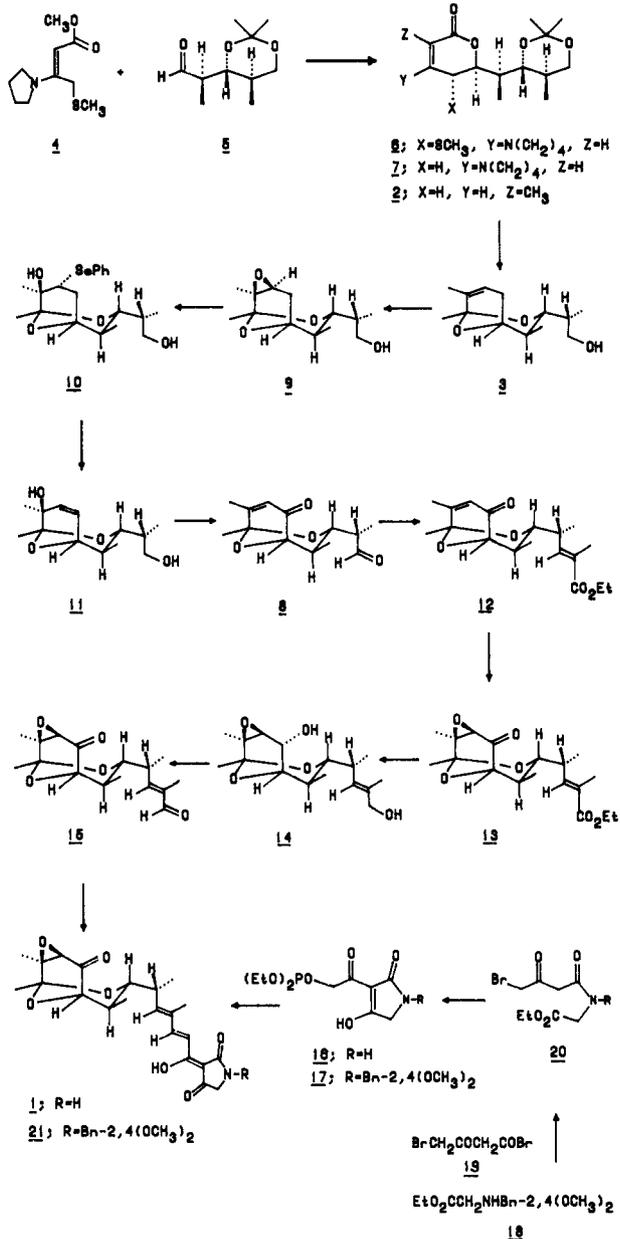


Scheme I



aldehyde ketone **15** (oil) in essentially quantitative yield. The latter substance was normally used without purification in the next synthetic step.

We now faced the introduction of the 3-acyltetramic acid portion of tirandamycin A. Boeckman and Thomas have described a reagent, **16**, which, as its dianion, undergoes an Emmons reaction with aldehydes. Unfortunately, the reaction conditions (THF/40 °C/24 h) defined by these authors for the condensation of the dianion of **16** and tiglic aldehyde were too vigorous for use with the sensitive unsaturated aldehyde **15**.^{20a} Therefore, we set out to prepare an *N*-benzyl derivative of this reagent, the 3-acyltetramic acid phosphonate **17**, believing that it would exhibit greater reactivity toward unsaturated aldehydes.

The 2,4-dimethoxy-*N*-benzylglycine derivative **18** was prepared in the usual manner,²¹ and reacted in CH₂Cl₂ solution at -40 °C with the acid bromide **19**²² to give the amide **20** (thick oil) in 95%

(20) (a) Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823. (b) DeShong, P.; Lowmaster, N. E.; Baralt, O. *Ibid.* **1983**, *48*, 1149.

