

# Chemo- and Regioselective Isomerization of Epoxides to Carbonyl Compounds via Palladium Catalysis

Sanjitha Kulasegaram and Robert J. Kulawiec\*

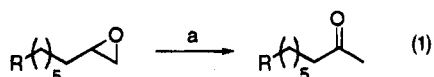
Department of Chemistry, Georgetown University, Washington, DC 20057-2222

Received September 7, 1994\*

**Summary:** Palladium(0)-tertiary phosphine complexes catalyze the chemo- and regioselective isomerization of epoxides to carbonyl compounds in good to excellent yields; alkyl-substituted epoxides afford methyl ketones, and aryl-substituted epoxides form aldehydes or ketones via cleavage of the benzylic C–O bond.

Epoxides are one of the more useful classes of substrates available to the synthetic organic chemist. As part of a research program directed toward the development of synthetically useful transformations of epoxides catalyzed by transition metal complexes,<sup>1</sup> we have investigated the reaction of epoxides with low-valent, electron-rich palladium complexes. This report describes our preliminary observation that a variety of different types of epoxides are isomerized to carbonyl compounds via Pd(0) catalysis, in a chemo- and regioselective manner.<sup>2</sup>

Treatment of an epoxide bearing a single aliphatic substituent with a catalytic amount of the palladium(0) complex<sup>3</sup> generated *in situ* from palladium(II) acetate and tri-*n*-butylphosphine (3 equiv per Pd) in refluxing toluene leads to rapid formation of the corresponding methyl ketone in good yield (eq 1). For example, 1,2-epoxydode-



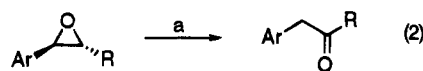
R = (CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> , 3 h	88%
R = (CH <sub>2</sub> ) <sub>3</sub> OH, 1 h	85%
R = (E)-(CH <sub>2</sub> ) <sub>2</sub> CH=CHCO <sub>2</sub> Et, 15 h	90%
R = (CH <sub>2</sub> ) <sub>3</sub> CN, 17 h	96%
R = CH=CH <sub>2</sub> , 2.5 h	90% <sup>b</sup>

(a) Pd(OAc)<sub>2</sub> (5-10%), PBU<sub>3</sub> (3 equiv/Pd), toluene, reflux; (b) isolated as a mixture of 4 isomeric olefinic ketones.

cane undergoes isomerization to 2-dodecanone in 88% yield.<sup>4</sup> The isomerization reaction is completely regioselective: no trace of aldehyde is observed by <sup>1</sup>H NMR or capillary GC analysis of the crude reaction mixture. Reactive functional groups such as primary hydroxyl, α,β-unsaturated ester, and nitrile are tolerated well. In the latter two examples, the longer reaction times required for complete isomerization suggest possible catalyst inhibition by competitive coordination of the electron-poor

double bond or the nitrile. Nevertheless, the yields of methyl ketone are nearly quantitative. A terminal olefinic group does not inhibit the isomerization of the epoxide, but is itself partially isomerized to a mixture of isomeric alkenes. In contrast to the isomerization of monosubstituted epoxides, substrates bearing two aliphatic substituents, either vicinal (such as 1,2-epoxycyclododecane), or geminal (such as 1-oxaspiro[11.2]tetradecane), are completely unreactive.<sup>5</sup> While the isomerization of aryl-, vinyl-, or keto-substituted epoxides by late transition metal complexes is well established,<sup>1</sup> the analogous isomerization of epoxides bearing *only* aliphatic substituents, particularly in synthetically useful yields, is quite rare.

Aryl-substituted epoxides undergo palladium-catalyzed isomerization in refluxing benzene, using the palladium(0) complex derived from palladium(II) acetate and triphenylphosphine (3 equiv per Pd), with exclusive cleavage of the benzylic C–O bond (eq 2). A simple



Ar = 2-naphthyl, R = H, 1.5 h	75%
Ar = 2-naphthyl, R = CH <sub>3</sub> , 2 h	92%
Ar = R = Ph, 43 h	83% <sup>b</sup>

(a) Pd(OAc)<sub>2</sub> (5%), PPh<sub>3</sub> (3 equiv/Pd), benzene, reflux; (b) PBU<sub>3</sub> used rather than PPh<sub>3</sub>.

monosubstituted epoxide affords the corresponding aryl acetaldehyde in moderate yield. Isomerization of *trans*-2-(2-naphthyl)-3-methyloxirane affords the methyl ketone in excellent yield, with the same complete regioselectivity in C–O activation; no trace of the ethyl ketone was observed by <sup>1</sup>H NMR analysis of the crude reaction mixture. *trans*-Stilbene oxide affords 1,2-diphenylethanol; however, acceptable turnover rates are observed only with PBU<sub>3</sub>. Presumably, the increased steric hindrance of the diaryl epoxide necessitates much longer reaction times.

