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Phosphine-Catalyzed Reductions of Alkyl Silyl Peroxides by Titanium Hydride Reducing Agents: Development of the Method and Mechanistic Investigations

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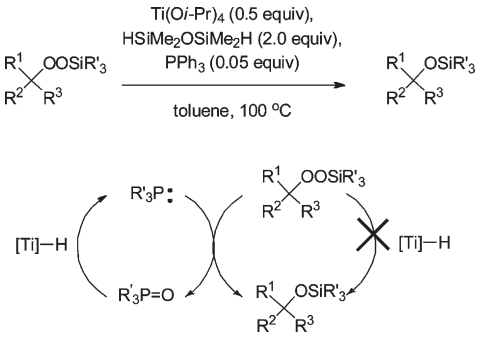

A method that allows for the reduction of protected hydroperoxides by employing catalytic amounts of phosphine is presented. The combination of a titanium(IV) alkoxide and a siloxane allowed for the chemoselective reduction of phosphine oxides in the presence of alkyl silyl peroxides. Subsequent reduction of the peroxide moiety by phosphine provided the corresponding silylated alcohols in useful yields. Mechanistic experiments, including crossover experiments, support a mechanism in which the peroxide group was reduced and the silyl group was transferred in a concerted step. Labeling studies with ^{17}O-labeled peroxides demonstrate that the oxygen atom adjacent to the silicon atom is removed from the silyl peroxide.

Introduction

Reductions of the oxygen−oxygen bonds of peroxides with phosphines provide useful methods for the synthesis of alcohols, ethers, and carbonyl compounds.[1] These reactions require the use of stoichiometric quantities of the phosphine, which generates an equivalent of a phosphine oxide that must be separated from the desired products. Phosphorus reagents attached to solid supports have been developed to address the problems associated with the use of stoichiometric quantities of phosphines.[2] The development of phosphine-catalyzed reductions of peroxides would also simplify isolation by reducing the amount of undesired phosphine oxide byproduct.[3]

The development of a phosphine-catalyzed reduction of peroxides requires surmounting a challenge in selectivity. Due to the mildness by which phosphines can reduce the peroxide moiety in the presence of other functional groups, we explored reaction conditions where only phosphine would be the active peroxide reductant. A terminal reductant is then needed to reduce a strong phosphorus−oxygen bond (approximately 130 kcal/mol)[4,5] in the presence of a weak oxygen−oxygen bond (approximately 34−50 kcal/mol).[5,6] Typical reducing agents used to convert phosphine oxides to phosphines, such as metal hydrides and silanes,[7] would be

(1) (a) Challenger, F.; Wilson, V. K. *J. Chem. Soc.* **1927**, 209–213. (b) Horner, L.; Jurgeleit, W. *Liebigs Ann. Chem.* **1955**, *591*, 138–152. (c) Horner, L.; Winkler, H. *Tetrahedron Lett.* **1964**, *5*, 3275–3277. (d) Gilchrist, T. L. In *Comprehensive Organic Synthesis − Selectivity, Strategy, and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Elsevier: Oxford, UK, 1991; Vol. 8; Chapter 2, pp 381−402.

(2) Relles, H. M.; Schluenz, R. W. *J. Am. Chem. Soc.* **1974**, *96*, 6469–6475 and references cited therein.

(3) For an example of a Wittig reaction with catalytic amounts of phosphine, see: O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6836–6839.

(4) Bedford, A. F.; Mortimer, C. T. *J. Chem. Soc.* **1960**, 1622–1625.

(5) Luo, Y. R. *Comprehensive Handbook of Chemical Bond Energies*; CRC: Boca Raton, 2007.

(6) Bach, R. D.; Ayala, P. Y.; Schlegel, H. B. *J. Am. Chem. Soc.* **1996**, *118*, 12758–12765.

(7) (a) Still, I. W. In *Comprehensive Organic Synthesis − Selectivity, Strategy, and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Elsevier: Oxford, UK, 1991; Vol. 8, Chapter 2, pp 403−415. (b) Honaker, M. T.; Hovland, J. M.; Salvatore, R. N. *Curr. Org. Synth.* **2007**, *4*, 31–45. (c) Allen, D. W. *Organophosphorus Chem.* **2008**, *37*, 13–53 and references cited within.

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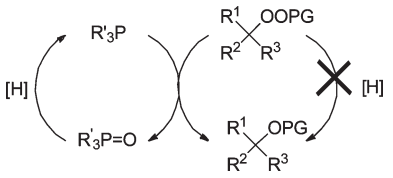
SCHEME 1. Proposed Catalytic Reduction of a Protected Peroxide with Phosphine



unsuitable because they decompose hydroperoxides to the corresponding alcohols.[1d,8,9] We hypothesized that the choice of an appropriate protecting group for the hydroperoxide in combination with a selective reducing agent could permit the chemoselective reduction of the thermodynamically more stable phosphine oxide in the presence of the fragile oxygen−oxygen bond (Scheme 1). The catalytic cycle outlined in Scheme 1 differs from typical metal-catalyzed oxygen transfer reactions because it requires a phosphine oxide and not a peroxide to serve as an oxygen transfer agent to the terminal reductant.[10]

In this paper, we present a phosphine-catalyzed reduction of silyl-protected hydroperoxides using a titanium hydride[11] as the terminal reducing agent. Electron paramagnetic resonance (EPR) spectroscopy revealed the formation a species consistent with decomposition of a titanium hydride complex. Crossover experiments and the use of ^{17}O-labeled substrates indicate that the phosphine removes the oxygen atom closest to the silyl group, and silyl transfer to the remaining oxygen atom occurs concurrently with reduction.

Results and Discussion

Exploration of Peroxide Protecting Group and Reducing Conditions. Our investigation began by protecting a hydroperoxide with groups that could survive conditions commonly employed to reduce phosphine oxides.[12−14] Typically, a free hydroperoxide moiety is intolerant of many strongly reducing conditions.[8] We chose to examine the silyl, benzyl,

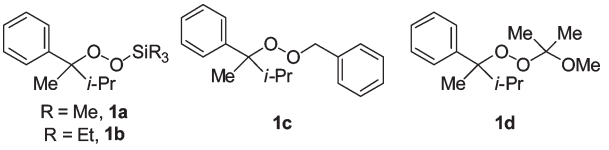


FIGURE 1. Substrates subjected to catalytic reduction conditions.

and ketal groups (**1a** and **1b**, **1c**, and **1d**, respectively, Figure 1) as masking groups due to their stability in reducing environments[15,16] and their anticipated ease of removal after reduction. Furthermore, reactivity between phosphines and these types of peroxides has been previously documented. In general, silyl and dialkyl peroxides undergo deoxygenation upon treatment with phosphines and phosphites,[17,18] but peroxy ketals can either fragment[19] or undergo deoxygenation[20] when treated with phosphines.[21]

Initial attempts to develop a phosphine-catalyzed reduction of peroxides were unsuccessful. The results with silyl-protected peroxides are representative (Table 1). When $LiAlH_4$ was used as the terminal reductant, mixtures of silyl ether **2a** or **2b** and alcohol **3** were observed (Table 1, entries 1 and 2). Alcohol **3** could be formed by reduction of the oxygen−oxygen bond of peroxides **1a** or **1b** by $LiAlH_4$,[8] or it could result from deprotection of silyl ethers **2a** or **2b**.[22] We surmise that direct reduction of the oxygen−oxygen bond by $LiAlH_4$ is more likely than deprotection because the substrate with the more labile trimethylsilyl group (**2a**) proceeds with less loss of the silyl group (Table 1, entry 1 vs entry 2). When Cl_3SiH was chosen as the stoichiometric reductant, complete decomposition to an intractable mixture of products was observed (Table 1, entry 3). Decomposition of silyl peroxide **1b** could be due to the acidity of the chlorosilane

(8) For examples of reductions of peroxides by metal hydrides, see: (a) Matic, M.; Sutton, D. A. *J. Chem. Soc.* **1952**, 2679–2682. (b) Russell, G. A. *J. Am. Chem. Soc.* **1953**, *75*, 5011–5013. (c) Davies, A. G.; Feld, R. *J. Chem. Soc.* **1956**, 665–670. (d) Baldwin, J. E.; Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1964**, 3312–3315.

(9) For an example of reductions of hydroperoxides by silanes and stannanes, see: Nakamura, E.; Sato, K.-i.; Imanishi, Y. *Synlett* **1995**, 525–526.