(21) (a) Fugger, J.; Tien, J. M.; Hunsberger, I. M. *J. Am. Chem. Soc.* **1955**, *77*, 1843. (b) Lee, V. J. Ph.D. Dissertation, University of Illinois, Urbana, IL, 1975.

(22) (a) Tabei, K.; Kawashima, E.; Kato, T. *Chem. Pharm. Bull.* **1979**, *27*, 1842. (b) Murakami, K.; Takasuka, M.; Motokawa, K.; Yoshida, T. *J. Med. Chem.* **1981**, *24*, 88.

yield. Treatment of **20** (1.0 equiv) with (EtO)₂POK (2.1 equiv) in THF solution (15 h) gave **17** (thick reddish oil) in 82% yield.²³ The dianion of **17** (1.0 equiv) was prepared in THF (0.5 M) using *t*-BuOK (2.1 equiv), and the resulting bright red solution added to freshly prepared **15** (0.5 equiv) dissolved in sufficient THF to bring the ultimate concentration of the reaction mixture to 0.4 M. After it was stirred for 12 h at 0 °C, the mixture was quenched with 5% HCl, extracted with CH₂Cl₂, and the extract chromatographed on silica gel to afford the Emmons adduct **21** (oil) in 80% yield from the diol epoxide **14**. The 2,4-dimethoxybenzyl residue was removed from **21** on treatment with TFA (neat, 0.1 M concentration of **21**) for 20 min at 22 °C. Chromatography of the reaction product as its sodium salt on Merck 7734 silica gel with CH₂Cl₂/MeOH, 9:1, gave tirandamycin A (**1**) as a yellow solid, mp 124–127 °C, in 85% yield.²⁴

Acknowledgment. We thank D. Graves for help in the preparation of aldehyde **5**. Financial support from the NIH, Merck, and the Sherman Clarke Fund are gratefully acknowledged.

(23) For examples of the reaction of the sodium salt of this species, see: Sturtz, G. *Bull. Soc. Chim. Fr.* **1964**, *31*, 2340.

(24) We thank Professors DeShong and Rinehart for kindly providing us with samples of naturally occurring tirandamycin A. Naturally occurring **1** as supplied to us by Professor DeShong exhibited a mp of 123–127 °C. Tirandamycin A is reported by Rinehart et al. (Rinehart, K. L., Jr.; Lee, V. J. *J. Antibiot.* **1980**, *33*, 408) to have a mp of 124–127 °C. All samples of tirandamycin A, both naturally occurring and synthetic, were crystallized from benzene. Rotations for new compounds are as follows: **6** [α]_D -67.4° (c 2.28, CH₂Cl₂), **7** [α]_D +69.0° (c 1.98, CH₂Cl₂), **2** [α]_D +26.1° (c 2.03, CH₂Cl₂), **3** [α]_D -75.9° (c 2.50, CH₂Cl₂), **9** [α]_D -7.1° (c 1.9, CH₂Cl₂), **10** [α]_D -39.1° (c 2.04, CH₂Cl₂), **11** [α]_D +195.6° (c 2.05, CH₂Cl₂), **12** [α]_D -174.4° (c 1.50, CH₂Cl₂), **13** [α]_D +34.0° (c 0.95, CH₂Cl₂), **14** [α]_D +20.6° (c 0.80, CH₂Cl₂), **21** [α]_D -5.7° (c 0.40, CH₂Cl₂), **1** [α]_D -8.4° (c 0.19, CHCl₃), for synthetic tirandamycin A prepared in these laboratories. A rotation of [α]_D -8.0° (CHCl₃) has been reported by Rinehart for naturally occurring tirandamycin A; see ref 5. Rotations for the aldehydes **8** and **15** were not obtained due to their marginally stable nature. Direct spectroscopic comparison between synthetic and natural tirandamycin A was made on the following instruments: ¹H NMR spectra, Bruker WH-400; ¹³C NMR spectra, G.E. QE-300; Nominal and high-resolution mass spectra, VG-7035; IR spectra, Perkin-Elmer 299B. In all cases these spectra were essentially identical. Tirandamycin A, as its sodium salt, is reported to have a rotation of [α]_D +51.0° (EtOH) by: Meyer, C. E. *J. Antibiot.* **1971**, *24*, 558. Recently, Professor P. DeShong (Pennsylvania State University) completed a total synthesis of **1** using the reagent **17**.

