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An Inexpensive Air-Stable Titanium-Based System for the Conversion of Esters to Primary Alcohols

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Polymethylhydrosiloxane, when combined with titanium(IV) isopropoxide, provides a convenient system for the conversion of esters to the corresponding primary alcohols in the presence of a wide range of functional groups. Reactions are carried out as mixtures of the neat reaction components; workup with aqueous alkaline THF affords primary alcohols in good to excellent yields. The system tolerates primary alkyl bromides and iodides, olefins, epoxides, and alkynes. Steric differentiation of methyl and *tert*-butyl esters is also possible. The results observed in the parent and related reactions argue against pathways involving Lewis-acid catalysis and anionic hydridosilicate-mediated reductions, and instead support a neutral titanium hydride complex or strongly associated titanium/silane complex as the active reducing agent.

The conversion of esters to the corresponding primary alcohols is a fundamental process in organic synthesis.[1] Most known methods for accomplishing this transformation can be categorized as reactions of main group metal hydride reducing agents, especially those of boron, aluminum, and silicon.[2] Several methods which involve transition metal-based reagents for the related hydrosilylation of organic carbonyls have also been developed.[3] Many of these reagents suffer from problems such as high reactivity (including pyrophoricity), low functional group tolerance, and expense.[4,5] Previously[6] our laboratory has reported several systems for the hydrosilylation/reduction of esters that overcome some of the drawbacks of more conventional protocols. Here we present a further improvement which involves air-stable, nonpyrophoric, and readily available reagents. Additionally, this new system allows for ester reduction without solvent under mild conditions, uses 0.25−1.0 equiv of a very inexpensive transition metal component and is tolerant of a wide range of functional groups.

Our initial report detailed the use of a titanocene catalyst and a potentially toxic trialkoxysilane as the ultimate reductant.[6a] Subsequent investigations showed that the titanocene catalyst could be replaced by the much cheaper titanium(IV) tetraisopropoxide ($Ti(O^iPr)_4$) which offered the further advantage of not requiring activation by alkyllithiums.[6b] We were, however, unable to extend this work, despite some effort, to allow for the substitution of polymethylhydrosiloxane (PMHS) for the undesirable trialkoxysilanes. It was subsequently discovered that PMHS could be used with a titanocene-based catalyst as the stoichiometric reductant, thus affording an improvement both in terms of reduced toxicity and reagent cost.[6c] A recent report of the reduction of phosphine oxides by PMHS in the presence of 1 equiv of $Ti(O^iPr)_4$ at higher temperatures[7] led us to reexamine ester reaction under similar conditions. During the course of our investigation, a report[8] appeared describing a related system that generally involved the use of large excesses of PMHS with $Ti(O^iPr)_4$ in various solvents; a limited number of functionalized substrates were examined. Here we detail our investigation of the reaction of a variety of functionalized esters with PMHS promoted by $Ti(O^iPr)_4$, as well as several other titanium reagents and silane reductants.

Results

The results of a series of reactions between functionalized methyl and ethyl esters **1** and 2.5 equiv PMHS (monomer weight = 60) in the presence of varying amounts of $Ti(O^iPr)_4$ are presented in Table 1 (see Scheme 1). These reactions were carried out simply by mixing together the neat reagents in an ordinary test tube open to the ambient atmosphere; only a calcium sulfate drying tube was used to exclude atmospheric moisture. Often, but not always, a deep purple color was noted in the reaction mixture; there was no noted correlation between the observance of this color and the rate or efficiency of the reaction. The reaction was judged to be complete when the starting material was no longer observable by TLC. Hydrolysis with aqueous sodium hydroxide/THF (or TBAF; see Experimental Section) both degraded the polymer backbone and freed the polymer-bound products **2** to afford primary alcohols **3**. The product alcohols were generally greater than 90% pure as judged by GC and ^1H NMR analysis.[9] Products were

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⊗ Abstract published in *Advance ACS Abstracts,* October 1, 1995.

[1] Greeves, N. In *Comprehensive Organic Synthesis, Vol. 8;* Trost, B. M., Ed.; Pergamon Press: New York, 1991.

[2] Larock, R. C. *Comprehensive Organic Transformations;* VCH Publishers, Inc.: New York, 1989.

[3] Ojima, I. In *The Chemistry of Organic Silicon Compounds;* Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1989.

[4] Hajós, A. *Complex Hydrides;* Elsevier Scientific Publishing Co.: New York, 1979.

[5] Barrett, A. G. M. In *Comprehensive Organic Synthesis, Vol. 8;* Trost, B. M., Ed.; Pergamon Press: New York, 1991.