(10) The formation of a phosphine oxide from a phosphine and oxygen is exothermic, so a phosphine oxide would not be expected to be a strong oxygen atom donor. Conversely, the formation of peroxide from an alcohol and oxygen is endothermic, so a peroxide would be more likely to serve as an oxygen transfer agent. For examples and a discussion, see: Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401–1449.

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(12) For examples of reductions of phosphine oxides by metal hydrides, see: (a) Hein, F.; Issleib, K.; Rabold, H. *Z. Anorg. Allg. Chem.* **1956**, *287*, 208–213. (b) Horner, L.; Hoffmann, H.; Beck, P. *Chem. Ber.* **1958**, *91*, 1583–1588. (c) Henson, P. D.; Naumann, K.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 5645–5646. (d) Busacca, C. A.; Raju, R.; Grinberg, N.; Haddad, N.; James-Jones, P.; Lee, H.; Lorenz, J. C.; Saha, A.; Senanayake, C. H. *J. Org. Chem.* **2008**, *73*, 1524–1531.

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(14) For examples of reductions of phosphine oxides by Ti(IV)/siloxane, see: (a) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625–628. (b) Berthod, M.; Favre-Réguillon, A.; Mohamad, J.; Mignani, G.; Docherty, G.; Lemaire, M. *Synlett* **2007**, 1545–1548.

(15) For examples of the stability of alkyl, ketal, and silyl peroxides toward hydride reduction, see: (a) Dussault, P.; Sahli, A.; Westermeyer, T. *J. Org. Chem.* **1993**, *58*, 5469–5474. (b) Lowe, J. R.; Porter, N. A. *J. Am. Chem. Soc.* **1997**, *119*, 11534–11535. (c) Porter, N. A.; Caldwell, S. E.; Lowe, J. R. *J. Org. Chem.* **1998**, *63*, 5547–5554. (d) Jin, H.-X.; Liu, H.-H.; Zhang, Q.; Wu, Y. *J. Org. Chem.* **2005**, *70*, 4240–4247 and references cited within. (e) Murakami, M.; Sakita, K.; Igawa, K.; Tomooka, K. *Org. Lett.* **2006**, *8*, 4023–4026.

(16) (a) Dussault, P.; Porter, N. A. *J. Am. Chem. Soc.* **1988**, *110*, 6276–6277. (b) Dussault, P. *Synlett* **1995**, 997–1003.

(17) (a) Brandes, D.; Blaschette, A. *J. Organomet. Chem.* **1975**, *99*, C33–C35. (b) Jefford, C. W.; Rimbault, C. G. *J. Am. Chem. Soc.* **1978**, *100*, 6437–6445. (c) Gorbatov, V. V.; Yablokova, N. V.; Aleksandrov, Y. A.; Ivanov, V. I. *Zh. Obsch. Khim.* **1983**, *53*, 1752–1755. (d) Ando, W.; Kako, M.; Akasaka, T.; Kabe, Y. *Tetrahedron Lett.* **1990**, *31*, 4177–4180. (e) Adam, W.; Albert, R. *Tetrahedron Lett.* **1992**, *33*, 8015–8016. (f) Einaga, H.; Nojima, M.; Abe, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2507–2512. (g) Terent'ev, A. O.; Platonov, M. M.; Tursina, A. I.; Chernyshev, V. V.; Nikishin, G. I. *J. Org. Chem.* **2009**, *74*, 1917–1922.

(18) For examples and studies of phosphines and phosphites reacting with dialkyl peroxides, see: (a) Denney, D. B.; Relles, H. M. *J. Am. Chem. Soc.* **1964**, *86*, 3897–3898. (b) Adam, W.; Rios, A. *J. Org. Chem.* **1971**, *36*, 407–411. (c) Bartlett, P. D.; Baumstark, A. L.; Landis, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 6486–6487. (d) Balci, M. *Chem. Rev.* **1981**, *81*, 91–108 and references cited therein. (e) Abe, M.; Sumida, Y.; Nojima, M. *J. Org. Chem.* **1997**, *62*, 752–754. (f) Greatrex, B. W.; Taylor, D. K. *J. Org. Chem.* **2004**, *69*, 2577–2579.

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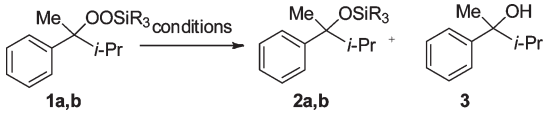
(20) (a) Clough, R. L.; Yee, B. G.; Foote, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 683–686. (b) Sugimoto, T.; Nakamura, N.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1991**, *56*, 1672–1674.

(21) Peroxyketals are stable to phosphines in the presence of ozonides at low temperature: (a) Dussault, P.; Sahli, A. *Tetrahedron Lett.* **1990**, *31*, 5117–5120. (b) Dussault, P.; Lee, I. Q.; Kreifels, S. *J. Org. Chem.* **1991**, *56*, 4087–4089.

(22) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031–1069.

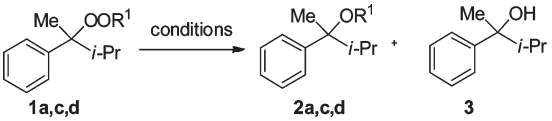
TABLE 1. Investigation of Other Stoichiometric Reducing Agents



entry	substrate	R	conditions	**2a**,**b**:**3**[a]	conv[a] (%)	yield[a] (%)
1	**1a**	Me	$LiAlH_4$ (1.0 equiv), PPh_3 (0.05 equiv), THF, rt, 24 h	52:48	> 98	81[b]
2	**1b**	Et	$LiAlH_4$ (1.0 equiv), PPh_3 (0.05 equiv), THF, rt, 24 h	2:98	51	29
3	**1b**	Et	Cl_3SiH (1.0 equiv), PPh_3 (0.05 equiv), toluene, 110 °C, 19 h	N.A.	> 98	0

[a]As determined by GC analysis of the unpurified reaction mixture relative to internal standard (dodecane). [b]Combined yields of **2a** and **3**. conv = conversion. RT = room temperature. N.A. = not applicable.

TABLE 2. Screen of Protecting Groups using Titanium(IV) and $HSiMe_2OSiMe_2H$ as Stoichiometric Reducing Agents



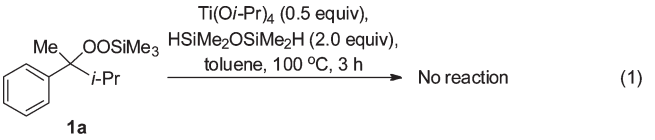
entry	substrate	R^1	conditions	**2a**,**c**,**d**:**3**	conv[a] (%)	yield[b] (%)
1	**1c**	CH_2Ph	Ti(O-*i*-Pr)$_4$ (0.5 equiv), $HSiMe_2OSiMe_2H$ (2.0 equiv), PPh_3 (0.05 equiv), toluene, 100 °C, 24 h	0: > 98	80	**2c**: 0; **3**: 31
2	**1d**	$CMe_2(OMe)$	Ti(O-*i*-Pr)$_4$ (0.5 equiv), $HSiMe_2OSiMe_2H$ (2.0 equiv), PPh_3 (0.05 equiv), toluene, 100 °C, 24 h	N.A.	> 98	**2d**: 0
3	**1a**	$SiMe_3$	Ti(O-*i*-Pr)$_4$ (0.5 equiv), $HSiMe_2OSiMe_2H$ (2.0 equiv), PPh_3 (0.05 equiv), toluene, 100 °C, 6 h	100:0	> 98	**2a**: 41 (98);[c] **3**: 13

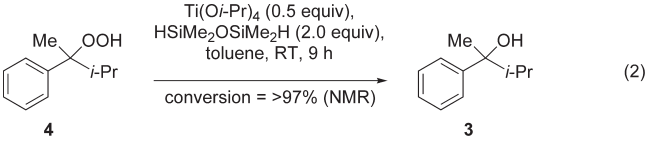
[a]As determined by GC analysis of the unpurified reaction mixture relative to an internal standard (dodecane). [b]Isolated yield. [c]Yield in parentheses is yield determined by GC analysis of the unpurified reaction mixture relative to an internal standard (dodecane). conv = conversion. N.A. = not applicable.

(pK_a in DMSO of 8.3),[23] which might result in deprotection to form the hydroperoxide, which would decompose at elevated temperatures.

