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Palladium-Catalyzed Functionalization of Lactones via Their Cyclic Ketene Acetal Phosphates. Efficient New Synthetic Technology for the Construction of Medium and Large Cyclic Ethers

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The functionalization of lactones (**I**, Figure 1) via their corresponding enolate derivatives (**II**) to afford substituted lactones (**III**) has been one of the most useful carbon−carbon bond-forming reactions in organic synthesis. In contrast, and despite its rich potential, the alternative mode of lactone functionalization to afford substituted cyclic enol ethers (**IV**) has only recently been investigated.[1] Current methodology for this process involves cyclic ketene acetal triflates (**II**, X = SO_2-CF_3), which often suffer from instability and low yields, both in their formation and in their coupling reactions.[1] In this paper, we introduce lactone-derived cyclic ketene acetal phosphates[2] [**II**, X = P(O)$(OR)_2$] as superior substrates for palladium(0)-catalyzed carbon−carbon bond-forming reactions. In addition to the lower cost of the reagents involved in their preparation, these substrates enjoy higher stability and efficiency in their formation and coupling reactions than their triflate counterparts. Most importantly, and as demonstrated below, these substrates offer excellent solutions to the well-recognized and challenging problem of constructing medium and large ring systems.[3]

The cyclic ketene acetal diphenyl phosphate[4] **2** (Scheme 1) was prepared from the 9-membered ring lactone **1**[5] via its potassium enolate (1.2 equiv of potassium bis(trimethylsilyl)-amide, KHMDS, 3.0 equiv of HMPA, 2.0 equiv of $(PhO)_2$P-(O)Cl, THF, −78 °C; add lactone to phosphoryl chloride and base) and proved to be quite stable at ambient temperatures and to silica gel flash chromatography. Reaction of **2** with a variety of vinylstannanes in the presence of $Pd(PPh_3)_4$ catalyst and LiCl[6] in refluxing THF resulted in the formation of a series of diene systems in excellent yields as shown in Scheme 1. In addition to their obvious usefulness in polyether construction, these

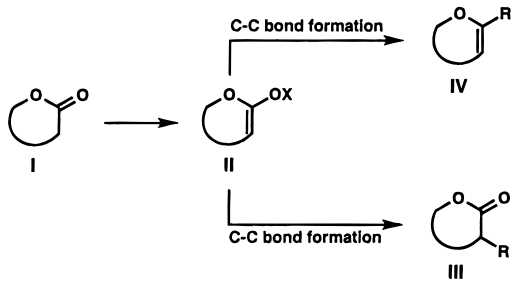
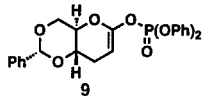
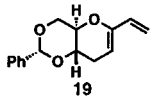
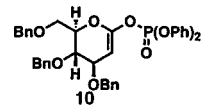
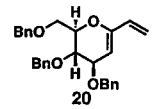
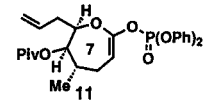
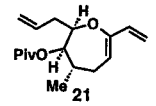
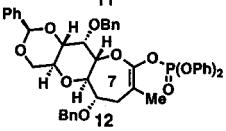
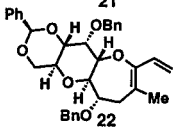
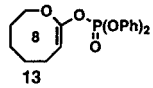
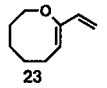
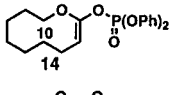
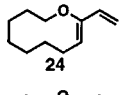
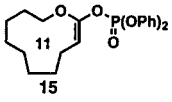
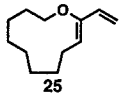
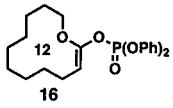
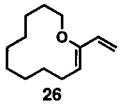
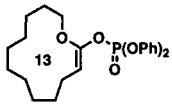
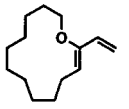
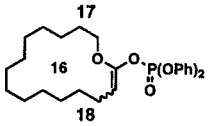
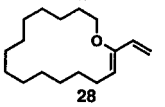


Figure 1. Two modes of lactone functionalization.

Table 1. Synthesis and Palladium-Catalyzed Coupling of Cyclic Ketene Acetal Phosphates

Entry	Phosphate[a]	Yield (%)	Coupling Product[b]	Yield (%)
1	 9	78	 19	82
2	 10	75	 20	75
3	 11	85	 21	81
4	 12	92	 22	58[c]
5	 13	82[d]	 23	85
6	 14	88	 24	80
7	 15	95	 25	82
8	 16	96	 26	84
9	 17	92	 27	86
10	 18	91[f]	 28	94[g]

[a] Conditions: 1.2 equiv of KHMDS, 2.0 equiv of HMPA, 2.0 equiv of $(PhO)_2$POCl, THF, −78 °C, 0.5 h; add base to lactone, phosphoryl chloride, and HMPA. [b] Coupling conditions as described in Scheme 1 for compound **3**. [c] Reaction performed in refluxing dioxane. [d] Formation conditions as described in Scheme 1 for compound **2**. [f] Obtained as a 1:4 *Z*/*E* mixture. [g] The geometry of the cyclic enolic double bond was determined by ^{1}H-ROESY. The same stereochemistry was assumed for the remaining medium and large ring-coupling products.

