Inversion of Acyclic Olefins by the Phosphorus Betaine Method. Scope and Limitations

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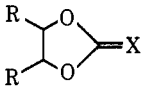
Abstract: Reaction of epoxides derived from di- or trisubstituted alkenes with lithium diphenylphosphide followed by methyl iodide affords phosphorus betaines which fragment to alkenes with overall inversion of stereochemistry (>98% stereospecific inversion). The method is not useful for inversion of alkene esters since lithium diphenylphosphide attacks the ester function. Ketones react with lithium diphenylphosphide to form enolates, but ketoepoxides can be deoxygenated in practical yields under carefully controlled conditions.

Increasingly sophisticated stereospecific routes to certain di-, tri-, and tetrasubstituted olefins have been devised as part of the effort directed toward synthesis of acyclic terpenoid polyenes and related substances.[3] A simple method for inverting stereochemistry about the double bond would be a valuable extension of the scope of these techniques for olefin synthesis, since any given method is often capable of generating only one of the possible cis–trans isomers. Considerable progress has been made toward the goal of stereospecific olefin inversion using concerted fragmentations of heterocyclic olefin precursors. Thus, 1,3-dioxolane-2-thiones (a),[4] 2-acyloxy-1,3-dioxolanes (b),[5] or 2-phenyl-1,3-dioxolanes[6] derived from vicinal diols fragment to olefins, respectively, upon treatment with trivalent phosphorus derivatives at 0–160° (depending on substrate and phosphine), pyrolysis at 120–140°, or reaction with *n*-butyllithium (18 hr at room temperature). Vicinal diols may be prepared by trans hydroxylation of alkenes, so the above cis fragmentations would result in inversion of starting alkene stereochemistry.



a, X = S
b, X = H, $OOCCH_3$
c, X = H, C_6H_5

From the practical viewpoint, the 1,3-dioxolane fragmentations "b" and "c" are limited to relatively simple molecules by the harsh experimental conditions which are necessary. Other heterocyclic compounds (thiiranes,[7] thiirane oxides[8] and dioxides,[9] 2,5-dihydrothiophenium salts,[10] 2,5-dihydrothiophene dioxides and derivatives,[11] 2,5-dihydropyrroles,[12] aziridine derivatives,[13] 3,6-dihydropyridazines and derivatives,[14] β-lactones,[15] and β-lactams[16]) fragment stereoselectively to olefins under appropriate conditions. Some of these reactions have potential for olefin inversion, but the necessary heterocyclic starting materials are often difficult to prepare stereospecifically. An unrelated method for olefin inversion has been described recently *via* the sequence trans bromination–cis debromination with bis(trimethylsilyl)mercury,[17] but the scope of this reaction has not yet been established. Finally, the older technique of trans chlorination–trans dehydrochlorination and lithium/ammonia reduction may be noted as a method for olefin inversion.[18]

Control of olefin stereochemistry can also be achieved *via* epoxides. Epoxides are transformed to the starting olefins with predominant retention of stereochemistry by the sequence of SN2 opening of epoxide by iodide and trans elimination with stannous ion,[19] or more cleanly by SN2 opening with triphenyltin anion and deoxystannation upon treatment with an acid catalyst.[20] Alternately, olefin inversion can be accomplished by a related sequence *via* epoxide if the olefin-forming step occurs by a cis-elimination mechanism. The well-known cis eliminations of phosphorus betaines and various β-hydroxyphosphonic acid derivatives to olefins can be used for this purpose. Epoxide opening by nucleophilic triaryl- or trialkylphosphines yields betaines, and, assuming a SN2 mechanism for the

(1) Alfred P. Sloan Fellow, 1971–1973.

(2) We thank the National Science Foundation for support of this work.

(3) For a review of stereoselective alkene synthesis, see J. Reucroft and P. G. Sammes, *Quart. Rev., Chem. Soc.*, **25**, 135 (1971).

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(12) D. M. Lemal and S. D. McGregor, *ibid.*, 88, 1335 (1966).