The combination of a titanium(IV) alkoxide and a siloxane proved to be a useful terminal reductant for the phosphine-catalyzed reduction of protected hydroperoxides.[11,14] When benzyl peroxide **1c** was treated with catalytic amounts of phosphine in the presence of titanium isopropoxide (Ti(O-*i*-Pr)$_4$) and $HSiMe_2OSiMe_2H$ (1,1,3,3-tetramethyldisiloxane, TMDS), only alcohol **3** and unreacted starting material **1c** were isolated from the reaction mixture (Table 2, entry 1). Ketal **1d** underwent decomposition to an unknown product under the catalytic reducing conditions (Table 2, entry 2).[24] Reduction was much cleaner when a silyl protecting group was used for the peroxide (Table 2, entry 3). Silyl ether **2a** was obtained in > 98% yield as determined by GC analysis of the unpurified reaction mixture. The isolated yield of the silyl ether **2a** was significantly lower than the yield determined by GC, however. We attribute the low isolated yield to deprotection of the labile trimethylsilyl group upon purification.

Control experiments indicated that the reductions of silyl peroxides in Table 2 proceeded with reduction of the peroxide by the phosphine and reduction of the phosphine oxide by a metal complex as envisioned in Scheme 1. In the absence of a phosphine, silyl peroxide **1a** did not react with the titanium(IV)−siloxane reducing agent, as determined by GC analysis (eq 1). On the other hand, protection with the silyl group was necessary to prevent reduction of the peroxide by the titanium reagent. Without protection, hydroperoxide **4** was cleanly converted to the alcohol **3** by Ti(O-*i*-Pr)$_4$ and $HSiMe_2OSiMe_2H$, as determined by NMR analysis (eq 2).[25] Because the titanium(IV)−siloxane system can neither reduce the silyl peroxide **1a** nor deprotect it (eq 1), observation of silyl ether **2a** in Table 2 (entry 3) indicates that the phosphine, not the titanium reagent, must reduce the silyl peroxide **1a**.





Scope of Catalytic Reduction. The phosphine-catalyzed reduction of silyl peroxides proceeded in good yields for a variety of triethylsilyl peroxides (Table 3). In addition to tertiary peroxides, the phosphine-catalyzed reduction can be applied to secondary silyl peroxides. Tertiary and secondary alkyl triethylsilyl peroxides can be prepared in one step from alkenes by a cobalt-catalyzed peroxidation reaction developed by Mukaiyama and Isayama.[26] Carbonyl compounds, readily formed under mildly basic conditions by α-deprotonation of

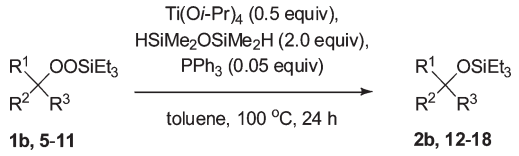
(23) Fu, Y.; Liu, L.; Li, R.-Q.; Liu, R.; Guo, Q.-X. *J. Am. Chem. Soc.* **2004**, *126*, 814–822.

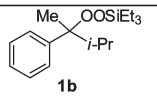
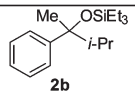
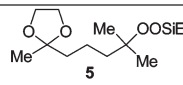
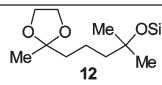
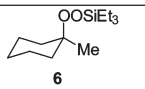
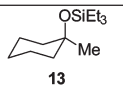
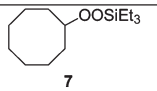
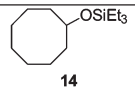
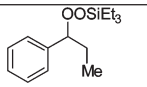
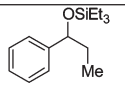
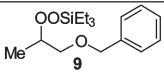
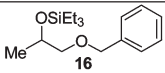
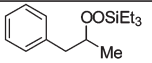
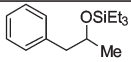
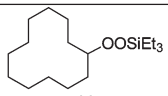
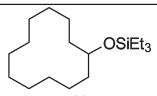
(24) Heating peroxy ketal **1d** in the absence of reducing agents also resulted in decomposition, presumably by homolytic decomposition of the oxygen−oxygen bond. See: Helgorsky, C.; Bevilacqua, M.; Degueil-Castaing, M.; Maillard, B. *Thermochim. Acta* **1997**, *297*, 93–100.

(25) It is unclear if peroxide reduction is occurring by a hydride equivalent attacking the O−O bond or from decomposition of a Ti^{IV}−OOR complex. For an example of decomposition of a Ti^{IV}−OOR complex, see: DiPasquale, A. G.; Kaminsky, W.; Mayer, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14534–14535.

(26) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573–576.

TABLE 3. Substrate Scope of Catalytic Reduction

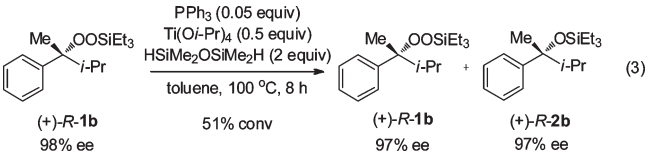


entry	substrate	product	yield(%)[a]
1	 1b	 2b	73
2	 5	 12	77 (+9% alcohol)
3	 6	 13	46
4	 7	 14	66
5	 8	 15	73
6	 9	 16	79
7	 10	 17	69
8	 11	 18	79

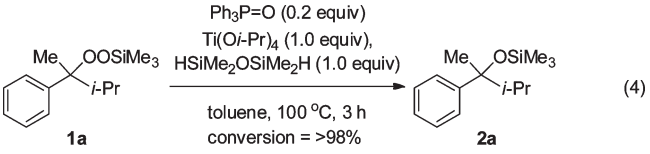
[a]Yields reported are isolated yields.

secondary peroxides,[27] were not observed in the reaction mixture. A wide range of functional group tolerance in the reduction of esters by a titanium(IV) alkoxide and a siloxane has been demonstrated by Buchwald and co-workers,[11] and this functional group tolerance was also observed in the phosphine-catalyzed reduction of alkyl silyl peroxides. For example, the reaction conditions were also compatible with the presence of protected ketones (entry 2), alkoxy groups (entry 6), and silyl ethers (entries 1−8). In general, the yields determined by analysis of the unpurified reaction mixture by GC or ^{1}H NMR spectroscopy were higher than the isolated yields. The lowered isolated yields were attributed, in part, to volatility of the products (e.g., silyl ether **13**, entry 3) and the challenge of separating the silyl ethers from the silicone polymers formed by titanium-catalyzed dehydrocoupling of the siloxane.[28] Basic hydrolysis of the reaction mixture was found to be the most reliable method to isolate the silyl ethers.[11] This workup precluded the use of trimethylsilyl peroxides because they were too susceptible to deprotection. In contrast, deprotection of the silyl group was generally avoided when the triethylsilyl ether was employed as the masking group; only one silyl peroxy ketal **5** afforded appreciable amounts (9%) of the free alcohol (Table 3, entry 2).

The phosphine-catalyzed reduction of chiral nonracemic silyl peroxides occurs with retention of configuration. Treatment of silyl peroxide (+)-(*R*)-**1b**[29] to the catalytic reductive conditions formed the silyl ether (+)-(*R*)-**2b** with retention of configuration (eq 3).[30] In addition, the optical purity of the starting material was retained. These studies indicate that the titanium complexes employed are not Lewis acidic enough to ionize either the starting material or product to form tertiary carbocations.



Variation of the reaction conditions for the phosphine-catalyzed reduction was tolerated.[31] Phosphine oxides could be used as a precatalyst for the reduction (eq 4). Additionally, these reactions could be performed in THF as the solvent. As noted in previous reports in the literature, these reactions could be performed without rigorous exclusion of oxygen and moisture.[11,14]



EPR Spectroscopy of a Titanium(IV) Decomposition Product. Because control experiments (eqs 1 and 2) suggested that the silyl peroxide oxidized the phosphine to the phosphine oxide, attention turned to determining the titanium-based reducing agent responsible for reduction of the phosphine oxide. The phosphine oxide could be reduced by a titanium(IV) hydride produced from a siloxane and a titanium alkoxide (Scheme 2).[32] Although many titanium(IV) hydrides with a variety of ligands have been reported,[33,34]

(27) (a) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880–881. (b) Buncel, E.; Davies, A. G. *J. Chem. Soc.* **1958**, 1550–1556.

