (or **10**), −78 °C → room temperature; 1 N HCl; (e) NaH, THF, 0 °C → room temperature; $PhNTf_2$, room temperature → 60 °C; (f) 0.1 equiv of $Pd(OAc)_2$, 0.4 equiv of Ph_3P, 2 equiv of Et_3N, CH_3CN, 70 °C; (g) *N*-phenyl-1,2,4-triazoline-3,5-dione, acetone, 23 °C (Tris = (2,4,6-triisopropylphenyl)sulfonyl).

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(2) For recent disclosures from other laboratories of palladium-catalyzed multiple carbocyclic ring forming reactions that involve intramolecular insertion of an alkyne or alkene in at least one step, see: (a) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. (b) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 38. (c) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (d) Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1984**, *54*, 2507.

(3) For initial reports of forming quaternary carbon centers by intramolecular Heck reactions, see: (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakan, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697. (b) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (c) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S. *Tetrahedron* **1989**, *45*, 3557.

(4) (a) Bartlett, P. A. In *Asymmetric Synthesis. Stereodifferentiating Addition Reactions Part B*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Chapter 5. (b) Curran, D. P. *Synthesis* **1988**, 489.

(5) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapters 6, 11, 14.

(6) Similar regioselectivity is seen in anionic cyclizations: Bailey, W. F.; Rossi, K. *J. Am. Chem. Soc.* **1989**, *111*, 765. Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *Ibid.* **1988**, *110*, 4788.

(7) One example of the intermolecular cross-coupling of this functionality with an alkene was reported during the course of our investigations: Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047.

(8) Few useful methods exist for catalytic asymmetric synthesis of quaternary carbon stereocenters. For recent reviews of chiral catalysis, see: (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 5. (b) Bosnich, B. *Asymmetric Catalysis*, NATO ASI Series E 103; Martinus Nijhoff Publishers: Dordrecht, 1986. (c) Nogradi, M. *Stereoselective Synthesis*; VCH Verlag: Weinheim, 1987. (d) Brunner, H. *Synthesis* **1988**, 645. (e) Kagan, H. B. *Bull. Soc. Chim. Fr.* **1988**, 846.

(9) Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977**, *42*, 3755.

(10) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

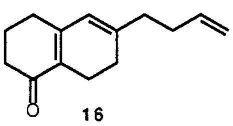
(11) (a) A typical experimental procedure for the cyclization step as well as copies of the IR, ^1H NMR, and ^{13}C NMR spectra of the cyclization products prepared during this study are provided as supplementary material. New compounds showed ^1H NMR, ^{13}C NMR, IR, and mass spectra in accord with their assigned structures. Elemental composition was secured by high-resolution mass spectrometry or elemental analysis. (b) Homonuclear ^1H COSY experiments were typically employed to define the 3-methylenecyclopentane or 3-methylenecyclohexane ring of the spirotricyclic products.

(12) Diagnostic UV λ max (ε) in hexane for cyclization products are as follows: **7**, 278 nm (1.8×10^4); **8**, 260 nm (7.5×10^3); **13**, 234 nm (7.7×10^3); **14**, 236 nm (9.5×10^3); **20**, 229 nm (9.8×10^3); and **21**, 234 nm (9.8×10^3).

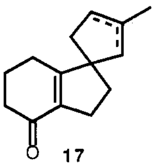
portunities for further structural elaboration.

The trienyl triflate **11** was assembled along standard lines in four steps and 40% overall yield from the 2,4,6-triisopropylbenzenesulfonylhydrazone of 5-hexen-2-one (Scheme I).[13] This triflate underwent bis-cyclization at 70 °C in the presence of 10 mol % of $Pd(OAc)_2$, 40 mol % of Ph_3P, and 2 equiv of Et_3N to provide the spirotricyclic hydrindenone **13** (IR 1668 and 1630 cm^{-1}) in 72% yield after purification on silica gel.[11,12] In a similar fashion, **12** underwent bis-cyclization to provide **14** in 70% yield.[11,12]

The cyclization of **11** was more rapid if 2 equiv of Ph_3P (per equivalent of Pd) is employed, although cyclizations carried out in acetonitrile (65 °C) with this catalyst system gave more (up to 9%) of the dienone **16**, which results from insertion of the initially formed palladacyclohexene intermediate in the endocyclic mode. This dienone was produced in trace amounts only when 3–4 equiv of Ph_3P (per equivalent of Pd) were employed. Replacing Ph_3P with the chelating diphosphine, dppe[14] (1 equiv/equiv Pd), allowed the cyclization of **11** to be carried out at 40 °C in acetonitrile, although migration of the exocyclic double bond of **13** to give dienones **17** occurred to the extent of 20–30% with this catalyst.[15] By far the best conditions we have found employ the chiral ligands (*R*,*R*)- or (*S*,*S*)-DIOP[14] and $Pd(OAc)_2$ in a 1:1 ratio. Cyclization of **11** in benzene in the presence of 10 mol % of this asymmetric catalyst system proceeded *cleanly within 2 h at room temperature to yield **13** in >90% yield*.[16,17] To determine the extent of absolute stereoinduction under these conditions, **13** was first allowed to react with *N*-phenyl-1,2,4-triazoline-3,5-dione to provide, as the major ene product, cycloadduct **15**. ^1H NMR analysis of **15** at 300 MHz using the chiral shift reagent $Yb(tfc)_3$ demonstrated that the sense of asymmetric induction was opposite with the two DIOP enantiomers and that in each case **13** was formed with an enantiomeric excess of 45%. The scope of this *highly promising method for catalytic asymmetric synthesis of quaternary carbon stereocenters* as well as the results obtained employing many other variations of ligand, solvent, and base will be reported in the near future.[18]