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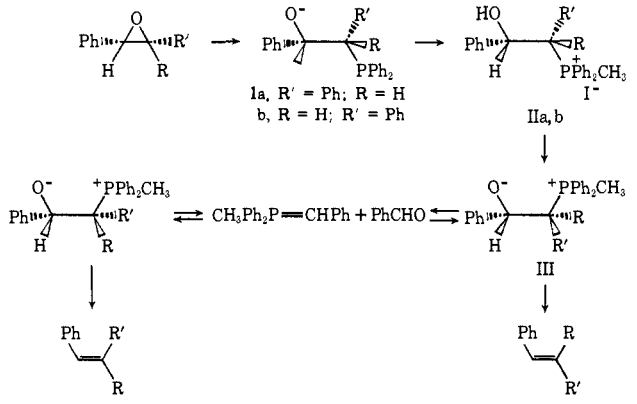
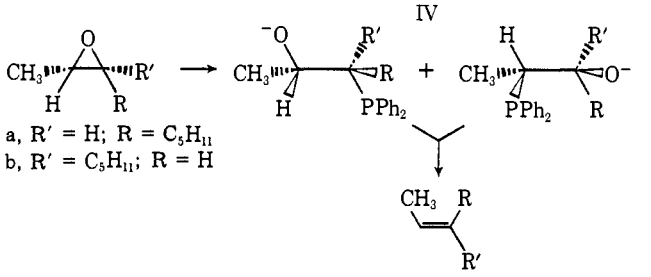
first step, fragmentation of the betaine to olefin should occur with net inversion of stereochemistry. However, deoxygenation of epoxides with phosphines requires elevated temperatures, and even in simple cases inversion is at most 80% stereospecific.[21]

Anionic phosphorus nucleophiles react with epoxides under milder conditions to form a carbon–phosphorus bond with inversion of stereochemistry. Corey and Cane have found that sodium bis(dialkylamino)-phosphite reacts slowly with epoxides at 25° to give β-hydroxyphosphonamides which fragment to olefins at 80°.[22] High (>95%) inversion of stereochemistry is observed, but the overall yield of olefin is less than 20%. Trippett and Jones have shown that β-hydroxyalkyldiphenylphosphines Ia and Ib can be prepared from sodium diphenylphosphide and *cis*- and *trans*-stilbene oxides, respectively.[23] Quaternization with methyl iodide converts Ia and Ib into the methiodide salts IIa and IIb (70% overall yield from epoxide) which, upon treatment with ethanolic ethoxide, afford stilbenes with 60–70% inversion of stereochemistry. In the presence of *m*-chlorobenzaldehyde the crossover product *m*-chlorostilbene is formed, and Trippett and Jones conclude that even under mild conditions the betaines IIIa and IIIb fragment reversibly to benzaldehyde and benzylidenetriphenylphosphorane. Loss of stereochemistry and the yield of crossover products depend on temperature and solvent, with higher stereoselectivity observed in tetrahydrofuran.[23]



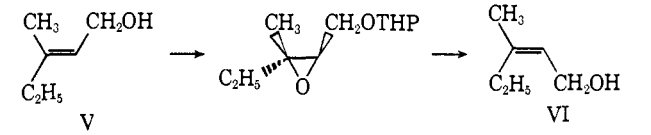
We have found that epoxides can be deoxygenated in excellent yield with inversion of stereochemistry by the phosphorus betaine route using lithium diphenylphosphide (LDP) as the nucleophile.[24] Lithium diphenylphosphide is conveniently prepared in tetrahydrofuran solution from chlorodiphenylphosphine and lithium wire,[25] and the solution thus obtained converts the isomeric stilbene oxides into Ia or Ib in high yield. The crude reaction product, upon treatment with methyl iodide at 25°, is converted directly to the betaine III which decomposes to stilbene under the reaction conditions. Thus, deoxygenation of *trans*-stilbene oxide to *cis*-stilbene is accomplished in 95% yield with >98% inversion of stereochemistry by a simple two-step procedure without isolation of intermediates. The β-hydroxyalkyldiphenylphosphines obtained by protonation of Ia,b are sensitive to air oxidation to the phosphine oxides, so isolation of the hydroxyphosphines is difficult and for the purpose of olefin inversion, unnecessary. The same sequence of LDP–methyl iodide converts *cis*-stilbene oxide into *trans*-stilbene in 95% yield with >99% stereospecificity; clearly, betaine fragmentation to ylide and benzaldehyde with resulting interconversion of betaines IIIa and IIIb does not compete with decomposition to stilbene under our conditions.

Epoxides of simple olefins such as 2-octene react more slowly with LDP than does stilbene epoxide, and 15–30 hr is required at 25° for opening of epoxide and discharge of the characteristic red color of diphenylphosphide anion. The intermediate alkoxy diphenylphosphine IV has not been characterized and we assume that two positional isomers are present, derived from either mode of SN2 epoxide opening. This complication in no way impairs conversion to olefin since treatment of IVa with methyl iodide at 25° affords *cis*-2-octene in 77% yield, >99.5% stereospecificity. Likewise, *cis*-2-octene oxide is transformed stereospecifically into *trans*-2-octene, 75% yield. No other product can be detected in significant quantity, excepting methyldiphenylphosphine oxide.



