Phosphine-Catalyzed Isomerization–Addition of Oxygen Nucleophiles to 2-Alkynoates

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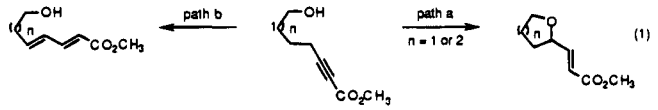
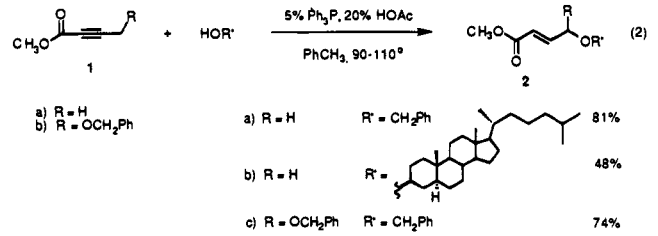
The widespread occurrence of tetrahydrofuran and tetrahydropyran rings in many classes of natural products makes it important to develop new methods for their syntheses.[1,2] Our recent discovery of the ability of phosphines to redirect the addition of carbon nucleophiles from the normal β-position (i.e., Michael addition) to the γ-position of 2-alkynoates led to consideration of eq 1 (path a) as a facile method for the synthesis of these heterocycles.[3] However, the fact that such substrates



(1)

can undergo simple migration of the unsaturation to form dienoates (eq 1, path b), a pathway that normally dominates, undermines such a proposal. Furthermore, the fact that alcohols are much poorer Michael donors than are carbon nucleophiles questions the viability of such a strategy. Nevertheless, we wish to report not only that this strategy succeeds but also that alcohols are better donors than carbon nucleophiles in our isomerization–addition in contrast to the Michael reaction.[4]

The feasibility of alcohol addition was tested in the reaction of methyl 2-butynoate (**1a**) with benzyl alcohol (eq 2). Heating



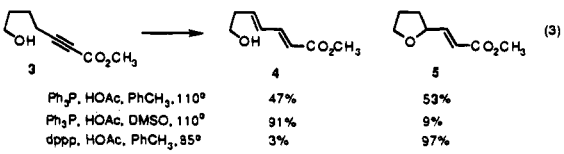
(2)

a 1 M solution of a 1:1 mixture of the two reactants in the presence of 5 mol % triphenylphosphine (TPP) and 20% acetic acid at 90 °C gave the desired adduct **2a** in 81% isolated yield.

For examining the reactivity of a secondary alcohol, we chose cholesterol. Performing the reaction at 0.5 M gave a 48% isolated yield of the desired product **2b** in the same time period (12 h) due to a lower conversion of the starting material, which indicates a slower reaction.

Attempts to effect isomerization–addition of dimethyl malonate to methyl 4-(benzyloxy)-2-butynoate led to none of the expected adduct. In complete contrast to this result, benzyl alcohol undergoes smooth addition under the conditions of eq 2. Thus, alcohols are superior to carbon nucleophiles in this isomerization–addition. This result is critical to the cyclization studies since isomerization–addition will be competing with simple isomerization to dienoates—the latter process completely dominating with carbon nucleophiles under our standard TPP conditions.

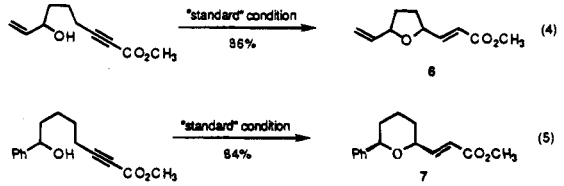
The higher reactivity of primary vs secondary alcohols led to an initial study with methyl 7-hydroxy-2-heptynoate (**3**) (eq 3). Our "standard" conditions produced a nearly 1:1 mixture



(3)

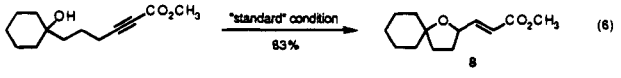
of the simple isomerization product **4**[5] and the isomerization–addition product **5**.[6] By manipulating the reaction parameters, either product could be made to dominate. For example, switching from toluene to the more polar DMSO strongly favored formation of dienoate **4**. On the other hand, switching from a monodentate phosphine to a bidentate one, dppp, strongly favored isomerization–addition. For our cyclization, we have adopted 5 mol % dppp and 20 mol % acetic acid in toluene at 85–90 °C as our standard conditions.

Secondary alcohols also cyclize to form both five- (eq 4) and six- (eq 5) membered rings. While the tetrahydrofuran **6**[5] was



(4) (5)

a diastereomeric mixture, the tetrahydropyran **7**[5] was virtually a single stereoisomer assigned *cis* on the basis of the axial–axial vicinal coupling constants (J = 11.2 and 11.5 Hz) of the hydrogens adjacent to oxygen. Even a tertiary alcohol led to successful isomerization–addition to form a spiro tetrahydrofuran **8**[5] (eq 6).