Diastereoselective [3 + 2]-Type Heterocyclic Synthesis via [2-(Acetoxymethyl)-3-allyl]tri-*n*-butylstannane

Barry M. Trost* and Peter J. Bonk

McElvain Laboratories of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

Received October 19, 1984

A [4 + 2] cycloaddition using carbonyl groups as acceptors for the synthesis of six-membered oxygen heterocycles permits easy access to this class of compounds with exceptional control of stereochemistry.¹ Developing analogous cycloaddition-like methods (eq 1) for the synthesis of five-membered heterocycles

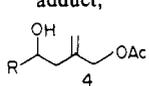
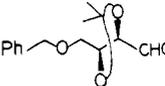
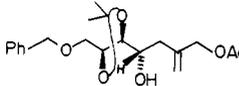
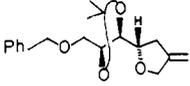
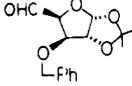
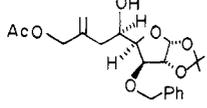
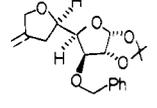
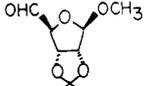
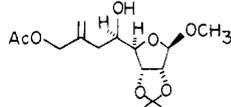
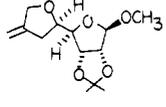
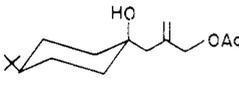
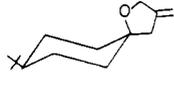
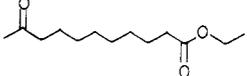
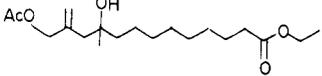
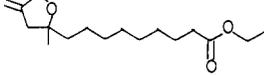


may provide similar benefits for these important classes of compounds. Unfortunately, the simplest solution to this problem using a palladium-catalyzed trimethylenemethane cycloaddition² failed. To resolve the impasse, we felt that a bifunctional conjunctive

(1) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2456. See also earlier references of this group.

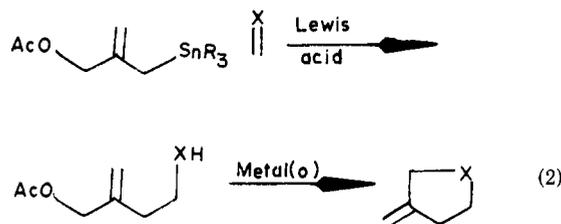
(2) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326.

Table I. 4-Methylenetetrahydrofuran Synthesis

entry	carbonyl partner RCHO	adduct, ^a 	yield, % ^b	ratio	cyclization product ^d 	yield, %
1	PhCHO	R = Ph	92			70
2			65	10:1		64
3			76	>20:1		66
4			89	12:1		60
5			76			80
6			74			62