(1) For the use of cyclic ketene acetal triflates in carbon−carbon bond-forming reactions, see: (a) Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313. (b) Tsushima, K.; Murai, A. *Chem. Lett.* **1990**, 761. (c) Barber, C.; Jarowicki, K.; Kocienski, P. *Synlett* **1991**, 197. (d) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345. (e) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171. (f) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *ibid* **1995**, *117*, 1173. (g) Fujiwara, K.; Tsunashima, M.; Awakura, D.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 8263. (h) Nicolaou, K. C.; Sato, M.; Miller, N. D.; Gunzner, J. L.; Renaud, J.; Untersteller, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 889.

(2) For a number of known transformations of cyclic ketene acetal phosphates, see: (a) Carbonnier, F.; Albert, M.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2303 (reduction of O−P bond). (b) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750 (cyclic ketene acetal phosphate → α-phosphono lactone rearrangement). (c) Cabezas, J. A.; Oehlschlager, A. C. *J. Org. Chem.* **1994**, *59*, 7523 (elimination to acetylenic ethers).

(3) For selected reviews of medium and large cyclic ether formation, see: (a) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 588. (b) Elliot, M. C. *Contemp. Org. Synth.* **1994**, *1*, 457. (c) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (d) Moody, C. J.; Davies, M. J. in *Studies in Natural Products Chemistry*; Atta-Ur-Rahman, Ed.; Elsevier: New York, 1992; Vol. 10, p 201.

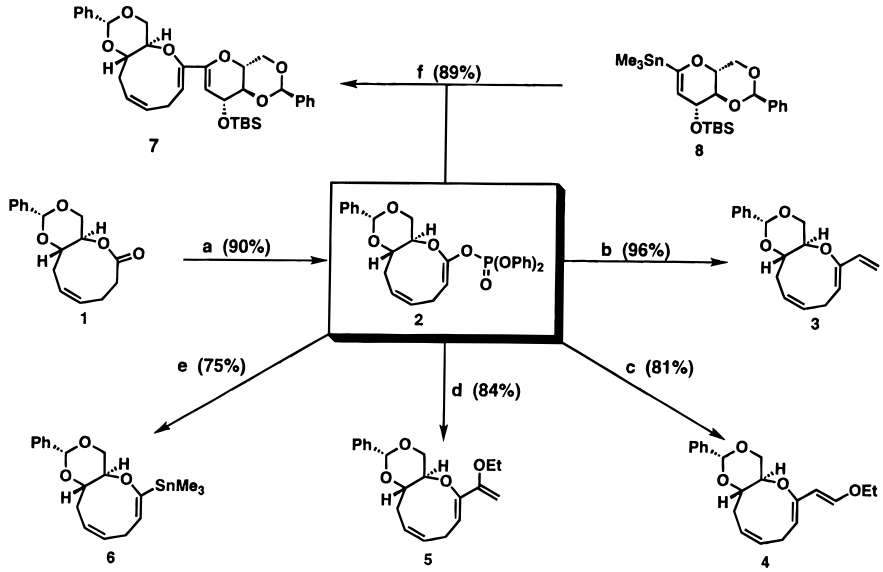
(4) Other phosphoryl chlorides such as $(EtO)_2$P(O)Cl may be used to form the corresponding phosphates which enter in similar coupling reactions. The diphenyl phosphates are, however, preferred for their higher stability, yields of formation and coupling reactivity.

(5) For the synthesis of this compound, see Supporting Information.

(6) Scott, W. J.; Stille, J. K *J. Am. Chem. Soc.* **1986**, *108*, 3033.

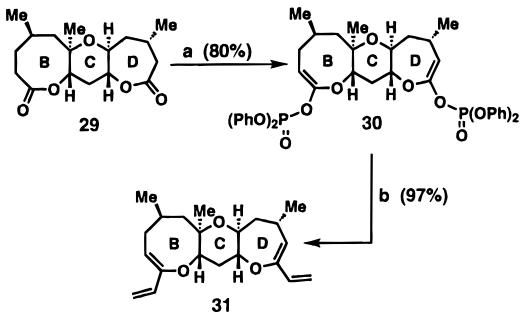
S0002-7863(97)00619-7 CCC: $14.00

Scheme 1. Synthesis of 9-Membered Ring Enol Ethers from Cyclic Ketene Acetal Phosphates[a]