[6] (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751 and *Ibid.* **1993**, *58*, 3221. (c) Barr, K. J.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 4323.

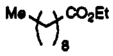
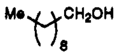
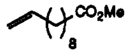
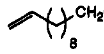
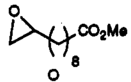
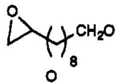
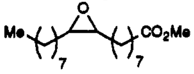
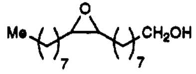
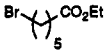
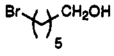
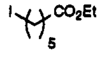
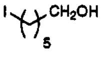
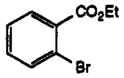
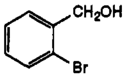
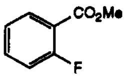
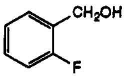
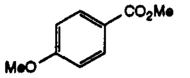
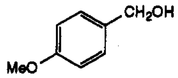
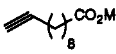
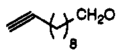
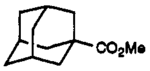
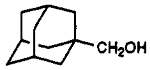
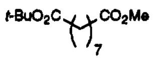
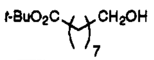
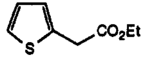
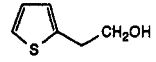
[7] Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625.

[8] Breedon, S. W.; Lawrence, N. J. *Synlett* **1994**, 833.

[9] The primary impurity observed in these reactions derived from degradation of the polymeric silane in the presence of the titanium catalyst. When PMHS was heated in the presence of $Ti(O^iPr)_4$, aqueous alkaline workup led to the isolation of a small amount of material that exhibited a multicomponent ^1H NMR spectrum but which by GC analysis was a single, discrete compound with a mass-to-charge ratio of 220 (observed for the parent peak by low-resolution GC/MS). The impurity present in the product alcohols appears identical to this material. Alkaline hydrolysis of PMHS in the presence of 2-propanol did not yield any material with physical characteristics similar to those of this impurity. The impurity could be removed by flash chromatography or distillation.

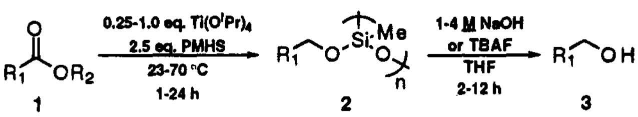
0022-3263/95/1960-7884\$09.00/0

Table 1. Ester Reductions with Polymethylhydrosiloxane as the Stoichiometric Reductant

compound[a]	esters, 1	time (h)	temp (°C)	mol % Ti(O*i*-Pr)$_4$	alcohols, 3	yield[b] (%)
a		24	65	25		93
b		24	70	25		78[c]
c		1.3	65	100		89[c]
d		8	65	100		58[d]
e		2.5	65	100		81[c]
f		5	65	100		85[c]
g		24	23	100		87[c]
h		24	23	100		79[c]
i		1.25	65	100		87[c]
j		2	65	100		80[c]
k		24	65	25		89
l		22	40	100		63[e]
m		24	70	25		>99
n		5.5	40	100		56[f]
o		24	65	25		8[g]

[a] for example, compound **3a** is 1-decanol. [b] isolated yield of material greater than 95% pure as judged by GC and ^{1}H NMR. [c] no reduction of functional groups other than ester was detected. [d] no ring-opened products detected. [e] yield of mixture that was 93:7 alkyne to olefin by ^{1}H NMR. [f] <4% *tert*-butyl isopropyl nonanedicarboxylate also isolated. [g] approx. 20% yield of the self-aldol condensation/reduction product also isolated (see ref 10).

Scheme 1



obtained (after further purification, if necessary) in good to excellent yields. It was observed that substrates containing a sterically bulky group (**1m**) or potentially coordinating functionality (e.g., **1b**–**f**, etc.) required heating or increased amounts of Ti(O^{i}Pr)$_4$ to effect complete conversion on a reasonable time scale. Control experiments showed that both Ti(O^{i}Pr)$_4$ and PMHS were necessary for reduction to occur.

Under these conditions esters bearing a wide variety of functional groups were tolerated, including terminal and internal olefins (**1b** and **1c**), an α-cyclopropyl ester (**1d**), epoxides (**1e** and **1f**), a primary alkyl bromide (**1g**) and iodide (**1h**), and an aryl bromide (**1i**) and fluoride (**1j**). The electron-rich methyl *p*-methoxybenzoate (**1k**) was also effectively reduced to the corresponding *p*-methoxybenzyl alcohol (**3k**) using this protocol. An ester bearing a terminal alkyne (**1l**) could be reduced to the corresponding alcohol if the reaction was run at 40 °C; less than 10% reduction of the alkyne to the olefin was observed. An ester containing a free hydroxyl group did not interfere with ester reduction if an extra 1 equiv of PMHS was added to the reaction mixture; however, cross-linking of the polymer occurred which caused the solidification of the reaction mixture to an amorphous glass. The desired diol could be recovered from this solid in low yield due to incomplete reaction.