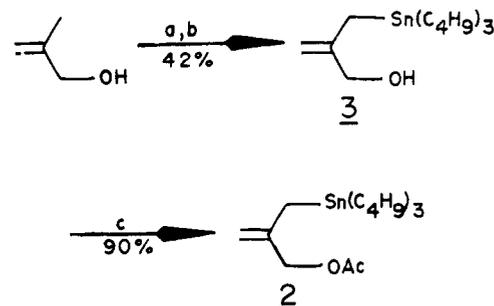
^aTo a 0.5 M solution of aldehyde in CH_2Cl_2 at -78°C is added 1.1–1.3 equiv of **2** and 3 equiv of $\text{BF}_3\cdot\text{Et}_2\text{O}$. After it is stirred at low temperature for 45 min., the reaction is quenched by pouring into saturated aqueous NH_4Cl and diluting with ether. The organic layer is separated, shaken with aqueous KF to remove the tin residues and then dried over Na_2SO_4 . Filtration, concentration, and column chromatography of the residue yields the pure product. If the chromatographic purification is omitted acetyl transfer among the hydroxyl groups will often occur. ^bIsolated yields. ^cA diastereomeric ratio determined by ^1H and ^{13}C NMR spectroscopy. ^dA general procedure for the Pd-catalyzed O-alkylation of **4** to form **5**: $\text{Pd}(\text{OAc})_2$ (0.05 equiv) and triphenylphosphine (0.25–0.35 equiv) are dissolved in dioxane under a nitrogen atmosphere. *n*-BuLi in hexane (0.1 equiv) is added and the mixture stirred for 15 min. DBU (1.5 equiv) is added, followed by **4** (1.0 equiv) as a solution in dioxane. The mixture is heated at reflux for 16–36 h. Removal of solvent by distillation and flash chromatography of the residue yields the desired product. For the amine substrate **6**, the procedure is similar except THF is used as the solvent and triethylamine is used as the base. Reaction times are generally on the order of 4 h or less.

reagent that is more organometallic-like was needed but, obviously, the increased nucleophilicity must still be compatible with the electrophilic center. In this regard [2-(acetoxymethyl)-3-allyl]-tri-*n*-butylstannane (**2**) was viewed as a good candidate to undergo a two-stage net cycloaddition using Lewis acids to initiate the first stage and transition metals the second (eq 2). The known re-



activity of allylstannanes with carbonyl partners in the presence of Lewis acid catalysts supports this suggestion.³ While to our knowledge the reaction of allylstannanes with imines has not been

(3) Use of mixed allylchlorostannanes resulted in diastereomeric ratios of 60:1. Reactions of crotyltrialkylstannanes can proceed with double diastereoselectivities of greater than 98:2. See: (a) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, 25, 1883. (b) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, 102, 7107. (c) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1983**, 191. (d) Naruta, Y. *J. Am. Chem. Soc.*, **1980**, 102, 3774. (e) Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1982**, 1297. (f) Gambaro, A.; Ganis, P.; Marton, D.; Peruzzo, V.; Tagliavini, G. *J. Organomet. Chem.* **1982**, 231, 307.

Scheme 1^a

^a (a) 2.2 equiv of *n*-BuLi, Et_2O -TMEDA-THF, 0°C \rightarrow room temperature, 24 h; (b) *n*-Bu₃SnCl (1.1 equiv); (c) AcCl, pyr, CH_2Cl_2 , $^\circ\text{C}$.

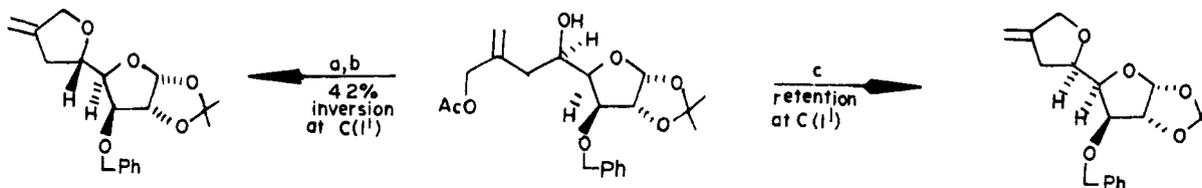
reported,⁴ such a reaction would provide a route to homoallylic amines. In this paper we report the preparation and use of **2** for the stereocontrolled synthesis of 2-substituted-4-methylenetetrahydrofurans⁵ and pyrrolidines,⁶ the former being potential pre-

(4) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1004. Hoffmann, R. W.; Eichler, G.; Endesfelder, A. *Liebigs Ann. Chem.* **1983**, 2000. Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, 106, 5031. Note Added in Proof: Recent reports have now described this reaction. See: Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, 50, 146.