Analysis of 2-octene mixtures may be performed by glpc using a silver nitrate column. Alternately, the olefin mixture can be converted into a cis–trans mixture of epoxides which is easily analyzed by nmr in the presence of 35 mol % tris(dipivaloylmethanato)-europium.[26] The cis isomer experiences substantially greater pseudo-contact shifts than the trans epoxide, presumably because one face of the epoxide is free of hindrance by alkyl groups.

Trisubstituted olefins such as the allylic alcohol V can also be inverted by the betaine elimination method. Because of the basic nature of lithium diphenylphosphide, the hydroxyl function must first be protected as the tetrahydropyranyl ether. Subsequent epoxidation and treatment with LDP, methyl iodide, and dilute acid effect stereospecific conversion of V into VI in



>60% overall yield without purification of the intermediates.

Extension of the betaine method to carbonyl-containing epoxides is possible in some cases, but a variety

(21) (a) M. J. Boskin and D. B. Denney, *Chem. Ind. (London)*, 330 (1959); (b) D. E. Bissing and A. J. Speziale, *J. Amer. Chem. Soc.*, 87, 2683 (1965).

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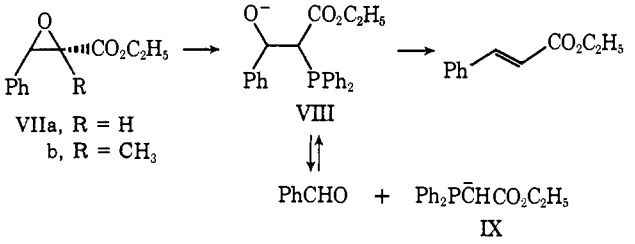
(25) Salt-free lithium diphenylphosphide, prepared from diphenylphosphine and *n*-butyllithium, may be used with similar results.

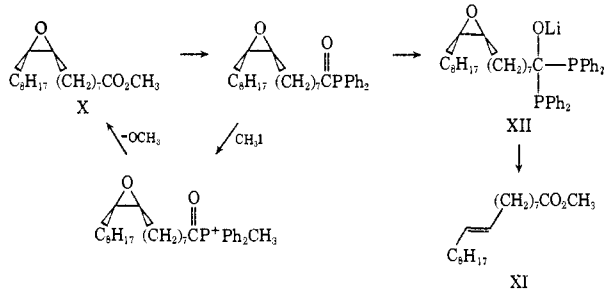
(26) L. H. Keith, *Tetrahedron Lett.*, 3 (1971); H. Hart and G. M. Lore, *ibid.*, 625 (1971).

of complications must be dealt with. Treatment of the glycidic ester VII with lithium diphenylphosphide affords a mixture of products derived from attack at the ester carbonyl as well as epoxide, as judged by nmr analysis. After addition of methyl iodide, *trans*-ethyl cinnamate can be isolated in 25–40% yield in addition to traces of benzaldehyde, but *cis*-ethyl cinnamate cannot be detected. Benzaldehyde is also observed prior to addition of methyl iodide, indicating that VIII fragments under the conditions of epoxide opening.

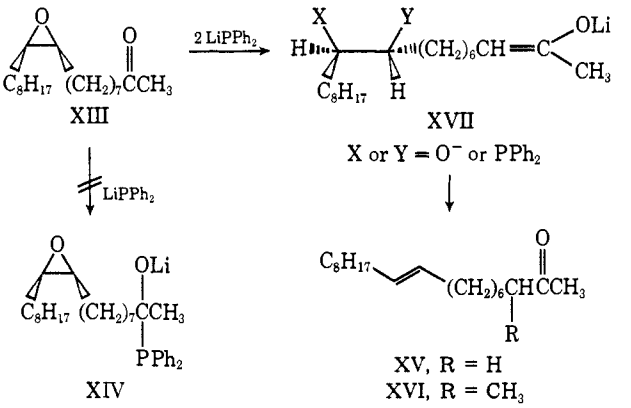


The appearance of *trans*-cinnamate instead of the inverted cis isomer can be explained by nonstereospecific recombination of IX and benzaldehyde, or by reversible fragmentation–recombination of the derived betaine.[21b] Preliminary experiments with VIIb indicate that a complex mixture of products is formed, but in this case ethyl α-methylcinnamate is not produced in detectable amounts.