The α–trisubstituted ester methyl adamantylformate (**1m**) reacted at 70 °C in 24 h to give 1-adamantylmethanol (**3m**) in quantitative yield; reactions carried out at 65 °C were incomplete after 24 h. Due to the elevated temperature necessary to effect complete conversion, it was inferred that the reaction was moderately sensitive to steric effects. A fair degree of chemoselectivity between methyl and *tert*-butyl esters could be achieved as seen by the formation and isolation of *tert*-butyl 9-hydroxynonanoate (**3n**) from the reduction of *tert*-butyl methyl 1,9-nonanedicarboxylate (**1n**). A small amount of the *tert*-butyl isopropyl 1,9-nonanedicarboxylate was

Scheme 2

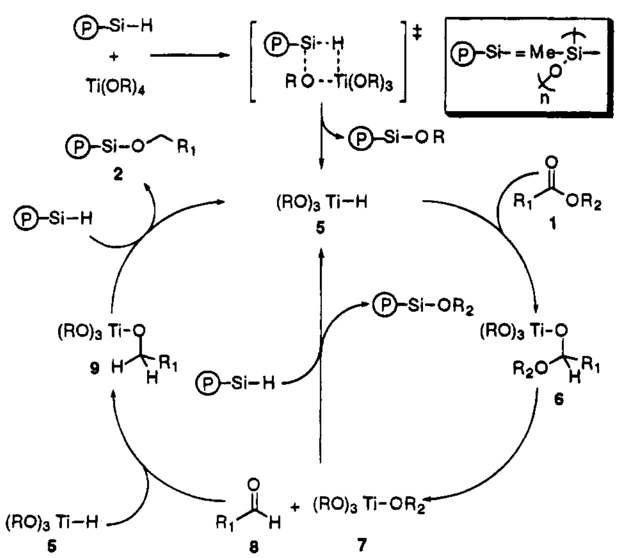


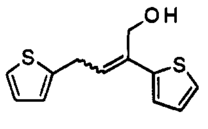
Table 2. Reduction of Ethyl Decanoate under Various Conditions

entry	time (h)	temp (°C)	catalyst	mol % catalyst	reductant	% conversion by GC[a]
1	24	65	$Ti(O^iPr)_4$	25	PMHS	100
2	25	23	$Ti(O^iPr)_4$	100	PMHS	100
3	2	65	$Ti(O^iPr)_4$	25	PMHS	100
4	25	65	$Ti(O^iPr)_4$	25	Ph_2SiH_2	100
5	24	23	$Ti(O^iPr)_4$	100	$HSiCl_3$	0[b]
6	24	65	$Ti(O^nBu)_4$	25	PMHS	75
7	2	65	$Ti(O^nBu)_4$	100	PMHS	90
8	96	23	$THEATi(O^iPr)$[c]	100	Ph_2SiH_2	0[b]

[a] When conversion was less than 100%, in general several products were noted (see ref 14). [b] Only starting material was detected. [c] $THEATi(O^iPr)$ = [tris(hydroxyethyl)aminato]titanium(IV) isopropoxide.

also isolated from this reaction; no 1,9-nonanediol was detected in the crude reaction mixture.

Ethyl (2-thiophene-yl)acetate (**1o**) underwent low-yield conversion to two products, 2-(2-thiophene-yl)ethan-1-ol (**3o**) and allylic alcohol **4**, which was identified on the basis of it's ^1H and ^{13}C NMR spectra. Compound **4** was isolated as a mixture of the *cis* and *trans* isomers of the self-aldol condensation product of the presumed corresponding aldehyde intermediate (see Scheme 2), which then underwent further 1,2 reduction to the primary allylic alcohol.[10]



4

Finally, we observed that under the conditions outlined above α,β-unsaturated esters underwent clean 1,2 reduction to the corresponding allylic alcohols; aryl nitro groups also survived these reaction conditions.[11]

Table 2 delineates the flexibility of the present scheme, as shown by the results of a series of reactions carried out on ethyl decanoate as the test substrate. Increasing the amount of $Ti(O^iPr)_4$ in the system allowed the rate and efficiency of the reaction to be maintained while performing the reaction at lower temperature (see Table 2, entries 1 and 2). Conversely, the reaction rate was accelerated by heating 1 equiv of $Ti(O^iPr)_4$ with the substrate in the presence of PMHS: at 65 °C, ethyl decanoate was completely and cleanly converted to decanol in 2 h (Table 2, entry 3).