We suggest that the reactivity of simple alkyl-substituted epoxides toward Pd(OAc)<sub>2</sub>/PBU<sub>3</sub> is a result of the decreased steric demand and increased electron-donating ability of the tri-*n*-butylphosphine ligand, compared to triarylphosphines. The more electron-rich Pd(0)-tri-alkylphosphine complex would be expected to undergo

\* Abstract published in *Advance ACS Abstracts*, November 1, 1994.

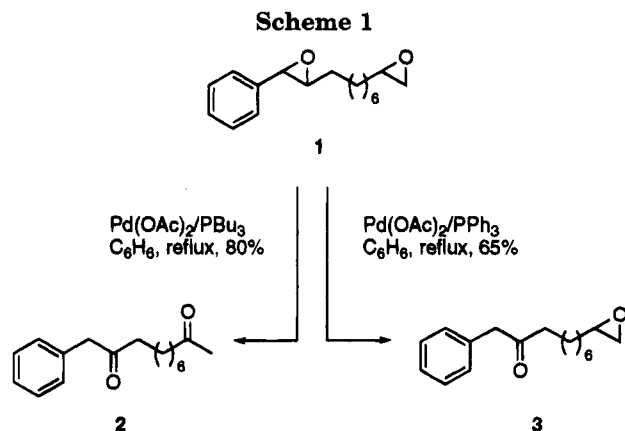
(1) For leading examples of transition-metal catalyzed isomerization of epoxides, see: (a) Eisenmann, J. L. *J. Org. Chem.* **1962**, *27*, 2706. (b) Alper, H.; Des Roches, D.; Durst, T.; Legault, R. *J. Org. Chem.* **1976**, *41*, 3611–3613. (c) Milstein, D.; Buchman, O.; Blum, J. *J. Org. Chem.* **1977**, *42*, 2299–2308. (d) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623–1625. (e) Vankar, Y. D.; Chaudhuri, N. C.; Singh, S. P. *Synth. Commun.* **1986**, *16*, 1621–1626.

(2) Part of this work was communicated at the 208th National Meeting of the American Chemical Society, August 21–25, 1994, Washington, DC; ORGN 0114.

(3) Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513–2516.

(4) An example of the experimental procedure employed is as follows: A suspension of Pd(OAc)<sub>2</sub> (10 mg, 45 μmol) in deoxygenated toluene (1 mL) is treated with PBU<sub>3</sub> (34 μL, 135 μmol) under N<sub>2</sub>, whereupon formation of the yellow Pd(0) complex ensues. The solution is treated with 1,2-epoxydodecane (195 μL, 0.94 mmol) and refluxed under N<sub>2</sub> for 3 h. The reaction mixture is then chromatographed directly on silica gel (6:1 hexane–ethyl acetate) to afford 2-dodecanone (152 mg, 88%), R<sub>f</sub> = 0.49. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): δ 2.44 (t, J = 7.0 Hz, 2H), 2.13 (s, 3H), 1.57 (m, 2H), 1.26 (m, 14H), 0.90 (t, J = 6.6 Hz, 3H).

(5) No products other than the starting epoxide were observed by <sup>1</sup>H NMR or capillary GC analysis, after refluxing in toluene for 24 h.



oxidative addition of the epoxide C–O bond more readily than  $\text{Pd(PPh}_3)_n$ . Indeed, 1,2-epoxydodecane is *completely inert* to reflux in the presence of  $\text{Pd(OAc)}_2/\text{PPh}_3$ . This chemoselectivity allows one to control the reactivity of electronically dissimilar epoxy groups within the same molecule, based merely on the choice of tertiary phosphine. For example, treatment of diepoxide **1**, having both aryl- and alkyl-substituted epoxy groups, with  $\text{Pd(OAc)}_2/\text{PBu}_3$  affords the diketone **2**, arising from simultaneous isomerization of both epoxy groups. In contrast, isomerization of **1** with the catalyst derived from  $\text{Pd(OAc)}_2/\text{PPh}_3$  yields epoxy ketone **3** as the sole product, via isomerization of *only* the aryl-substituted epoxy group; the alkyl-substituted epoxy group is completely unaffected. This type of reagent-based selectivity avoids the use of protecting groups and is of great potential importance in the selective transformation of polyfunctional substrates.