Table II. 4-Methylenepyrrolidine Synthesis

entry	imine	adduct ^a	yield, %	cyclization prod ^b	yield, %
1			81		90
2			88		72
3			70		88
4			64		91

^a To a 0.5–1.0 M solution of the imine in CH_2Cl_2 at -78°C is added 1.2–1.5 equiv of **2**, followed by 3 equiv of $\text{BF}_3\cdot\text{Et}_2\text{O}$. The solution is allowed to warm to room temperature for 16 h and then quenched by pouring it into ice cold NH_4Cl and diluting with ether. The aqueous layer (pH 1) is separated, made strongly basic with ice cold 6 N NaOH , and then repeatedly extracted with 1:1 hexane:ether. Drying (Na_2SO_4) and solvent removal give the desired product. By working with cold solutions ester hydrolysis is avoided. ^b See footnote *d* Table I for procedure.

Scheme II^a

^a (a) MsCl , Et_3N , CH_2Cl_2 , -5°C ; (b) KOH , $\text{H}_2\text{O}/\text{MeOH}$, 5/1, reflux; (c) $\text{Pd}(0)$, see text.

cursors to ionophore antibiotics.

The preparation of **2** from methallyl alcohol (Scheme I) parallels the formation of the related trimethylsilyl compound⁷ but with several significant differences. The dianion of methallyl alcohol is trapped with only 1.1 equiv of tri-*n*-butyltin chloride to give **3** directly. No *O*-stannylated or bis(stannylated) products are obtained even when larger amounts of trap are used.⁸ In contrast, trapping the dianion with trimethyltin chloride requires at least 2.3 equiv of trap to maximize the yield.

The reaction of **2** with aldehydes in the presence of boron trifluoride etherate is rapid and is complete within 45 min at -78°C (see Table I). When ketones are used as substrates, after mixing at -78°C , stirring for several hours at -5°C is needed to get complete reaction (see Table I). Warming above 0°C often results in the formation of dehydrated products.

The boron trifluoride etherate mediated addition of **2** to chiral aldehydes occurs with good diastereoselectivity (entries 2–4, Table I), better than what has been reported^{3a} for allyl tri-*n*-butylstannane. Use of chelating Lewis acids (TiCl_4 or ZnCl_2) resulted in the formation of mixtures with poorer selectivity.

Imines also serve as acceptors for **2** in the presence of boron trifluoride. Their poorer electrophilicity demands somewhat more vigorous conditions—typically 16 h at room temperature. Table II summarizes some of the examples.

At first glance, the second stage of this net cycloaddition appears plagued with problems. The geometrical demands of a 5-endo-trig closure are unfavorable. Combining poor stereoelectronic factors with the fact that oxygen nucleophiles are generally poorer than more polarizable nucleophiles in metal-catalyzed allylic alkylations^{5a,d,9} led us to expect the initially encountered difficulties. However, using an in situ generation of a palladium(0) catalyst and DBU as base at less than 0.2 M leads to smooth cyclization as summarized in Table I. As expected, the amine¹⁰ cyclizations summarized in Table II proceeded more readily and did not suffer any ill effects from the unfavorable stereoelectronics.

The high diastereoselectivity associated with the initial addition translates into a high diastereoselectivity of the methylenetetrahydrofurans. An intriguing aspect of this two-stage process is the ability to manipulate the overall stereoselectivity by choosing the method of cyclization for the second step as shown in Scheme II. Both epimers of the methylenetetrahydrofuran are readily available from the initial single epimeric adduct. The importance of such joined heterocycles in the synthesis of ionophores makes this approach particularly useful.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their generous support of our programs.