Other silanes were used as stoichiometric reductants. Diphenylsilane (2.5 equiv per ester) served equally well as PMHS under standard reaction conditions (Table 2, entry 4). Phenylsilane was also used effectively as the stoichiometric reductant. However, when trichlorosilane (2.5 equiv per ester) was combined with $Ti(O^iPr)_4$ and ethyl decanoate, a highly exothermic reaction took place that nonetheless did not result in the formation of reduction products; a GC trace of the reaction mixture quenched with aqueous acid showed only unreacted starting material after 24 h (Table 2, entry 5).

The efficacy of two other titanium reagents was explored. Titanium(IV) *n*-butoxide ($Ti(O^nBu)_4$), in combination with PMHS, effected the reduction of ethyl decanoate: albeit at a slower rate than the analogous reaction with $Ti(O^iPr)_4$, as evidenced by the lower conversion to alcohol under identical temperatures, times, and titanium reagent loadings (Table 2, entries 6 and 7). Titanium(IV) trialkoxy amino complexes have recently been proposed[12] as possibly superior catalysts for reactions involving titanium-mediated transformations. However, decanol was not detected in a mixture of ethyl decanoate and PMHS in the presence of [tris(hydroxyethyl)aminato]titanium(IV) isopropoxide ($THEATi(O^iPr)$) even after prolonged exposure at room temperature (Table 2, entry 8).

Discussion

The primary advantage of this system is the utilization of inexpensive, readily available, stable, and relatively innocuous reagents. Both components of this system are commercially available in multikilogram lots and may be handled with little or no special precautions (in comparison to LAH and other highly reactive hydride reagents which are pyrophoric and must be handled with extreme care). In contrast with systems that employ monomeric alkoxysilanes which are poisonous and can cause blindness,[6b] PMHS is, to our knowledge, nontoxic. Furthermore, although titanium complexes have been shown to catalyze the disproportionation of alkoxysilanes to silane gas,[6b] no pyrophoric products were observed to have been produced by the action of $Ti(O^iPr)_4$ on PMHS, even after prolonged heating under an inert atmosphere, either in the presence or absence of substrates.

The fact that reactions may be run without solvent is a second major advantage to this system. Although these reductions may be carried out in common laboratory solvents such as THF, diethyl ether, and toluene, it is possible and desirable to simply mix the neat reagents. The elimination of solvent from the reaction itself is a significant step toward reducing the volume of solvent waste, although it remains necessary to dissolve the reaction mixtures in a small amount of THF in order to effect hydrolysis of the polymer and to facilitate extraction and isolation of the product. It is further unnecessary to maintain rigorously anhydrous and oxygen-free conditions. Adventitious water that may be contained in the starting ester was typically accounted for by using 2.5 equiv of SiH per ester; yields and reaction times were

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(10) A similar product was noted in the reduction of methyl phenacetate by the authors of ref 8.

(11) In concurrence with ref 8.

(12) Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 6142.

not altered by drying the esters with activity I alumina immediately prior to use. These observations combine to make an extremely simple and attractive protocol for ester reduction: simply mixing the reagents and monitoring the reaction by TLC, followed by hydrolysis and extraction, provides the desired primary alcohol in good yield and purity.

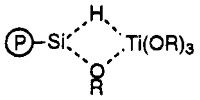
This system is compatible with a wide range of common, synthetically relevant, and sensitive functional groups; functional group incompatibilities demonstrated by previous protocols[6] have been reduced or eliminated. The tolerance of aryl and alkyl bromides, alkyl iodides, and aryl fluorides is especially noteworthy, as several of these transformations were previously[6c] carried out in the presence of PMHS only with difficulty and concomitant hydrodehalogenation. The selective reduction of methyl esters in the presence of terminal alkynes and *tert*-butyl esters should be contrasted with the often nonselective highly reactive main-group hydrides. In general, the mildness of these reagents should allow successful application of this protocol to synthetic schemes with less need for complicated protection and masking strategies.

The flexibility of this system contributes to its applicability to a wide variety of substrates. As noted above, several substrates required the addition of larger amounts $Ti(O^iPr)_4$ or gentle heating in order to effect completion of the reaction in a reasonable time. The amenability of this reagent system to alteration of the variables of reaction time, temperature, titanium reagent loading, and reductant make it extremely adaptable and therefore useful under a wide variety of circumstances. For example, monomeric aryl silanes can be used as stoichiometric reductants in this transformation.[13] In cases where the product of the reaction is sensitive to the conditions required to hydrolyze the polymer, use of silanes of this type would obviate the need for aqueous alkaline workup; mild aqueous workup and removal of solvent and excess silane under reduced pressure would afford the alcohol.