(28) (a) Aitken, C.; Harrod, J. F.; Samuel, E. *J. Organomet. Chem.* **1985**, *279*, C11–C13. (b) Harrod, J. F. *Coord. Chem. Rev.* **2000**, *206*−*207*, 493–531.

(29) Driver, T. G.; Harris, J. R.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3836–3837.

(30) Davies, A. G.; Feld, R. *J. Chem. Soc.* **1958**, 4637–4643.

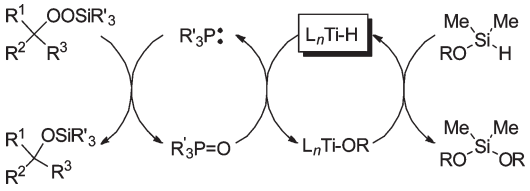
(31) Although this study has focused on using triphenylphosphine as the peroxide reductant, we have observed that other alkyl- and arylphosphines behave with equal efficiency. For sterically hindered phosphines, e.g., tricyclohexylphosphine, the use of smaller alkyl trimethylsilyl peroxides is required for efficient conversions.

(32) A strongly associated titanium/silane complex or a titanium-(η^2)-silane could also be the active reductant. For a discussion, see: (a) Reference 11b. (b) Crabtree, R. H. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 789–805. (c) Corey, J. Y.; Braddock-Wilking, J. *Chem. Rev.* **1999**, *99*, 175–292. (d) Lin, Z. *Chem. Soc. Rev.* **2002**, *31*, 239–245.

(33) Titanium(IV) hydrides have been proposed in the reaction between titanium(IV) alkoxides and silanes/siloxanes; see: (a) Albizzati, E.; Abis, L.; Pettenati, E.; Giannetti, E. *Inorg. Chim. Acta* **1986**, *120*, 197–203. (b) Reference 11.

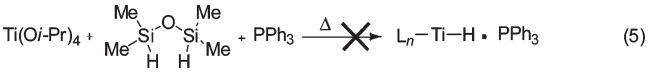
(34) For examples of Ti(IV) hydrides without cyclopentyldienyl ligands, see: (a) Cummins, C. C.; Schrock, R. R.; Davis, W. M. *Organometallics* **1992**, *11*, 1452–1454. (b) Bennett, J. L.; Wolczanski, P. T. *J. Am. Chem. Soc.* **1994**, *116*, 2179–2180. (c) Nöth, H.; Schmidt, M. *Organometallics* **1995**, *14*, 4601–4610. (d) Bennett, J. L.; Wolczanski, P. T. *J. Am. Chem. Soc.* **1997**, *119*, 10696–10719. (e) Liu, X.; Wu, Z.; Cai, H.; Yang, Y.; Chen, T.; Vallet, C. E.; Zuhr, R. A.; Beach, D. B.; Peng, Z.-H.; Wu, Y.-D.; Concolino, T. E.; Rheingold, A. L.; Xue, Z. *J. Am. Chem. Soc.* **2001**, *123*, 8011–8021. (f) Turculet, L.; Tilley, T. D. *Organometallics* **2004**, *23*, 1542–1553.

SCHEME 2. Proposed Catalytic Cycle for Peroxide Reduction Involving a Titanium Hydride



direct evidence for a titanium(IV) hydride produced from a titanium(IV) alkoxide and a silane has not been obtained.

We attempted to observe a titanium(IV) hydride directly by mixing equimolar amounts of Ti(O-*i*-Pr)$_4$, HSiMe$_2$OSiMe$_2$H, and PPh$_3$ in toluene-d_8 (eq 5).[34c] Analysis of the reaction mixture by ^{1}H NMR spectroscopy did not provide any signals consistent with a titanium(IV) hydride. When ^{1}H NMR spectroscopy was used to monitor the reaction progress during the catalytic reduction, slight line broadening of the resonances was occasionally observed.[33a,35b] This line broadening could result from the formation of a paramagnetic titanium(III) species.[35]



Evidence for the formation of a titanium(III) species was obtained by EPR spectroscopy. When equimolar amounts of Ti(O-*i*-Pr)$_4$ and HSiMe$_2$OSiMe$_2$H were mixed in toluene, a dark blue solution was formed. EPR spectroscopy of the resulting solution at ambient temperature gave a complex line shape with a center field resonance of $g = 1.963$,[36] which is similar to the g values of other titanium(III) alkoxides.[37] A titanium(III) species could be formed from a titanium(IV) hydride by bimetallic reductive elimination to form H_2 (eq 6).[33a,34c,38] Alternatively, reduction of the phosphine oxide could occur from a titanium-(III) hydride,[28b,39,40] or a titanium(IV) species may be serving as a one-electron reductant.[41] The EPR experiments do not differentiate between these possibilities.

$$2\ R_3Ti^{IV}{-}H \rightarrow 2\ R_3Ti^{III} + H_2 \qquad (6)$$

Examination of Oxygen-Atom Transfer in the Reduction of Silyl Peroxides by Phosphines. An unresolved mechanistic question regarding the reduction of silyl peroxides by phosphines involves assigning which oxygen atom is transferred to the phosphine during the reaction. Previous investigations of the deoxygenation of alkyl silyl peroxides by phosphines and phosphites suggested the oxygen atom adjacent to the silicon atom is removed.[15e,17b] Computational studies[42] and the preferential deoxygenation of an alkyl silyl peroxide in the presence of a dialkyl peroxide[17g] also both suggest that the oxygen atom adjacent to the silicon atom is transferred to heteroatom nucleophiles. A kinetic study, however, concluded that the oxygen atom attached to the carbon atom was transferred to trimethylphosphite.[17c] We envisioned that experiments using an unsymmetrically isotopically-labeled hydroperoxide[15b,c] would enable the fate of each oxygen atom to be determined unambiguously.

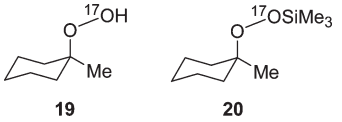


FIGURE 2. Unsymmetrical ^{17}O-labeled peroxides synthesized for oxygen atom transfer studies.

An ^{17}O-labeled peroxide was prepared to determine which oxygen atom was transferred during the reduction. The use of the ^{17}O isotope enabled the use of NMR spectroscopy to analyze the products. The low natural abundance of ^{17}O (0.037%) ensured that the signal-to-noise ratio of all spectra would be good, even with low enrichment of the heavier isotope.[43] Our use of ^{17}O-labeled peroxides was inspired by Porter and co-workers' use of substrates with an ^{18}O isotope to determine which oxygen atom was transferred in the reduction of hydroperoxides by phosphines.[15b,c] Because of the nondestructive nature of ^{17}O NMR spectroscopy, low levels of enrichment in the ^{17}O isotope (1%) can be used to perform the analysis compared to use of the ^{18}O label, which often requires analytical methods such as mass spectrometry or elemental analysis.[44] Using the method of Porter,[15b,c,45] hydroperoxide **19** and silyl peroxide **20** were prepared with approximately 1% ^{17}O enrichment (Figure 2).[46]

The use of the ^{17}O-labeled peroxides and ^{17}O NMR spectroscopy revealed that triphenylphosphine removed the oxygen atom remote to the carbon atom from both hydroperoxide **19** and silyl peroxide **20**. Treatment of hydroperoxide **19** and silyl peroxide **20** with triphenylphosphine in CD_2Cl_2 gave similar ^{17}O NMR resonances at δ 47 ppm (eqs 7 and 8). An independently synthesized sample of Ph$_3$P=^{17}O (**22**) also displayed a ^{17}O chemical shift of δ 47 ppm.[47] The ^{17}O chemical shifts of the unpurified reaction mixtures did not correspond to ^{17}O-labeled alcohol **24** (δ 56 ppm, Figure 3), which was prepared independently.[48] These results demonstrate that the oxygen atom adjacent to hydrogen in hydroperoxide **19** or

(35) Treatment of cyclopentyldienyltitanium(IV) compounds with silanes has resulted in EPR active products; see: (a) Samuel, E.; Harrod, J. F. *J. Am. Chem. Soc.* **1984**, *106*, 1859–1860. (b) Aitken, C. T.; Harrod, J. F.; Samuel, E. *J. Am. Chem. Soc.* **1986**, *108*, 4059–4066. (c) Woo, H. G.; Harrod, J. F.; Hénique, J.; Samuel, E. *Organometallics* **1993**, *12*, 2883–2885. (d) Lunzer, F.; Marschner, C.; Landgraf, S. *J. Organomet. Chem.* **1998**, *568*, 253–255. (e) Wang, Q.; Corey, J. Y. *Can. J. Chem.* **2000**, *78*, 1434–1440.