[a] Key: (a) 1.2 equiv of KHMDS, 3.0 equiv of HMPA, 2.0 equiv of $(PhO)_2POCl$, THF, −78 °C, 0.5 h; add lactone to base, phosphoryl chloride, and HMPA; (b) 2.0 equiv of tri-*n*-butyl(vinyl)tin, 0.05 equiv of $Pd(PPh_3)_4$, 3.0 equiv of LiCl, THF, Δ, 2 h; (c) 2.0 equiv of tri-*n*-butyl(2-ethoxyvinyl)tin, 0.05 equiv of $Pd(PPh_3)_4$, 3.0 equiv of LiCl, THF, Δ, 1.5 h; (d) 2.0 equiv of tri-*n*-butyl(1-ethoxyvinyl)tin, 0.05 equiv of $Pd(PPh_3)_4$, 3.0 equiv of LiCl, THF, Δ, 6 h; (e) 2.0 equiv of hexamethylditin, 0.05 equiv of $Pd(PPh_3)_4$, 3.0 equiv of LiCl, THF, Δ, 3 h; (f) 2.0 equiv of **8**, 0.05 equiv of $Pd(PPh_3)_4$, 3.0 equiv of LiCl, THF, Δ, 7 h.

Scheme 2. Bis(functionalization) of Bis(lactone) **29** and Synthesis of Tetraene System **31**[a]



[a] Key: (a) 3.0 equiv of KHMDS, 4.0 equiv of HMPA, 4.0 equiv of $(PhO)_2POCl$, THF, −78 °C, 0.5 h; add lactone to base, phosphoryl chloride, and HMPA; (b) 4.0 equiv of vinyltri-*n*-butyltin, 0.1 equiv of $Pd(PPh_3)_4$, 6.0 equiv of LiCl, THF, Δ, 3 h.

products (e.g., **3**−**7**, Scheme 1) may also find applications in other areas of chemistry, particularly in Diels−Alder reactions. The generality and scope of the method is further illustrated in Table 1. Thus, a series of cyclic ketene acetal phosphates have been prepared as described above from the corresponding lactones and purified by flash column chromatography. These substrates were then subjected to the Pd-catalyzed coupling reaction, furnishing the expected dienes in high yields. Most noteworthy is the success of the method in forming medium-sized rings, where the corresponding triflate technology either fails (e.g., 8-membered ring)[1a,c] or results in low yields.[1d]

A striking application of the described technology is the two-directional functionalization of bis(lactone) **29**[7] (Scheme 2). Thus, exposure of **29** to 3.0 equiv of KHMDS, 4.0 equiv of HMPA, and 4.0 equiv of $(PhO)_2P(O)Cl$ in THF at −78 °C furnished the bis(enol phosphate) **30** in 80% yield after flash chromatography.[8] Coupling of this intermediate with vinyltri-*n*-butylstannane in the presence of LiCl and a catalytic amount of $Pd(PPh_3)_4$ in THF at reflux resulted in the formation of bis-(diene) **31** in 97% yield. The latter compound may serve as a useful intermediate in the total synthesis of brevetoxin A.[9,10]

The chemistry described above demonstrates the usefulness of cyclic ketene acetal phosphates as stable and easily accessible substrates for palladium-catalyzed coupling reactions. Their superiority over cyclic ketene acetal triflates in terms of cost and availability of reagents for their synthesis, stability, and efficiency of formation and coupling should make them the substrates of choice for such operations. Other reactions and applications of ketene acetal phosphates are currently under investigation.[11]

Acknowledgment. We thank Drs. Dee H. Huang and Gary Siuzdak for their superb NMR and mass spectroscopic assistance, respectively. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, the American Chemical Society (a graduate fellowship sponsored by the Aldrich Chemical Co. to J.L.G.), and the Austrian Science Foundation (an Erwin Schrödinger Postdoctoral Fellowship to P.G.).

Supporting Information Available: Procedures for the preparation of **2** and its coupling with vinyl tri-*n*-butylstannane, listing of selected data for compounds **2**, **3**, **5**, **7**, **30**, and **31** and ^1H and ^{13}C NMR spectra for compounds **2**−**7**, **9**−**28**, **30**, and **31** (34 pages). See any current masthead page for ordering and Internet access instructions.

JA970619+

(7) Nicolaou, K. C.; McGarry, D. G.; Sommers, P. K. *J. Am. Chem. Soc*. **1990**, *112*, 3696.

(8) It is interesting to note that the cyclic ketene acetal triflate counterpart of **30** could not be isolated upon attempted preparation from bis(lactone) **29**.

(9) For the structure of brevetoxin A, see: (a) Shimizu, Y.; Chou, H. N.; Bando, H.; Van Duyne, G.; Clardy, J. *J. Am. Chem. Soc*. **1986**, *108*, 514. (b) Pawlak, M.; Tempesta, M. S.; Golik, J.; Zagorski, M. G.; Lee, M. S.; Nakanishi, K.; Iwashita, T.; Gross, M. L.; Tomer, K. B. *J. Am. Chem. Soc*. **1987**, *109*, 1144.

(10) For a synthetic approach to brevetoxin A, see: (a) Nicolaou, K. C.; Prasad, C. V. C.; Ogilvie, W. W. *J. Am. Chem. Soc*. **1990**, *112*, 4988. (b) Nicolaou, K. C.; Veale, C. A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C. V. C.; Ogilvie, W. W. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 299. (c) Reference 7.

(11) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.