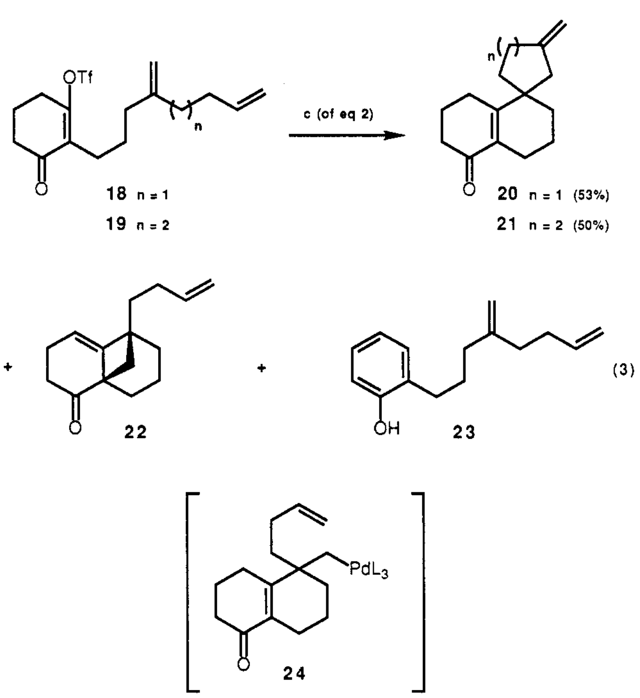


16



17

Bis-cyclizations could also be successfully accomplished with substrates in which the proximal double bond was one atom further removed from the cyclohexane ring (eq 3). For example, triflate **18**[19] cyclized to provide, after purification on silica gel, the spirotricyclic decalenone **20** as the major product (53% yield).[11,12] The homologue **21**[11,12] was also the major product obtained from palladium-catalyzed cyclization of trienyl triflate **19**. Also isolated from the cyclization of **18** was a small amount (10%) of the phenol **23**[20] and a second tricyclic product (5%) which retained the terminal vinyl group. Extensive ^1H NMR investigations at 500 MHz established the constitution of this material to be **22**, a product which presumably arises from an unprecedented[21] endocyclic insertion of bicyclic neopentylpalladium intermediate **24** into the carbon–carbon π-bond of the enone. It is of interest to note that no trace of a product of this type was detected in the cyclizations reported in Scheme I.



In summary, spirocyclic carbon skeleta that are not available from polyene cyclization reactions of carbenium ions or free radicals can be assembled efficiently by transition-metal-catalyzed cyclizations. When the palladium-catalyzed cascade is initiated from an enol triflate derivative of a 1,3-diketone, the enone or dienone functionality that resides in the polycyclic products provides an attractive handle for further structural elaboration. A promising new method for catalytic asymmetric synthesis of quaternary carbon centers has been demonstrated, although further optimization will be required to achieve high levels of enantioselectivity.

Acknowledgment. Financial support was provided by PHS Grant GM-30859. NMR and mass spectra were determined with spectrometers purchased with the assistance of NSF Shared Instrumentation Grants.

Supplementary Material Available: Experimental details for a typical cyclization (of **18**) and characterization data for **20**, **22**, and **23**; copies of ^1H NMR, ^{13}C NMR, and IR spectra of cyclization products, triflate precursors, and ene product **15**; copies of the ^1H NMR analysis of optically active **15** in the presence of $Yb(tfc)_3$ (29 pages). Ordering information is given on any current masthead page.

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[13] Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. Kabalka, G. E.; Varma, M.; Varma, R. S. *Ibid.* **1986**, *51*, 2386.

[14] dppe = 1,2-bis(diphenylphosphino)ethane, DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, and $Yb(tfc)_3$ = tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]ytterbium(III).

[15] The decalin dienone **16** was also formed to the extent of 5–10% under these conditions.

[16] Byproducts **16** and **17** were formed to an extent of <2% under these conditions. This experiment was conducted by Dr. A. Sarkar in these laboratories.

[17] Cyclization under similar conditions proceeded more slowly and less cleanly when the ligand was dppb or dppp.[14]

[18] Asymmetric Heck cyclizations that form new tertiary carbon stereocenters were recently described, see: Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738.

[19] Prepared from 4-bromo-4-penten-1-ol and 4-bromo-1-butene (or 5-bromo-1-pentene) by a sequence analogous to that reported in Scheme I for the preparation of **12**.

[20] This product presumably results from palladium-catalyzed isomerization of the endocyclic double bond of **18** followed by elimination of CF_3SO_3H.

[21] Exocyclic "back" insertion to form cyclopropanes has been reported by Negishi[2c] and observed also by us in other systems.