(36) The amount of paramagnetic species was not quantified.

(37) (a) Billiau, F.; Folcher, G.; Marquet-Ellis, H.; Rigny, P.; Saito, E. *J. Am. Chem. Soc.* **1981**, *103*, 5603–5604. (b) Covert, K. J.; Wolczanski, P. T.; Hill, S. A.; Krusic, P. J. *Inorg. Chem.* **1992**, *31*, 66–78.

(38) (a) Shiihara, I.; Kawai, W.; Ichihashi, T. *J. Polym. Sci.* **1962**, *57*, 837–854. (b) Barber, J. J.; Willis, C.; Whitesides, G. M. *J. Org. Chem.* **1979**, *44*, 3603–3604. (c) Fischer, J. M.; Piers, W. E.; Pearce Batchilder, S. D. P.; Zaworotko, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 283–284. (d) Johnson, A. L.; Davidson, M. G.; Mahon, M. F. *Dalton Trans.* **2007**, 5405–5411.

(39) Hoskin, A. J.; Stephan, D. W. *Coord. Chem. Rev.* **2002**, *233−234*, 107–129 and references cited therein.

(40) (a) Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784–6785. (b) Shu, R.; Harrod, J. F.; Lebuis, A.-M. *Can. J. Chem.* **2002**, *80*, 489–495 and references cited therein.

(41) Based on a detailed mechanistic analysis on the reduction of phosphine oxides by titanium(IV) alkoxides and siloxanes, a titanium(IV) species has been proposed to serve as a one-electron reductant: Petit, C.; Favre-Reguillon, A.; Albela, B.; Bonneviot, L.; Mignani, G.; Lemaire, M. *Organometallics* **2009**, *28*, 6379–6382.

(42) Estévez, C. M.; Dmitrenko, O.; Winter, J. E.; Bach, R. D. *J. Org. Chem.* **2000**, *65*, 8629–8639.

(43) Silver, B. L.; Luz, Z. *Q. Rev. Chem. Soc.* **1967**, *21*, 458–473.

(44) Jones, J. R. *J. Labelled Compd.* **1969**, *5*, 305–311.

(45) For earlier studies of O−O bond formation through alkoxy radicals, see: Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1966**, *88*, 4518–4520 and additional references cited in ref 15b,c.

(46) Details are provided as Supporting Information.

(47) Lapidot, A.; Irving, C. S. *J. Chem. Soc., Dalton Trans.* **1972**, 668–670.

(48) Boykin, D. W. *^{17}O NMR Spectroscopy in Organic Chemistry*; CRC: Boca Raton, 1991; pp 21−39.

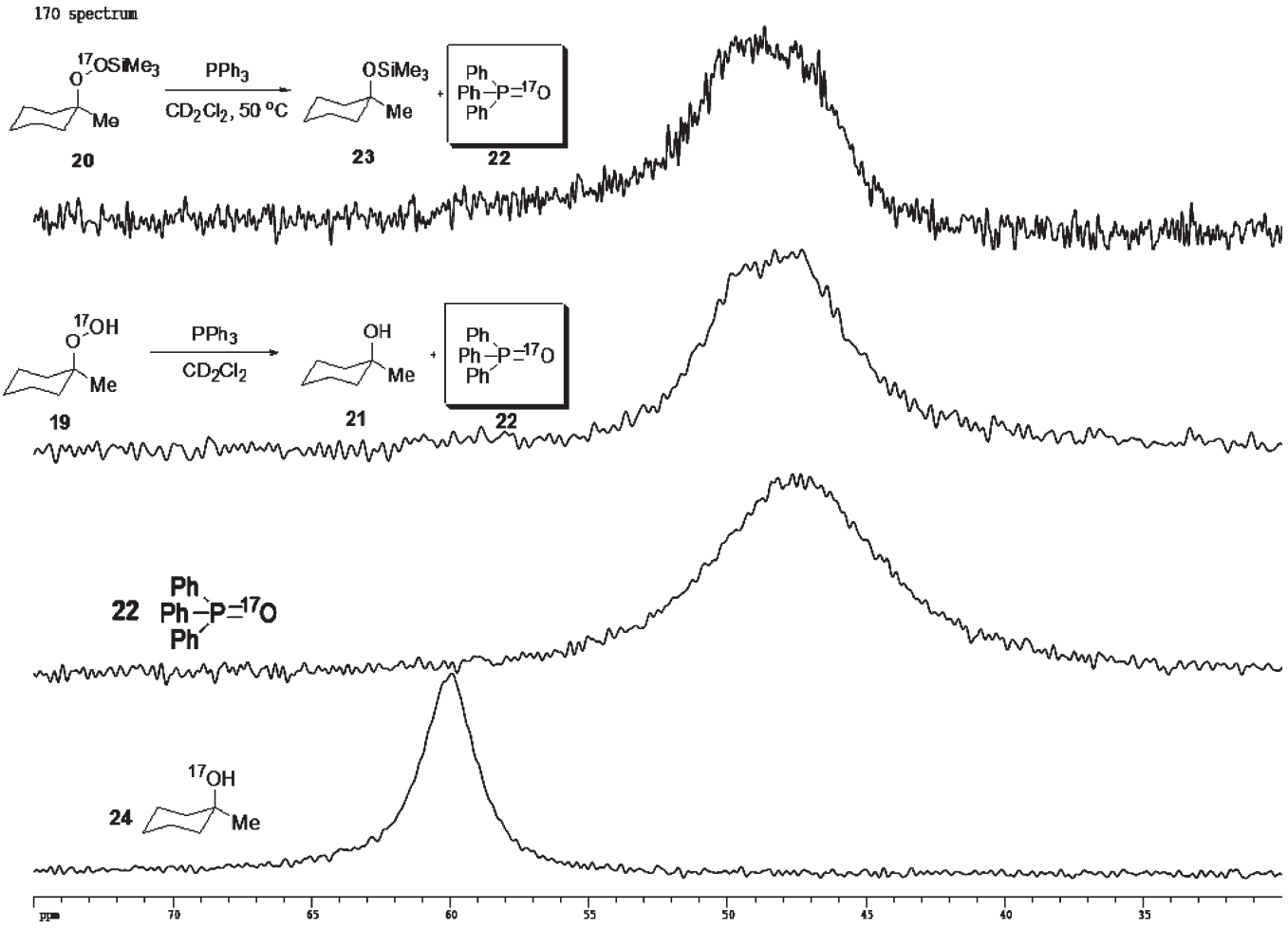
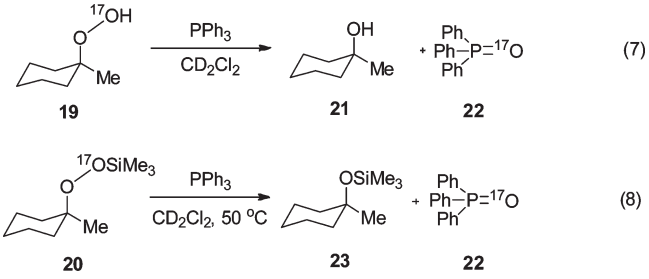


FIGURE 3. ^{17}O NMR spectra of independently synthesized alcohol **24** and phosphine oxide **22** with unpurified reaction mixtures of labeled peroxides **19** and **20**.

adjacent to the silicon atom in silyl peroxide **20** is transferred to triphenylphosphine.



(7)

(8)

Mechanism of Silyl Transfer in Peroxide Reduction. The oxygen-transfer experiments raise the question of how the silyl group is transferred from the starting materials to the products during the reduction. The observation that the oxygen atom connected to the silyl group of silyl peroxide **20** is transferred to the phosphine requires that the silyl group be moved to the other oxygen atom to account for the formation of the silyl ether **23** (eq 8). Two mechanisms to explain silyl-group transfer are presented in Scheme 3. Both mechanisms would involve a dialkoxyphosphorane intermediate (e.g., **25**) formed by formal oxidative addition of the phosphine into the oxygen−oxygen bond of the silyl peroxide (Scheme 3).[18a,b,49,50] Intermediate **25** could undergo concerted silyl transfer (e.g., **26**, Scheme 3) to give the silyl ether and phosphine oxide products. Alternatively, dialkoxyphosphorane **25** could undergo heterolysis[18d,e] to form the ion pair **27** and **28**, and the silylated phosphine oxide **28** could silylate the alkoxide ion **27** (Scheme 3).[51] Because the concerted and ionic and mechanisms involve intra- and intermolecular silyl group transfer, respectively, a crossover experiment could distinguish between them.