Registry No. **2**, 94956-83-9; **3**, 94203-06-2; **4** ($\text{R} = \text{H}$, Ph), 94956-84-0; **4** ($\text{R} = \text{H}$, 5-[(benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl)

(5) (a) Stork, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073. (b) Magnus, P.; Gange, D.; Bass, L.; Arnold, E. V.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 2134. (c) Eaton, P. E.; Copper, G. F.; Johnson, R. C.; Mueller, R. H. *J. Org. Chem.* **1972**, *37*, 1947. (d) Godleski, S. A.; Stanton, S.; Felman, S.; Shutte-Parkhurst, C. *J. Am. Chem. Soc.* **1983**, *105*, 1964. (e) Piers, E.; Karunaratne, V. *J. Org. Chem.* **1983**, *48*, 1774. (f) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1981**, *46*, 3349.

(6) Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L. *J. Org. Chem.* **1982**, *47*, 1069. Chavdarian, C. G. *J. Org. Chem.* **1983**, *48*, 1529.

(7) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.

(8) This may be due to *O*-stannylation followed by rearrangements to give the more stable alkoxide anion.

(9) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230.

(10) Amines are excellent nucleophiles. See: Trost, B. M.; Genet, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 8516. Trost, B. M.; Godleski, P. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 7779. Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451. Trost, B. M.; Cossy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6881. Godleski, S. A.; Heacock, D. J.; Meinhart, J. D.; Van Wallendael, S. *J. Org. Chem.* **1983**, *48*, 2101. Genet, J. P.; Balabane, M.; Backvall, J. E.; Nystrom, J. E. *Tetrahedron Lett.* **1983**, *24*, 2745. Backvall, J. E.; Nordberg, R. E.; Zetterberg, K.; Akermarck, B. *Organometallics* **1983**, *2*, 1625.

(isomer 1), 94978-11-7; **4** (R = H, 5-[(benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl) (isomer 2), 95043-21-3; (*R**)-**4** (R = H, (1 α ,5 α ,6 α ,7 α)-6-(benzyloxy)-3,3-dimethyl-2,4,8-trioxabicyclo[3.3.0]octan-7-yl), 94978-03-7; **4** (R = H, 3,3-dimethyl-8-methoxy-2,4,7-trioxabicyclo[3.3.0]octan-6-yl) (isomer 1), 94978-04-8; **4** (R = H, 3,3-dimethyl-8-methoxy-2,4,7-trioxabicyclo[3.3.0]octan-6-yl) (isomer 2), 95042-59-4; *cis*-**4** (R = CH₂CH₂CH(*t*-Bu)CH₂CH₂), 94956-85-1; **4** (R = Me, (CH₂)₈C(O)OEt), 94956-86-2; **5** (R = H, Ph), 80997-79-1; (*S**,*S**,*S**)-**5** (R = H, 5-[(benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl), 94956-87-3; (*R**)-**5** (R = H, (1 α ,5 α ,6 α ,7 α)-6-(benzyloxy)-3,3-dimethyl-2,4,8-trioxabicyclo[3.3.0]octan-1-yl), 94978-05-9; (*S**)-**5** (R = H, (1 α ,5 α ,6 α ,7 α)-6-(benzyloxy)-3,3-dimethyl-2,4,8-trioxabicyclo[3.3.0]octan-7-yl), 95042-61-8; (*R**)-**5** (R = H, (1 α ,5 α ,6 α ,8 α)-3,3-dimethyl-8-methoxy-2,4,7-trioxabicyclo[3.3.0]octan-6-yl), 94978-06-0; *cis*-**5** (R = CH₂CH₂CH(*t*-Bu)CH₂CH₂), 94956-88-4; **5** (R = Me, (CH₂)₈C(O)OEt), 94956-89-5; **6** (R = R' = Ph), 94956-90-8; **6** (R = Pr, R' = Ph), 94956-91-9; **6** (R = Pr, R' = *i*-Pr), 94956-92-0; **6** (R = Me, R' = 3-pyridinyl), 94956-93-1; **7** (R = R' = Ph), 94956-94-2; **7** (R = Pr, R' = Ph), 94956-95-3; **7** (R = Pr, R' = *i*-Pr), 94956-96-4; **7** (R = Me, R' = 3-pyridinyl), 94956-97-5; PhCHO, 100-52-7; CH₃C(O)-(CH₂)₈C(O)OEt, 36651-38-4; PhCH=NPh, 538-51-2; PhCH=NPr, 6852-55-7; (CH₃)₂CHCH=NPr, 2875-39-0; CH₂=C(CH₃)CH₂OH, 513-42-8; Bu₃SnCl, 1421-22-9; BF₃·Et₂O, 109-63-7; TiCl₄, 7550-45-0; ZnCl₂, 7646-85-7; Ph₃P, 603-35-0; Pd(OAc)₂, 3375-31-3; *trans*-2,2-dimethyl-5-[(benzyloxy)methyl]-1,3-dioxolane-4-carboxaldehyde, 95042-60-7; (1 α ,5 α ,6 α ,7 α)-3,3-dimethyl-6-(benzyloxy)-2,4,8-trioxabicyclo[3.3.0]octane-7-carboxaldehyde, 87938-29-2; (1 α ,5 α ,6 α ,8 α)-3,3-dimethyl-8-methoxy-2,4,7-trioxabicyclo[3.3.0]octan-6-carboxaldehyde, 58056-24-9; 4-*tert*-butylcyclohexanone, 98-53-3; 3-[(methylimino)methyl]pyridine, 16273-54-4.