PMHS has been used for many years as a source of carbonyl reducing hydride.[17] Several protocols have been advanced for the removal of the PMHS reside upon the completion of these reactions.[18,19] In our hands, however, only hydrolysis of the polymeric residue in the presence of aqueous alkaline THF proved reliable for the removal of the majority of polymeric reaction products. Indeed, the only impurity observed in these reactions is derived from the polymer.[9]

The mechanism and nature of the reducing species involved in reactions of this type have been proposed[6] but not examined in depth.

The proposed reaction cycle, which is semicatalytic for substoichiometric amounts of $Ti(O^iPr)_4$ (see Scheme 2) involves an initial σ-bond metathesis reaction[6b] to generate a titanium hydride-like species. The exact structure of this complex is not known; an intermediate Ti−H−Si bridging species such as **10** has been proposed.[8] For simplicity we have formulated it as $(RO)_3TiH$ (see **5** in Scheme 2). Following the formation of **5**, the ester **1** is reduced to the titanium acetal **6** which then decomposes *via* β-alkoxide elimination to the titanium mixed alkoxide **7** and aldehyde **8**. Note that the production of allylic alcohol **4** by the reaction of 2-(2-thiophene-yl)ethan-1-ol, $Ti(O^iPr)_4$, and PMHS (*vide supra*) can most easily be explained by an aldehyde intermediate. The titanium alkoxide **7** can regenerate **5** via another σ-bond metathesis, while aldehyde **8** is further reduced by another 1 equiv of **5**. The resulting titanium alkoxide **9** undergoes σ-bond metathesis to regenerate **5** and afford the product alcohol bound to the polymer, **2**.



10

The observation that $Ti(O^nBu)_4$ effects the reaction of PMHS with esters more slowly than the isopropyl analog provides insight into one aspect of the mechanism of this reaction. *A priori*, one would expect an *n*-butoxy substituted species to react faster than isopropoxy complex in any associative mechanism (based on simple steric arguments). In the present case, σ-bond metathesis between Si−H and Ti−O bonds is complicated by the fact that the Si−H bond is incorporated in a polymer. The approach of a titanium alkoxide to the polymer should therefore be especially sensitive to steric effects. It is known, however, that the state of aggregation of titanium(IV) branched alkoxides is generally lower than that of straight chain homologs;[19] therefore the $Ti(O^iPr)_4$ is likely to be relatively more able to react with the polymer than $Ti(O^nBu)_4$. $THEATi(O^iPr)$ is, presumably, too sterically encumbered to interact with the polymer.

Alternatives to the hypothesis of a titanium hydride (or titanium/silane adduct) as the active reductant include Lewis-acid catalyzed silane reductions,[20] anionic hydridosilicate reducing agents,[21] and radical-induced reduction. In the present case, all three of these alternatives are unlikely. Although the necessity of increasing reaction times and titanium reagent concentration when the substrate contains coordinating functionality makes Lewis-acid catalyzed silane addition to the carbonyl plausible, we note that neither the rate nor the efficiency of the reaction was altered by the presence of 20 equiv of pyridine (relative to titanium). Anionic hydridosilicates are capable of reducing esters, and ligand transfer from titanium to silicon could produce an anion of this type (see Scheme 3). Two observations make this alternative unlikely. First, anionic hydridosilicates react with nucleophiles;[21] that primary alkyl bromides and iodides are not reduced suggests that would such species are not produced. Second, anionic hydridosilicates are known to function as electron transfer agents;[21] halides have been shown to dimerize in the presence of such molecules. Finally, any kind of radical-induced carbonyl reduction

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(13) Although activated silanes (those with aryl or alkoxy substituents) have been shown to be useful in these reactions, trichlorosilane was not found to be effective as the ultimate reductant. Observation of only starting ester after an exothermic reaction between trichlorosilane and ethyl decanoate in the presence of $Ti(O^iPr)_4$ suggests that decomposition of the $Ti(O^iPr)_4$[14] is occurring. $Ti(O^iPr)_4$ is a known transesterification catalyst;[15,16] however, no transesterification products were detected in the reaction depicted in Table 2, entry 5.

(14) Incomplete reactions generally gave four products: (1) the desired alcohol, (2) the starting ester, (3) the ester of the alkoxide ligand originally present in the titanium catalyst, and (4) the ester of the product alcohol.

(15) Otera, J. *J. Chem. Rev.* **1993,** *93,* 1449.