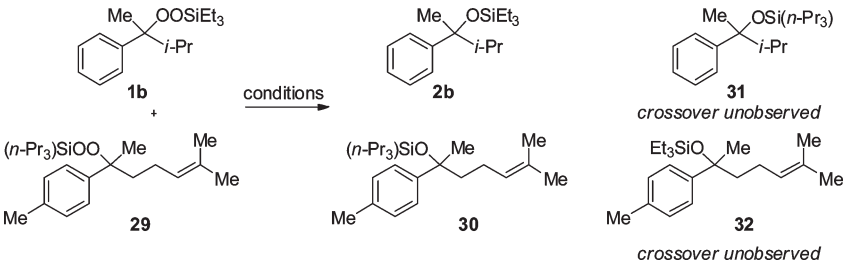
The results of the crossover experiment are consistent with a concerted intramolecular transfer of the silyl group from

(49) For observations of cyclic O−P^V−O intermediates, see: (a) Denney, D. B.; Gough, S. T. D. *J. Am. Chem. Soc.* **1965**, *87*, 138–139. (b) Adam, W.; Ramírez, R. J.; Tsai, S.-C. *J. Am. Chem. Soc.* **1969**, *91*, 1254–1256. (c) Reference 18c. (d) Bartlett, P. D.; Baumstark, A. L.; Landis, M. E.; Lerman, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 5267–5268. (e) Barlett, P. D.; Landis, M. E.; Shapiro, M. J. *J. Org. Chem.* **1977**, *42*, 1661–1662. (f) Clennan, E. L.; Heah, P. C. *J. Org. Chem.* **1981**, *46*, 4105–4107. (g) Clennan, E. L.; Heah, P. C. *J. Org. Chem.* **1982**, *47*, 3329–3331. (h) Clennan, E. L.; Heah, P. C. *J. Org. Chem.* **1983**, *48*, 2621–2622.

(50) For indirect detections of acyclic O−P^V−O intermediates, see: (a) Greenbaum, M. A.; Denney, D. B.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1956**, *78*, 2563–2565. (b) Denney, D. B.; Greenbaum, M. A. *J. Am. Chem. Soc.* **1957**, *79*, 979–981. (c) Denney, D. B.; Adin, N. G. *Tetrahedron Lett.* **1966**, *7*, 2569–2572. (d) Denney, D. B.; Denney, D. Z.; Hall, C. D.; Marsi, K. L. *J. Am. Chem. Soc.* **1972**, *94*, 245–249.

(51) Liu, X.; Verkade, J. G. *Heteroat. Chem.* **2001**, *12*, 21–26 and references cited therein.

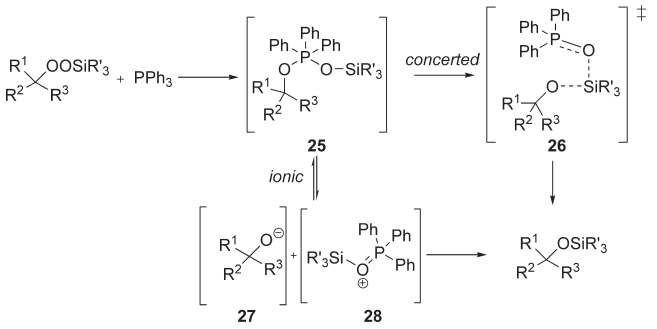
TABLE 4. Crossover Experiment To Determine the Mechanism of Silyl Transfer



entry	conditions	**2b**+**30**:**31**:**32**[a]
1	PPh_3 (1.0 equiv), toluene, 100 °C	100:0:0
2	PPh_3 (1.0 equiv), MeCN, 70 °C	100:0:0
3	PPh_3 (1.0 equiv), neat, 100 °C	100:0:0
4	Ti(O-*i*-Pr)$_4$ (0.5 equiv), $HSiMe_2OSiMe_2H$ (2.0 equiv), PPh_3 (0.05 equiv), toluene, 100 °C	100:0:0

[a]Relative ratios of silyl ethers **2b**+**30** to crossover products **31** or **32** by GC analysis of the unpurified reaction mixtures. Some free alcohols of the silyl ethers were observed; details are provided as Supporting Information.

SCHEME 3. Potential Silyl Group Transfer Pathways



the peroxide to the hydroxyl group. The triethylsilyl and tri-*n*-propylsilyl peroxides **1b** and **29** (Table 4) were chosen for this study because they undergo reduction of the peroxide at similar rates. Under all conditions examined, crossover products **31** and **32** were not observed.[52] Varying the solvent polarity (Table 4, entries 1 and 2) or reagent concentrations (Table 4, entry 3) did not lead to scrambling of the silyl protecting groups. Performing the double-labeling experiment under the catalytic conditions also did not produce crossover products (Table 4, entry 4). The concerted transfer of the silyl group from the terminal oxygen of the peroxide to the internal oxygen atom (Scheme 3) accounts for these results. This crossover experiment, however, is also consistent with the formation of a short-lived ion pair **27** and **28** (Scheme 3)[18d,e] that transfers the silyl group before diffusion out of the solvent cage can occur.[53] That mechanism is less likely considering that no crossover was observed even in more polar solvents.

Conclusions

A method to reduce silylated hydroperoxides with catalytic quantities of phosphines has been demonstrated.[54] Catalytic quantities of phosphine can be used because the resulting phosphine oxide is subsequently reduced by a secondary reducing system based on a Ti(IV) catalyst and a siloxane. Control experiments demonstrate that the phosphine is responsible for fragmentation of the oxygen−oxygen bond. Mechanistic investigations revealed that the phosphine attacks the silyl peroxide at the oxygen atom adjacent to the silicon atom, and the silyl group is transferred in a concerted step to the forming alkoxide.

Experimental Section

General experimental details are provided as Supporting Information.

Trimethylsilyl Peroxy Ether 1a. To a cooled (0 °C) solution of hydroperoxide **4**[29] (1.06 g, 5.88 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (1.64 mL, 11.8 mmol) and Me_3SiCl (0.82 mL, 6.5 mL). The reaction mixture was warmed to ambient temperature over 1 h and then partitioned between CH_2Cl_2 (20 mL) and H_2O (30 mL). The layers were separated, and the organic layer was washed with brine (1 × 30 mL), passed through cotton, and concentrated under reduced pressure. Purification by column chromatography (100% hexanes) afforded the trimethylsilyl peroxy ether **1a** (0.95 g, 64%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.7 Hz, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 2.00 (sp, J = 6.9 Hz, 1H), 1.62 (s, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.73 (d, J = 7.0 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 127.5, 126.8, 88.1, 37.7, 18.8, 17.8, 17.7, −0.94; HRMS (ESI) m/z calcd for $C_{14}H_{24}O_2SiNa$ $(M + Na)^+$ 275.1443, found 275.1443. Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.83; H, 9.59.

Triethylsilyl Peroxy Ether 1b. To a cooled (0 °C) solution of hydroperoxide **4**[29] (0.26 g, 1.4 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (0.58 mL, 4.2 mmol) and Et_3SiCl (0.35 mL, 2.1 mmol). The reaction mixture was warmed to ambient temperature over 2 h and then partitioned between EtOAc (20 mL) and H_2O (30 mL). The layers were separated, and the organic layer was washed with H_2O (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (100% hexanes) afforded triethylsilyl peroxy ether **1b** (0.40 g, 95%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.24 (m, 1H), 1.98 (sep, J = 6.9 Hz, 1H), 1.61 (s, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.86 (d, J = 6.9 Hz, 3H), 0.74 (d, J = 6.9 Hz, 3H), 0.68 (q, J = 7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 127.6, 126.9, 126.6, 88.2, 37.8, 19.3, 17.9, 7.0, 4.1; IR (thin film) 2957, 1236, 741 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{30}O_2SiNa$ $(M + Na)^+$ 317.1913, found 317.1922. Anal. Calcd for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27. Found: C, 69.34; H, 10.50.

(52) Authentic samples of the crossover products **31** and **32** were prepared for comparison purposes. Details are provided as Supporting Information.