(6)

Formation of fused bicyclic systems proved most interesting. Using a cyclopentyl scaffold, the *trans* and *cis* substrates **9** and

(1) For a sampling of recent efforts, see: Trost, B. M.; Flygare, J. A. *Tetrahedron Lett.* **1994**, *35*, 4059. Mukai, C.; Ikeda, Y.; Sugimoto, Y.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 2179; 2183. Busato, S.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 92. Lee, E.; Tae, J. S.; Chong, Y. H.; Park, Y. C.; Yun, M.; Kim, S. *Tetrahedron Lett.* **1994**, *35*, 129. Phillips, E. D.; Whitham, G. H. *Tetrahedron Lett.* **1993**, *34*, 2541. Horita, K.; Noda, I.; Tanaka, K.; Miura, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1993**, *49*, 5979. Hori, K.; Kazuno, H.; Nomura, K.; Yoshii, E. *Tetrahedron Lett.* **1993**, *34*, 2183. D'Aniello, F.; Mattii, D.; Taddei, M. *Synlett* **1993**, *119*. Desai, M. C.; Doty, J. L.; Stephens, L. M.; Brighty, K. E. *Tetrahedron Lett.* **1993**, *34*, 961. Takacs, J. M.; Chandramoreli, S. V. *J. Org. Chem.* **1993**, *58*, 7315. Ma, S.; Zhu, G.; Lu, X. *J. Org. Chem.* **1993**, *58*, 270. Trost, B. M.; Sharma, S.; Schmidt, T. *Tetrahedron Lett.* **1993**, *34*, 7183. Annby, V.; Stenkula, M.; Andersson, C.-M. *Tetrahedron Lett.* **1993**, *34*, 8545. Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205. Grieco, P. A.; Moher, E. D. *Tetrahedron Lett.* **1993**, *34*, 5567. Reetz, M. T.; Gansäuer, A. *Tetrahedron* **1993**, *49*, 6025. Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468. Mitsunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 22–28.

(2) For reviews, see: Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 367–397. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323.

(3) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167.

(4) For reviews of conjugate additions, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.1, pp 1–67. During the course of this work, formation of phenol adducts was observed during phosphine-induced isomerization of alkynoates to dienoates, see: Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659. For phosphine-induced isomerization of alkynoates to dienoates, see: Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933. Guo, C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921.

(5) All new compounds have been fully characterized by spectroscopy and by combustion analysis; see supplementary material.

(6) Priepke, H.; Brucker, R. *Chem. Ber.* **1990**, *123*, 153.

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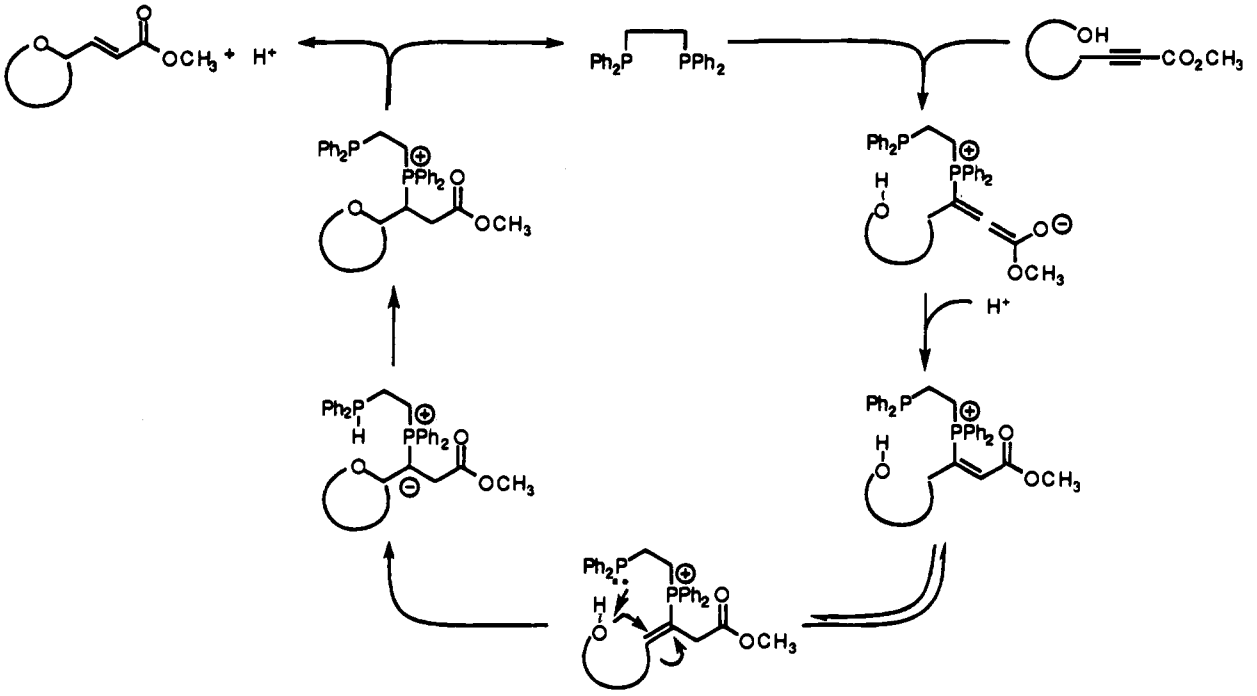
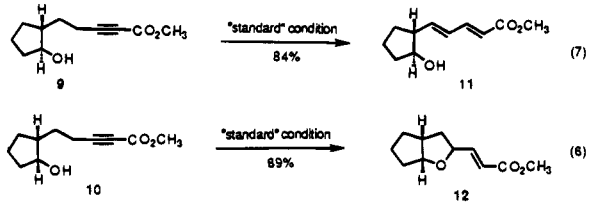
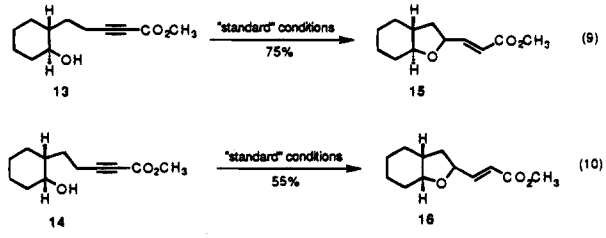
Scheme 1. Mechanistic Rationale for Phosphine-Catalyzed Internal Redox