We have also encountered complications in the case of the epoxy ester X. Reaction of X with 3 mol of lithium diphenylphosphide followed by excess methyl iodide affords the inverted alkene ester XI in 40% yield. However, treatment of X with the usual 1 mol (or 2 mol) of phosphide followed by methyl iodide results in 60% recovery of starting epoxide and only traces of XI. Apparently, lithium diphenylphosphide attack at the ester carbonyl is faster than attack at the epoxide. The resulting acyldiphenylphosphine is converted back to X after quaternization and acyl cleavage by the lithium methoxide which is formed in the initial step. The need for 3 mol of lithium diphenylphosphide is explained by consumption of 2 mol of phosphide to form XII,[27] followed by epoxide opening, quaternization, betaine fragmentation, and (finally) regeneration of the ester by methoxide.

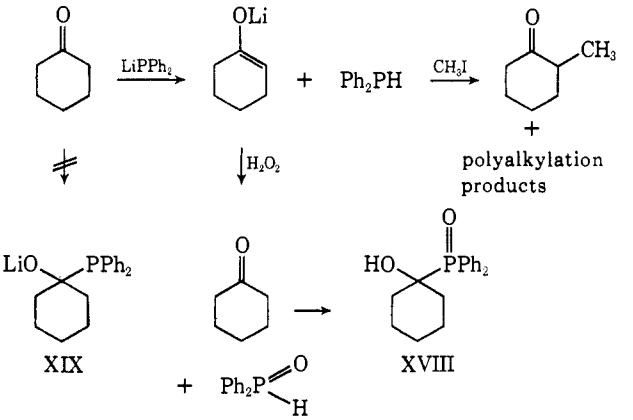


On the basis of our experience with the epoxy ester X and a literature report that lithium diphenylphosphide adds to cyclohexanone to form a hydroxyphosphine,[28] it appeared likely that treatment of ketoepoxides such as XIII with 2 equiv of phosphide and excess methyl iodide would afford inverted ketoalkenes. However, the major product proved to be the methylated ketoalkene XVI (>80%), formed *via* alkylation



of the enolate XVII. The undesired C-methylation can be avoided by carefully neutralizing the enolate with 1 equiv of acetic acid *prior* to addition of methyl iodide. With this modification, XIII is converted into the inverted ketoalkene XV in 85% yield.

Since lithium diphenylphosphide converts XIII into an enolate instead of the anticipated adduct XIV, we have reexamined the reported addition to cyclohexanone. Treatment of cyclohexanone with LDP followed by hydrogen peroxide does afford the phosphine oxide XVIII as claimed.[28] However, if methyl iodide is added instead of hydrogen peroxide, the product contains methylcyclohexanones (35–40%) but no cyclohexanone (<1%). The absence of cyclohexanone rules out the adduct XIX as an intermediate, while formation of methylcyclohexanones indicates that enolate formation is the initial reaction. The phosphine oxide XVIII is probably formed by oxidation of diphenylphosphine to diphenylphosphinous acid and precedented addition of the latter to cyclohexanone.[29]



In summary, we can recommend the phosphorus betaine method as a practical and stereospecific technique for inversion of the stereochemistry of acyclic di- or trisubstituted alkenes. Acyclic tetrasubstituted epoxides or highly hindered trisubstituted epoxides such as 2,2,3,6,6-pentamethylhept-3-ene oxide react very slowly with LDP and alkenes are not obtained in good yield. Ketone carbonyl groups interfere with the reaction sequence owing to enolate formation,

(27) A similar reaction has been reported between acycl halides and lithium diphenylphosphide: K. Issleib and E. Priebe, *Chem. Ber.*, **92**, 3183 (1959).

(28) A. M. Aguiar, J. Giacin, and H. J. Greenberg, *J. Org. Chem.*, 28, 3545 (1963).

(29) L. Horner and W. Klink, *Tetrahedron Lett.*, 2467 (1964).

but good yields of alkene can be achieved from keto-epoxides under carefully controlled conditions. Ester functions interfere by consuming 2 mol of phosphide anion, and epoxy esters cannot be deoxygenated in practical yield. Lithium diphenylphosphide is a strong base as well as an excellent nucleophile, so potential proton donors and electrophilic functional groups must be protected by conventional means.

Cyclic epoxides are also deoxygenated by the betaine technique provided that excessive ring strain is not present in the inverted alkene. Applications of the method for preparation of *trans*-cyclooctene derivatives and related systems are described in another paper.[24b]

Experimental Section

Epoxides were prepared from commercially available alkenes by standard means. All reactions involving trivalent phosphorus intermediates were performed under static argon pressure. Tetrahydrofuran was purified by distillation from $CaSO_4$–Cu_2Cl_2 followed by distillation from lithium aluminum hydride prior to use. Products were analyzed by gas chromatography using a Varian-Aerograph 90-P3 unless stated otherwise.