(53) (a) Winstein, S.; Klinedinst, P. E., Jr.; Robinson, G. C. *J. Am. Chem. Soc.* **1961**, *83*, 885–895. (b) Loupy, A.; Tchoubar, B.; Astruc, D. *Chem. Rev.* **1992**, *92*, 1141–1165.

(54) Details on experimental procedures, handling, and purifying organic peroxides are provided in the Supporting Information. Although no difficulties were observed in handling and purifying organic peroxides in this report, organic peroxides are potentially explosive: Zabicky, J. In *The Chemistry of Peroxides*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 2006; Vol. 2, Chapter 7, pp 597−774.

Benzyl Peroxy Ether 1c. The procedure of Moulines and co-workers was used.[55] To a cooled (0 °C) suspension of powdered KOH pellets (0.058 g, 1.04 mmol) and tetrabutylammonium bromide (0.030 g, 0.094 mmol) in CH_2Cl_2 (1 mL) were added hydroperoxide **4**[29] (0.170 g, 0.944 mmol) and benzyl bromide (0.11 mL, 0.94 mmol) in CH_2Cl_2 (1 mL) by addition funnel. The reaction mixture was warmed to ambient temperature over 4 h and then decanted into H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with pentane (3 × 2 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography afforded benzyl peroxy ether **1c** as a colorless oil (0.16 g, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.31 (m, 8H), 4.93 (m, 2H), 2.01 (sep, J = 6.9 Hz, 1H), 1.63 (s, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 136.7, 129.3, 128.4, 128.2, 127.8, 126.9, 126.8, 87.9, 77.1, 37.3, 18.4, 17.9, 17.8; IR (thin film) 2964, 1371, 1028, 756, 698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{22}O_2Na$ $(M + Na)^+$ 293.1518, found 293.1519.

Peroxy Ketal 1d. The procedure of Dussault and co-workers was used.[15a] To a cooled (0 °C) solution of hydroperoxide **4**[29] (0.111 g, 0.616 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (0.015 g, 0.062 mmol) in CH_2Cl_2 (20 mL) was added 2-methoxypropene (0.085 mL, 0.92 mmol). After 1 h at 0 °C, a solution of saturated $NaHCO_3$ (10 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, passed through cotton, and concentrated under reduced pressure. Purification by column chromatography (5−10% EtOAc/hexanes) afforded the peroxy ketal **1d** as a colorless oil (0.13 g, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.31 (m, 2H), 7.23 (m, 1H), 3.24 (s, 3H), 2.01 (sp, J = 6.9 Hz, 1H), 1.63 (s, 3H), 1.39 (s, 3H), 1.29 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 127.6, 126.8, 126.7, 104.0, 86.7, 49.4, 37.6, 23.9, 22.7, 18.6, 18.0, 17.9; IR (thin film) 2991, 1446, 1369, 1207, 1072, 854 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{24}O_3Na$ $(M + Na)^+$ 275.1623, found 275.1625. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.68; H, 9.67.

General Procedure for Catalytic Reduction of Silyl Peroxides 1b and 5−11. To a solution of the silyl peroxide (1.0 equiv) in a threaded screw-cap vial in toluene (0.3 M) were added PPh_3 (0.05 equiv), Ti(O-*i*-Pr)$_4$ (0.5 equiv), and 1,1,3,3-tetramethyldisiloxane (TMDS, 2.0 equiv). The vial was sealed, and the solution was heated to 100 °C (oil bath) for 24 h. The reaction mixture was then cooled to ambient temperature, transferred to a separate flask with EtOAc, and hydrolyzed with an equal volume of 1 N NaOH. After 10 h, the layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography afforded the silyl ethers as colorless oils.

Silyl Ether 2b (Table 3, Entry 1). The general procedure was followed using silyl peroxide **1b** (0.110 g, 0.372 mmol), PPh_3 (0.0048 g, 0.019 mmol), Ti(O-*i*-Pr)$_4$ (0.055 mL, 0.19 mmol), and TMDS (0.136 mL, 0.744 mmol). Purification by column chromatography (5% CH_2Cl_2/hexanes) afforded silyl ether **2b** as a colorless oil (0.76 g, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.4 Hz, 2H), 7.28 (t, J = 7.7 Hz, 2H), 7.19 (t, J = 7.7 Hz, 1H), 1.86 (sp, J = 6.8 Hz, 1H), 1.56 (s, 3H), 0.90 (t, J = 8.0 Hz, 9H), 0.82 (d, J = 6.8 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H), 0.52 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 127.5, 126.3, 126.2, 79.4, 41.4, 24.5, 17.9, 17.8, 7.4, 7.0; IR (thin film) 2956, 1456, 1371, 1236, 1128, 802, 701 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{30}OSiNa$ $(M + Na)^+$ 301.1964, found 301.1962. Anal. Calcd for $C_{17}H_{30}OSi$: C, 73.31; H, 10.86. Found: C, 73.19; H, 10.80.

(55) Moulines, J.; Bougeois, M. J.; Campagnole, M.; Lamidey, A. M.; Maillard, B.; Montaudon, E. *Synth. Commun.* **1990**, *20*, 349–353.

Silyl Ether 12 (Table 3, Entry 2). The general procedure was followed using silyl peroxide **5** (0.123 g, 0.387 mmol), PPh_3 (0.0051 g, 0.019 mmol), Ti(O-*i*-Pr)$_4$ (0.057 mL, 0.19 mmol), and TMDS (0.141 mL, 0.774 mmol). Purification by column chromatography (10% Et_2O/hexanes) afforded silyl ether **12** (0.077 g, 79%) and the corresponding free alcohol (0.0068 g, 9%) as colorless oils. Analytical data for silyl ether **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (m, 4H), 1.63 (m, 2H), 1.44 (m, 4H), 1.32 (s, 3H), 1.19 (s, 6H), 0.94 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.4, 73.6, 64.9, 45.4, 39.9, 30.1, 23.9, 19.3, 7.3, 7.0; IR (thin film) 2957, 1474, 1391, 1260, 1081, 761 cm^{-1}; HRMS (CI) m/z calcd for $C_{16}H_{35}O_3Si$ $(M + H)^+$ 303.2355, found 303.2368. Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.65; H, 11.33. Found: C, 63.56; H, 11.31.

Deprotected Alcohol (Table 3, entry 2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (m, 4H), 1.65 (m, 2H), 1.62 (br s, 1H), 1.48 (m, 4H), 1.33 (s, 3H), 1.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.3, 71.2, 64.8, 44.2, 39.8, 29.5, 24.0, 19.1; IR (thin film) 3403, 2968, 1377, 1189, 1060, 872 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{20}O_3Na$ $(M + Na)^+$ 211.1310, found 211.1313.

Silyl Ether 13 (Table 3, Entry 3). The general procedure was followed using silyl peroxide **6** (0.145 g, 0.594 mmol), PPh_3 (0.0078 g, 0.029 mmol), Ti(-O*i*-Pr)$_4$ (0.088 mL, 0.29 mmol), and TMDS (0.217 mL, 1.19 mmol). Purification by column chromatography (0−2% CH_2Cl_2/pentane) afforded silyl ether **13** as a colorless oil (0.063 g, 46%). Spectroscopic data match those reported in the literature:[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (m, 2H), 1.54 (m, 2H), 1.46 (m, 1H), 1.35 (m, 4H), 1.26 (m, 1H), 1.20 (s, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.57 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.7, 40.8, 30.0, 26.1, 22.9, 7.4, 7.2; IR (thin film) 2938, 1460, 1170, 1027, 742 cm^{-1}; HRMS (CI) m/z calcd for $C_{13}H_{29}OSi$ $(M + H)^+$ 229.1988, found 229.1983. Anal. Calcd for $C_{13}H_{28}OSi$: C, 68.35; H, 12.35. Found: C, 68.08; H, 12.18.