(16) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: New York, 1986.

(17) Lipowitz, J.; Bowman, S. A. *Aldrichim. Acta* **1973,** *6,* 1.

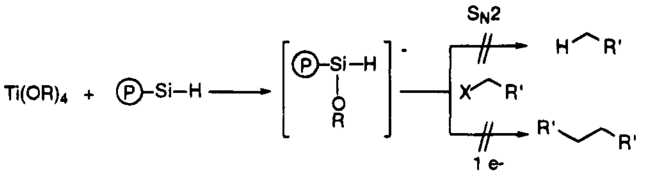
(18) Jaxa-Chamiec, A.; Shah, V. P.; Kruse, L. I. *J. Chem. Soc. Perkin Trans. 1* **1989,** 1705.

(19) Lipowitz, J.; Bowman, S. A. *J. Org. Chem.* **1973,** *38,* 162.

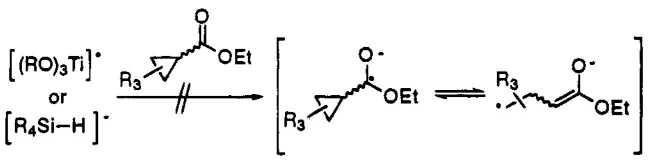
(20) Calas, R. *Pure Appl. Chem.* **1966,** *13,* 61 and references cited therein.

(21) (a) Corriu, R. J. P.; Guerin, C.; Henner, B. J. L.; Wang, Q. *Organometallics* **1991,** *10,* 3574. (b) for a recent review of anionic silicon compounds, see Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993,** *93,* 1371.

Scheme 3



Scheme 4



pathway would likely cause ring opening of an α-cyclopropyl ester[22] (see Scheme 4), as well as significant decomposition of alkyl and aryl halides, neither of which were observed.

Conclusion

We have shown that $Ti(O^iPr)_4$ effects the efficient hydrosilylation of carboxylic esters in the presence of PMHS; primary alcohols are obtained upon aqueous alkaline THF workup of the polymer-bound reaction products. This system is tolerant of a diverse set of common organic functional groups and is tunable over a range of temperatures, reaction times, and titanium reagent loadings. On the basis of the simplicity, inexpense, environmental friendliness, and flexibility of this system, we recommend it as a promising tool for organic chemists.

Note added in proof: When the reduction of terminal epoxy ester **1e** with 2.5 equiv of PMHS was carried out on a 40 mmol scale at 65 °C in the presence of 1 equiv of $Ti(O^iPr)_4$, both 1,10- and 1,11-undecanediol (approximately 15% diols relative to the product alcohol **3e** by integration of the GC trace of the crude reaction mixture) were observed, as a result of reduction of the epoxide. The mixture of diols could be separated from **3e** by flash chromatography and converted to the corresponding diacetates. Their identity was confirmed by ^1H NMR and low-resolution GC/MS. Close examination of GC traces of the products of small-scale (3 mmol) reactions run under identical conditions revealed varying amounts of the same diols. Similarly, reactions carried out at 40 °C evidenced the presence of approximately 7% diols by GC analysis. By adding a known amount of the diol mixture (relative to an internal standard) to crude reaction mixtures, it was established that the diols were not extracted during aqueous alkaline workup. Epoxide opening could be effectively and reliably curtailed ($\leq 2.5\%$ diols by GC) by carrying out the reaction at 23 °C over 44 h in the presence of 1 equiv of $Ti(O^iPr)_4$. Workup according to method 1 afforded an 85% yield (3.0 mmol scale) of **3e** after flash chromatography.

Experimental Section

General. All reactions were carried out in ambient air in disposable test tubes. The tubes were capped with rubber septa through which a small drying tube containing indicating $CaSO_4$ (Drierite, W.A. Hammond Co.) had been inserted. Esters that were liquids could be passed through a short plug of activity I alumina immediately prior to use, as could PMHS (MW ≈ 2270, Aldrich); however, it was found that substrates could be used as received. Solid esters were used as received. $Ti(O^iPr)_4$ was handled and stored under argon and transferred by syringe to minimize hydrolysis by atmospheric moisture. Unless otherwise noted, all other reagents and solvents were either commercially available or prepared accordingly to standard procedures and were used as obtained from the supplier.

Flash column chromatography was performed on Kieselgel 60 (230–400 mesh). Proton NMR spectra were recorded at 300 MHz; carbon spectra were recorded at 75 MHz. Melting points were obtained on a Haake-Buchler melting point apparatus and are uncorrected. Yields, unless otherwise stated, refer to isolated yields of compounds >95% pure as assessed by capillary GC and ^1H NMR.