Lithium Diphenylphosphide.[30] Chlorodiphenylphosphine (Aldrich, freshly distilled) was added dropwise to 4 g-atoms of lithium wire in dry tetrahydrofuran (THF), and the mixture was stirred and cooled as necessary during the initial exothermic period. After 2 hr of vigorous stirring at 25°, the reaction was complete. Aliquots of the deep red solution were standardized by Gilman double titration, indicating *ca.* 98% phosphide and 2% additional soluble base. Solutions were prepared in the concentration range 0.7–1.2 *M* and could be stored several days under argon without significant deterioration. The excess lithium metal was allowed to remain in the flask and aliquots were removed by syringe as needed.

General Procedure for Olefin Inversion. A solution of the epoxide (0.005 mol) in purified tetrahydrofuran (15 ml) was added over a few minutes to a solution of lithium diphenylphosphide in tetrahydrofuran (4.15 ml, 1.15 *M* in phosphide) under argon at 25°. The resulting solution was allowed to stand until the red color of phosphide was discharged. Purified methyl iodide (1.5 equiv) was then added and the mixture was allowed to stand for 0.5 hr at 25°. After aqueous work-up, the organic phase was concentrated using a Vigreux column and analyzed by glpc *vs.* internal standard to afford alkenes as summarized in Table I.

Inversion of (*E*)-3-Methylpent-2-en-1-ol. (*E*)-3-Methylpent-2-en-1-oic acid[31] (2.4 g) in ether (10 ml) was added dropwise to lithium aluminum hydride (0.74 g) in ether (10 ml). The mixture was stirred 14 hr and treated cautiously with water; the organic product was extracted with ether *vs.* water. After drying over $MgSO_4$, the solvent was removed using a Vigreux column.

The crude alcohol from above (1.66 g) was stirred with dihydropyran (1.54 g) and *p*-toluenesulfonic acid (*ca.* 0.02 g) for 12 hr at 25°, then dissolved in ether, washed with saturated sodium carbonate, dried ($MgSO_4$), and evaporated under vacuum. The crude tetrahydropyranyl ether (2.5 g) was then treated with *m*-chloroperbenzoic acid (1.1 equiv) in CH_2Cl_2 at 25° for 18 hr; the solution was filtered and washed with sodium bisulfite and then with sodium carbonate solution. The resulting epoxide was then deoxygenated according to the general procedure to afford (*Z*)-3-methylpent-2-en-1-ol tetrahydropyranyl ether, >99% *Z* isomer by glpc analysis on 10 ft × 1/4 in. 10% Carbowax/20M Chrom W at 100°.

Inversion of *cis*-Nonadec-10-en-2-one Epoxide (XIII). The epoxide (0.276 g, 0.000934 mol) in dry THF (5 ml) was treated with LDP (3.4 ml of a 0.55 *M* solution, 0.00187 mol) for 20 hr at 25°. Acetic acid (0.056 g, 0.000934 mol) was then added, followed by methyl iodide (0.142 g). The usual work-up afforded *trans*-nonadec-10-en-2-one (0.215 g, 85%), mp 39–40° (lit. mp 40–41°[32]).

The above procedure was carried through without addition of acetic acid and using excess methyl iodide. According to nmr analysis, the product was 3-methyl-*trans*-nonadec-10-en-2-one (XVI) (methyl doublet at δ 0.90, J = 6 Hz) in *ca.* 90% yield.

Table I

Epoxide	Overall yield of alkene, %	Product geometry, %	Glpc column
trans-Stilbene	95	>98 cis	20% SE-30/Chrom P, 5 ft × 0.25 in.
cis-Stilbene	95	>99 trans	As above
trans-2-Octene	77	>99 cis	20% UCON 50 HB100 + 5% $AgNO_3$, 10 ft × 0.25 in.
cis-2-Octene	75	>99 trans	As above
trans-4-Octene	95	>99 cis	As above
Methyl *cis*-octadec-9-en-1-oate	40[a]	>90 trans[b]	

[a] Three moles of LDP was used. [b] Estimated lower limit from the infrared trans alkene absorption at 10.3 μ.

(30) We thank Professor A. M. Aguiar for providing the essentials of the experimental procedure.

(31) Kindly provided by Professor B. M. Trost.

(32) L. K. Dalton and J. A. Lamberton, *Aust. J. Chem.*, **11**, 46 (1958).