In control experiments, neither  $\text{Pd(OAc)}_2$  nor  $\text{PBu}_3$  alone catalyzes the isomerization of 1,2-epoxydodecane.<sup>5</sup> We find that other low-valent, late transition metal species (e.g.,  $\text{Ni(0)}$  and  $\text{Rh(I)}$  tertiary phosphine complexes) also catalyze the isomerization of 1,2-epoxydodecane to 2-dodecanone, but much more slowly, and in considerably lower isolated yields.<sup>6</sup>

It has been suggested<sup>7</sup> that the isomerization of epoxides by late transition metal complexes proceeds via oxidative addition of the C–O bond to a low-valent metal fragment to yield a metallaoxetane. Subsequent  $\beta$ -hydride elimination to form a hydrido–enolate species, followed by reductive elimination, would afford the carbonyl compound and regenerate the active catalyst. Although we have not yet completed any mechanistic studies, the validity of such a mechanism is supported by the isolation of metallaoxetane<sup>7a</sup> and hydrido–enolate<sup>7b</sup> complexes from the reactions of low-valent group 9 metal complexes with epoxides.

The importance of this new isomerization procedure

arises from its chemo- and regioselectivity. These properties suggest a useful alternative to the Wacker oxidation<sup>8</sup> of terminal alkenes to methyl ketones: namely, alkene epoxidation, followed by palladium-catalyzed isomerization of the epoxide to the methyl ketone. This two-step protocol should be applicable to substrates which are unstable to the Lewis-acidic conditions of the Wacker oxidation, or which react unselectively. For example, Wacker oxidation of  $\alpha,\beta$ -unsaturated esters yields  $\beta$ -keto esters;<sup>8,9</sup> thus, oxidation of a substrate bearing both conjugated and nonconjugated double bonds should be unselective, resulting in oxidation of both. However, *m*-CPBA selectively epoxidizes the nonconjugated double bond; the resulting epoxy ester is then cleanly isomerized to the methyl ketone, as we have shown (eq 1). Similarly, the Wacker oxidation of *trans*- $\beta$ -methylstyrene shows poor regioselectivity: a 3:1 mixture of 1-phenyl-2-propanone and 1-phenyl-1-propanone was obtained.<sup>10</sup> In contrast, the two-step protocol of epoxidation/Pd-catalyzed isomerization (eq 2) of the 2-naphthyl analog forms the 1-aryl 2-ketone with complete regioselectivity.

The advantage of palladium catalysis over traditional Lewis acid-mediated epoxide isomerization<sup>11</sup> arises both from regioselectivity and from chemoselectivity. Mixtures of ketones and aldehydes have been obtained in the isomerization of both alkyl-substituted and aryl-substituted epoxides with group 1 and 2 metal catalysts.<sup>12</sup> In contrast, the  $\text{Pd(0)}$  complexes reported in this work show complete regioselectivity in isomerization. Also, substrates bearing acid-sensitive functionality should tolerate the Lewis-basic conditions employed herein quite well. We are continuing to investigate the scope, mechanism, and synthetic utility of this potentially useful reaction.

**Acknowledgment.** R.J.K. thanks the Camille and Henry Dreyfus Foundation for a New Faculty Award and Georgetown University for a Summer Academic Grant, in partial support of this work.

**Supplementary Material Available:** Experimental procedures, including synthesis of substrates and characterization data on all new compounds (9 pages). This material is contained in 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.

(8) For recent reviews on heteroatom–nucleophile addition to palladium(II)–olefin complexes, including the Wacker oxidation, see: (a) Tsuji, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, Chapter 3.4, pp 449–468. (b) Hegedus, L. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, Chapter 3.1, pp 551–569.

(9) Tsuji, J.; Nagashima, H.; Hori, K. *Chem. Lett.* **1980**, 257–260.

(10) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474–3480.

(11) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, Chapter 3.3, pp 733–775.

(12) For a recent report of highly selective aluminum- and antimony-catalyzed isomerization of epoxides, see: Maruoka, K.; Murase, N.; Bureau, R.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3663–3672 and references therein.

(6) Kulasegaram, S.; Kulawiec, R. J. Unpublished observations, 1994.

(7) (a) Calhorda, M. J.; Galvão, A. M.; Ünaleroğlu, C.; Zlota, A. A.; Frolow, F.; Milstein, D. *Organometallics* **1993**, *12*, 3316–3325. (b) Milstein, D.; Calabrese, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3773–3774 and references therein.