Method 1. General Procedure for the Reduction of Esters. Into a 15 mL test tube were weighed the ester to be reduced (3.0 mmol) and PMHS (450 mg, 7.5 mmol). A Teflon coated magnetic stirring bar was placed in the tube, which was then capped with a septum. $Ti(O^iPr)_4$ (0.75 mmol, 0.223 mL) was added via syringe, and a drying tube was inserted through the septum. The mixture was shaken to homogeneity; slight warming of the tube and the evolution of a small amount of gas were noted. In several cases the reaction mixture turned a deep purple-black for several minutes and then returned to the usual pale yellow to orange-red color during the course of the reaction. The reaction tube was placed in an oil bath regulated at the specified temperature to ±1 °C (all esters that were solids at room temperature dissolved to give a homogeneous solution at the temperature of the reaction). After stirring for the specified time, the reaction mixture was cooled to room temperature and diluted with THF (20 mL) and transferred to a 100 mL round-bottomed flask. To this flask was added SLOWLY with rapid stirring 4 M aqueous sodium hydroxide (20 mL). THE MIXTURE OFTEN BUBBLED BRIEFLY BUT VIGOROUSLY UPON THE ADDITION OF THE BASE. The mixture was stirred, loosely capped, for 6–12 h; the resulting cloudy white mixture was then extracted with diethyl ether (~20 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed (2 × 10 mL 1 N HCl (aq), 1 × 20 mL saturated brine) and dried ($MgSO_4$). The solution was filtered to remove the drying agent and concentrated on the rotary evaporator to afford the crude product, 90–100% pure by GC and/or NMR. The products were easily seperable from the PMHS-derived impurities by flash column chromatography (hexane/ethyl acetate) to yield analytically pure material; Kugelrohr distillation was also used as noted to remove this impurity.

Method 2. Alternate Fluoride Workup. The cooled reaction mixture was diluted with THF (20 mL) and transferred to a 100 mL round-bottomed flask. A commercially available solution of tetrabutylammonium fluoride in THF (1 M, 15 mL) was added SLOWLY; THE MIXTURE BUBBLED BRIEFLY BUT VIGOROUSLY. The mixture was stirred at room temperature for 20 min, and the solvent was removed by rotary evaporation. The resulting viscous oil was partitioned between 1 N aqueous hydrochloric acid and diethy ether (~20 mL ea), and the layers were separated. The organic layer was washed (1 × 20 mL 1 M aqueous sodium hydroxide, 1 × 20 mL saturated brine); any solids which formed were disposed of with the aqueous layer. The ethereal solutions were dried ($MgSO_4$) and filtered to remove the drying agent; concentration on the rotary evaporator afforded the crude product, which could be purified as described in method 1.

Compound 3a. 1-Decanol. Ethyl decanoate (601 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; $Ti(O^iPr)_4$ (0.223 mL, 0.75 mmol) was added and the reaction was carried out at 65 °C. After stirring 24 h, the reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 to afford the crude product. Kugelrohr distillation (65 °C, 8×10^{-3} Torr) afforded the product as a clear colorless oil, 443 mg, 93%. The ^1H NMR spectrum was consistent with the published spectrum.[6b]

Compound 3m. 1-Adamantylmethanol. Methyl 1-adamantylformate (582 mg, 3.0 mmol) and PMHS (450 mg, 7.5

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[22] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, 3rd ed.; Plenum Press: New York, 1991; pp 656–658.

mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.26b mL, 0.75 mmol) was added, and the reaction was carried out at 65 °C. After stirring 24 h, the reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 and concentrated to afford the product as a white solid, 499 mg, 99%. Mp: 119–120 °C (lit. mp: 115–118 °C.)[23] The ^{1}H NMR spectrum was consistent with the published spectrum.[24]

Compound 3c. 10-Undecen-1-ol. Methyl 10-undecenoate (595 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.26b mL, 0.75 mmol) was added and the reaction was carried out at 70 °C. After stirring 23 h, the reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 to afford the crude product. Kugelrohr distillation (65 °C, 8 × 10^{-3} Torr) afforded the product as a clear colorless oil, 399 mg, 78%. The ^{1}H NMR spectrum was consistent with the published spectrum.[6b]

Compound 3c. 9-*cis*-Octadecen-1-ol. Methyl oleate (890 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; Ti(O$_i$Pr)$_4$ (0.890 mL, 3.0 mmol) was added, and the reaction was carried out at 65 °C. After stirring 2 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 to afford the crude product. Flash column chromatography (1.5:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 718 mg, 89%. The ^{1}H NMR spectrum was consistent with the published spectrum.[6b]