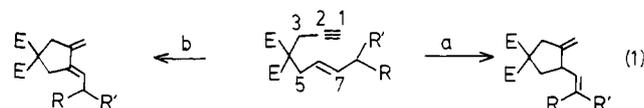
Cyclization via Isomerization: A Palladium(2+)-Catalyzed Carbocyclization of 1,6-Enynes to 1,3- and 1,4-Dienes

Barry M. Trost* and Mark Lautens

McElvain Laboratories of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

Received October 19, 1984

The development of routes for the synthesis of five-membered rings continues to attract attention due largely to the wide variety of natural products containing this structural unit.^{1,2} As part of our continuing effort to expand the utility of transition-metal-catalyzed alkylations,³ we turned our attention to the synthesis of 1,6-enynes. Synthetic routes to such species would offer an efficient entry into highly substituted cyclopentane derivatives via thermal ene reactions.⁴ During the course of these studies, we made the unanticipated observation that palladium(2+) salts catalyze cyclizations via an isomerization to lead to related products under very mild conditions as summarized in eq 1, paths



a and b. The factors that influence the pathway traversed and

(1) For reviews, see: (a) Trost, B. M. *Chem. Soc. Rev.* **1981**, *11*, 141. (b) Ramaiah, M. *Synthesis* **1984**, 529. (c) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1.

(2) For leading references, see: Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315.

(3) For alkylations catalyzed by palladium(0), see: Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385; *Aldrichimica Acta* **1981**, *14*, 43. Trost, B. M.; Verhoeven, T. R. *Compr. Organomet. Chem.* **1982**, *8*, 799-938. Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer-Verlag: Berlin, 1980. For a review on palladium-assisted reactions of monoolefins, see: Hegedus, L. *Tetrahedron* **1984**, *40*, 2415.

(4) For reviews on the intramolecular ene reaction, see: Taber, D. F. "Intramolecular Diels-Alder and Alder Ene Reactions"; Springer-Verlag: Berlin, 1984. Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. Hoffman, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556.

the generality of this new cyclization are the subject of this communication.

The starting enynes⁵ are readily prepared by using the palladium(0)-catalyzed coupling of allylic carboxylates with dimethyl propargylmalonate anion [3-5 mol % (Ph₃P)₄Pd, NaH, THF, 1-16 h at reflux]. As seen in Table I the yields are consistently good (55-90%) with high chemo-, regio-, and stereoselectivity associated with the alkylation process. As previously noted, palladium-catalyzed allylic alkylations³ tend to favor formation of the isomer that results from attack at the less substituted terminus of the π -allylmethyl intermediate.