Silyl Ether 14 (Table 3, Entry 4). The general procedure was followed using silyl peroxide **7** (0.174 g, 0.674 mmol), PPh_3 (0.0088 g, 0.034 mmol), Ti(O-*i*-Pr)$_4$ (0.10 mL, 0.34 mmol), and TMDS (0.247 mL, 1.35 mmol). Purification by column chromatography (5−10% CH_2Cl_2/hexanes) afforded silyl ether **14** as a colorless oil (0.107 g, 66%). A previous literature report does not provide analytical data for the compound:[57] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (m, 1H), 1.66 (m, 7H), 1.51 (td, J = 5.8, 11.7 Hz, 4H), 1.43 (m, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.58 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.7, 35.7, 27.6, 25.6, 23.1, 7.1, 5.1; IR (thin film) 2925, 1465, 1238, 1068, 1027, 742 cm^{-1}; HRMS (CI) m/z calcd for $C_{14}H_{34}NOSi$ $(M + NH_4)^+$ 260.2410, found 260.2405. Anal. Calcd for $C_{14}H_{30}OSi$: C, 69.35; H, 12.47. Found: C, 69.15; H, 12.60.

Silyl Ether 15 (Table 3, Entry 5). The general procedure was followed using silyl peroxide **8** (0.107 g, 0.403 mmol), PPh_3 (0.0053 g, 0.020 mmol), Ti(O-*i*-Pr)$_4$ (0.059 mL, 0.20 mmol), and TMDS (0.148 mL, 0.805 mmol). Purification by column chromatography (2−6% CH_2Cl_2/hexanes) afforded silyl ether **15** as a colorless oil (0.074 g, 73%). Spectroscopic data match those reported in the literature:[58] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 4H), 7.22 (m, 1H), 4.56 (t, J = 6.2 Hz, 1H), 1.69 (m, 2H), 0.87 (m, 12H), 0.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 128.1, 127.0, 126.2, 76.4, 33.9, 10.3, 7.0, 5.1; IR (thin film) 2958, 2877, 1105, 1056, 1010 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{26}OSiNa$ $(M + Na)^+$ 273.1651, found 273.1658.

Silyl Ether 16 (Table 3, Entry 6). The general procedure was followed using silyl peroxide **9** (0.161 g, 0.543 mmol), PPh_3 (0.0071 g, 0.027 mmol), Ti(O-*i*-Pr)$_4$ (0.080 mL, 0.27 mmol), and

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TMDS (0.20 mL, 1.1 mmol). Purification by column chromatography (2.5−5% Et_2O/hexanes) afforded silyl ether **16** as a colorless oil (0.12 g, 79%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.30 (m, 1H), 4.56 (m, 2H), 4.00 (m, 1H), 3.43 (dd, J = 5.7, 9.4 Hz, 1H), 3.31 (dd, J = 5.8, 9.4 Hz, 1H), 1.19 (d, J = 6.2 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.61 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 128.5, 127.8, 127.7, 76.4, 73.5, 67.7, 21.3, 7.0, 5.1; IR (thin film) 2955, 1457, 1111, 1018, 741 cm^{-1}; HRMS (CI) m/z calcd for $C_{16}H_{32}NO_2Si$ $(M + NH_4)^+$ 298.2202, found 298.2196. Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 68.52; H, 10.06. Found: C, 68.34; H, 10.01.

Silyl Ether 17 (Table 3, Entry 7). The general procedure was followed using silyl peroxide **10** (0.110 g, 0.543 mmol), PPh_3 (0.0054 g, 0.021 mmol), Ti(O-*i*-Pr)$_4$ (0.061 mL, 0.21 mmol), and TMDS (0.151 mL, 0.823 mmol). Purification by column chromatography (0−5% Et_2O/pentane) afforded silyl ether **17** as a colorless oil (0.071 g, 69%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.18 (m, 3H), 3.98 (sext, J = 6.1 Hz, 1H), 2.78 (dd, J = 13.2, 6.6 Hz, 1H), 2.65 (dd, J = 13.2, 6.3 Hz, 1H), 1.15 (d, J = 6.1 Hz, 3H), 0.89 (t, J = 8.0 Hz, 9H), 0.49 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 129.8, 128.3, 126.2, 70.1, 46.7, 23.8, 7.0, 5.0; IR (thin film) 2958, 2877, 1259, 1088, 1029, 800 cm^{-1}; HRMS (CI) m/z calcd for $C_{15}H_{30}NOSi$ $(M + NH_4)^+$ 268.2097, found 268.2093. Anal. Calcd for $C_{15}H_{26}OSi$: C, 71.93; H, 10.46. Found: C, 71.81; H, 10.45.

Silyl Ether 18 (Table 3, Entry 8). The general procedure was followed using silyl peroxide **11** (0.125 g, 0.399 mmol), PPh_3 (0.0052 g, 0.020 mmol), Ti(O-*i*-Pr)$_4$ (0.059 mL, 0.20 mmol), and TMDS (0.150 mL, 0.797 mmol). Purification by column chromatography (5% CH_2Cl_2/hexanes) afforded silyl ether **18** as a colorless oil (0.093 g, 79%): ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (m, 1H), 1.62 (m, 2H), 1.37 (m, 20H), 0.96 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.9, 32.8, 24.8, 24.4, 23.5, 23.4, 21.1, 7.2, 5.2; IR (thin film) 2938, 1469, 1096, 1060, 724 cm^{-1}; HRMS (CI) m/z calcd for $C_{18}H_{39}OSi$ $(M + H)^+$ 299.2770, found 299.2765. Anal. Calcd for $C_{18}H_{38}OSi$: C, 72.41; H, 12.83. Found: C, 72.62; H, 13.03.

(+)-(*R*)-Silyl Peroxide 1b. To a solution of enantiomerically enriched (+)-(*R*)-silyl peroxide **1b**[29] (0.049 g, 0.17 mmol) in toluene (0.6 mL) were added PPh_3 (0.002 g, 0.008 mmol), Ti(O-*i*-Pr)$_4$ (0.024 mL, 0.084 mmol), and TMDS (0.061 mL, 0.33 mmol). The reaction mixture was heated to 100 °C (oil bath) for 8 h. GC analysis of the unpurified reaction mixture showed a 51:49 ratio of starting silyl peroxide **1b** (GC t_R = 10.530 min) and silyl ether **2b** (GC t_R = 10.109 min). The reaction mixture was poured into EtOAc (5 mL) and hydrolyzed with 1 N NaOH (2 mL). After 8 h, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (2−8% CH_2Cl_2/hexanes) afforded recovered silyl peroxy ether **1b** (0.019 g, 40%) and reduced silyl ether **2b** (0.021 g, 42%) as colorless oils. Deprotection of silyl peroxy ether **1b** with TBAF (0.210 mL, 0.210 mmol, 1 M) in THF (1 mL) gave (+)-(*R*)-hydroperoxide **4** with a 97% ee as determined by chiral HPLC [Chiracel OD-H column (250 mm × 4.6 mm i.d) with *i*-PrOH/hexanes (5:95 v/v), flow rate 1.0 mL·min^{-1}, detection by UV absorbance at 220 nm, t_R major: 9.342 min, t_R minor: 15.583 min]. Deprotection of silyl ether **2b** with TBAF (0.200 mL, 0.200 mmol, 1 M) in THF (1 mL) gave (+)-(*R*)-alcohol **3** with a 97% ee as determined by chiral HPLC [Chiracel OD-H column (250 mm × 4.6 mm i.d.) with *i*-PrOH/hexanes (5:95 v/v), flow rate 1.0 mL·min^{-1}, detection by UV absorbance at 220 nm, t_R major: 6.917 min, t_R minor: 5.725 min].

Labeled Phosphine Oxide 22 (eq 7). To a cooled (0 °C) solution of labeled hydroperoxide **19** (0.049 g, 0.37 mmol) in $CDCl_3$ (0.80 mL) was added PPh_3 (0.098 g, 0.37 mmol). After 6 h, analysis of the unpurified reaction mixture by ^{17}O NMR spectroscopy indicated a broad resonance at δ 47 ppm, which corresponds to labeled $Ph_3P{=}^{17}O$ (**22**)[47] (Figure 3). No other visible ^{17}O resonances were observed.

Labeled Phosphine Oxide 22 (eq 8). To a solution of the labeled silyl peroxide **20** (0.067 g, 0.33 mmol) in $CDCl_3$ (0.80 mL) was added PPh_3 (0.087 g, 0.33 mmol). The reaction mixture was heated to 50 °C (oil bath) for 8 h. Analysis of the unpurified reaction mixture by ^{17}O NMR spectroscopy indicated a broad resonance at δ 47 ppm, which corresponds to labeled $Ph_3P{=}^{17}O$ (**22**)[47] (Figure 3). No other visible ^{17}O resonances were observed.

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Supporting Information Available: Complete experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.