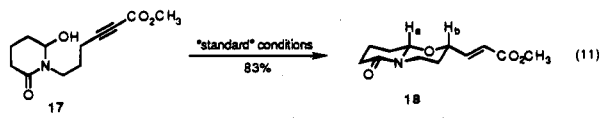
10 gave quite distinct results. Whereas the *trans* isomer **9** gave only dienoate **11**[5] (eq 7), the *cis* isomer **10** gave the isomerization–addition product **12**[5] as a 55:45 diastereomeric mixture (eq 8). On the other hand, using a cyclohexyl scaffold, the *trans*



and *cis* hydroxyalkynoates **13** and **14** successfully cyclize to the tetrahydrofurans **15**[5] and **16**,[5] respectively, as diastereomeric mixtures (eqs 9 and 10). In the former case, a small amount of the dienoate product was detected.



Other oxygen heterocycles may also be constructed by this method. Cyclization of the aminol **17** generates the 1,3-oxazine **18**[5] diastereomerically pure (eq 11). The presence of axial–axial coupling constants of 13.2 and 11.8 Hz for H_a and H_b, respectively, suggests the *cis* isomer as depicted.



A typical experimental procedure follows (eq 5). Acetic acid (6 mg, 0.1 mmol) was added to a solution of methyl 8-hydroxy-8-phenyl-2-octynoate (123 mg, 0.5 mmol) and dppp (6 mg, 0.0015 mmol) in 1 mL of toluene. After being heated 15 h at 90 °C, the cooled reaction mixture was concentrated *in vacuo* and flash chromatographed (12:1 hexane:ethyl acetate) to give 103 mg (84% yield) of **7**. Characterization data appear in the supplementary material.

A mechanism to account for this remarkable cyclization is presented in the Scheme 1. The advantage of a bidentate phosphine may stem from the ability of the second phosphine to function as a general base catalyst. The delicate balance between isomerization to dienes and isomerization–addition is highlighted by the dramatic effect of solvent (eq 3) and geometry (eq 7). Nevertheless, excellent yields of tetrahydrofurans, tetrahydropyrans, and a 1,3-oxazine have been obtained in many cases.

The simplicity and mildness of this method for the construction of oxygen heterocycles should impart selectivity. Thus, many functional groups, including conjugated and unconjugated olefins, unconjugated acetylenes, alcohols, acids, esters, ketones, etc., should be compatible. The fact that the hydroxyl oxygen adds in preference to a carboxylic acid oxygen, a carboxylic acid being required as a cocatalyst, presumably reflects the importance of electron density rather than polarizability for the donor group. The ease of construction of acetylenic substrates due to the ability of this linkage to facilitate both nucleophilic and electrophilic reactions adds power to the method. The presence of an enoate in the product offers great opportunity for further structural elaboration. The ability to trigger folding of an acyclic hydroxyalkynoate to cyclic ethers constitutes a cycloisomerization, a highly atom economical type of reaction.

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Supplementary Material Available: Characterization data for **2b**, **2c**, **4**, **6**, **7**, **8**, **11**, **12**, **15**, **16**, and **18** (3 pages). This material is contained in many 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.