Carbocyclizations were conveniently carried out by heating a mixture of the enyne with a catalytic amount (3-10 mol %) of a palladium salt in a variety of organic solvents at 60-70 °C for 1-4 h.

A Pd(0) species such as (Ph₃P)₄Pd does *not* catalyze reaction after 12 h at reflux in THF. The effectiveness of the Pd(2+) species appears related to the Lewis acidity of the catalyst. For example, bis(acetonitrile)palladium chloride⁶ catalyzes cyclization of **3** to **4** very slowly (16% after 6.5 h in refluxing THF). On the other hand, L₂Pd(OAc)₂ effects complete reaction in THF at room temperature to reflux depending on L. Palladium acetate (5 mol %) cyclizes enyne **3** to give diene **4** in 50% yield in THF at room temperature. Best yields and cleanest reactions derive from use of preformed (Ph₃P)₂Pd(OAc)₂⁷ or [(*o*-CH₃C₆H₄)₃P]₂Pd(OAc)₂ although heating is required. Changing solvent polarity (PhH, THF, CHCl₃, or CH₃CN) does not appreciably affect the *rate* of the reaction. Again, yields appear maximized by use of nonpolar solvents like benzene. A phosphine to Pd ratio as high as 5-6:1 slows the reaction further but does not inhibit reaction.

Substrates containing methyl or methylene groups in allylic positions (Table I, entries 1-4) undergo the isomerization yielding 1,4-dienes. The reaction exhibits a high degree of stereoselectivity (entry 1) yielding the *trans* olefin. Furthermore, no isomerization to the α,β -unsaturated ester is observed in the preparation of **4**. Examination of a case producing vicinal substituents shows the reaction is diastereoselective—producing a 3:1 *trans/cis* mixture of cyclopentanes (entry 3). Attempts to further improve the selectivity involving manipulation of phosphine ligands are in progress.

The cyclization of enyne **7** is somewhat puzzling. It is the only case examined to date where one of the double bonds (in this case the cyclohexenyl one) suffers further isomerization. Among several phosphines examined to minimize isomerization of the $\Delta^{6,7}$ isomer to the $\Delta^{7,8}$ one, 5 mol % of dppb with 5 mol % Pd(OAc)₂ in PhH produces the best ratio (5.7:1). In the absence of ligands or by using phosphites as ligands, extensive (25%) isomerization of the exocyclic double bond to an endocyclic position occurred.

The discovery of the cyclization process offers several advantages over simple thermal ene methodology. For example, all attempts to thermalize **3** result in the recovery of starting material (<650 °C) or decomposition (>675 °C) in contrast to normal reactivity in the palladium-catalyzed reaction. It is also possible to carry out a "one-pot" alkylation-carbocyclization by simply adding a catalytic amount (~5 mol %) of palladium acetate to the original Pd(0)-catalyzed alkylation reaction mixture. In this way, diene **4** arises directly from the allylic acetate in 68% overall yield.

Entries 5-7 reveal that an alternative pathway is possible when the allylic carbon (C-8 in eq 1) is disubstituted. NMR analysis of the crude reaction mixtures reveal that only 1,3-dienes are produced with no trace of the 1,4-diene. Again a wide variety of functional groups are tolerated and the utility of such products

(5) All new compounds have been fully characterized by spectral means including combustion analysis and/or high-resolution mass spectroscopy.

(6) For examples of this catalyst in Cope rearrangements, see: Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225 and references therein. Cyclizations of such systems to cyclohexenes are also reported: Overman, L. E.; Renaldo, A. F. *Tetrahedron Lett.* **1983**, *24*, 2235.

(7) Preparation of phosphine complexes of palladium, see: Stephenson, T. A.; Morehouse, S. M.; Powell, A. R.; Heffer, J. P.; Wilkinson, G. *J. Chem. Soc.* **1965**, 3632.