Compound 3l. 10-Undecyl-1-ol. Methyl 10-undecynoate (590 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.890 mL, 3.0 mmol) was added, and the reaction was carried out at 40 °C. After stirring 22 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 to afford the crude product. Flash column chromatography (2:1 hexand/ethyl acetate) afforded the product as a 93:7 mixture (by integration of the appropriate ^{1}H NMR signals) of the desired alkynyl alcohol and 10-undecen-1-ol. The product was a clear colorless oil, 317 mg, 63%. The ^{1}H NMR spectrum was consistent with the published spectrum.[6b]

Compound 3d. Chrysanthemumyl Alchol. Methyl chrysanthemumate (mixture of *cis* and *trans*, 590 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.890 mL, 3.0 mmol) was added and the reaction was carried out at 40 °C. After stirring 8 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 to afford the crude product. By GC and ^{1}H NMR the only products present were the alcohol (same *cis/trans* ratio as ester) and a trace of isopropoxy chrysanthemumate. Flash column chromatography (2.5:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 269 mg, 58%. The ^{1}H NMR spectrum was consistent with the published spectrum.[6b]

Compound 3e. 10,11-Epoxyundecan-1-ol. Methyl epoxy-10-undecenoate (110 mg, 0.5 mmol) and PMHS (66 mg, 1.1 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.150 mL, 0.5 mmol) was added, and the reaction was carried out at 65 °C. After stirring 2.5 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 to afford the crude product. Flash column chromatography (2:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 75 mg, 81%. The ^{1}H NMR spectrum was consistent with the published spectrum.[6b]

Compound 3f. *cis*-9,10-Epoxyoctadecan-1-ol. Methyl epoxyoleate (160 mg, 0.5 mmol) and PMHS (75 mg, 1.25 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.150 mL, 0.5 mmol) was added, and the reaction was carried out at 65 °C. After stirring 5 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 to afford the crude product. Flash column chromatography (2:1 hexane/ethyl acetate) afforded the product as a white solid, 121 mg, 85%. Mp: 55–56 °C (lit. mp: 52–53 °C.)[6b] The ^{1}H NMR spectrum was consistent with the published spectrum.[6b]

Compound 3g. 6-Bromohexan-1-ol. Ethyl 6-bromohexanoate (669 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.893 mL, 3.0 mmol) was added, and the reaction was carried out at room temperature. After stirring 23 h, the reaction mixture was hydrolyzed (12 h) and worked up according to method 1 to afford the crude product. Flash column chromatography (4:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 475 mg, 87%. The ^{1}H NMR spectrum was consistent with the published spectrum.[6b]

Compound 3h. 6-Iodohexan-6-ol. Ethyl 6-iodohexanoate (810 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.893 mL, 3.0 mmol) was added, and the reaction was carried out at room temperature. After stirring 23 h, the reaction mixture was hydrolyzed (12 h) and worked up according to method 1 to afford the crude product. Flash column chromatography (4:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 541 mg, 79%. The ^{1}H NMR spectrum was consistent with the published spectrum.[25]

Compound 3k. 4-Methoxybenzyl Alcohol. Methyl 4-methoxybenzoate (831 mg, 5.0 mmol) and PMHS (750 mg, 12.5 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.372 mL, 1.25 mmol) was added, and the reaction was carried out at 65 °C. After stirring 23 h, the reaction mixture was hydrolyzed (12 h, 4 M NaOH) and worked up according to method 1 to afford the crude product. Flash column chromatography (1:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 614 mg, 89%. The ^{1}H NMR spectrum was consistent with the published spectrum.[25]

Compound 3i. 2-Bromobenzyl Alcohol. Ethyl 2-bromobenzoate (590 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.890 mL, 3.0 mmol) was added, and the reaction was carried out at 65 °C. After stirring 1.25 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h) and worked up according to method 1 to afford the product as a white solid, 487 mg, 87%. Mp = 80–81 °C (lit.[23] mp = 79–82 °C). The ^{1}H NMR spectrum was consistent with the published spectrum.[25]

Compound 3j. 2-Fluorobenzyl Alcohol. Methyl 2-fluorobenzoate (500 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.890 mL, 3.0 mmol) was added, and the reaction was carried out at 65 °C. After stirring 2 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 to afford the crude product. Flash column chromatography (2:1 hexane/ethyl acetate) afforded the product as a clear colorless oil, 301 mg, 80%. The ^{1}H NMR spectrum was consistent with the published spectrum.[25]

Compound 3n. *tert*-Butyl 9-Hydroxynonanoate. *tert*-Butyl methyl 1,9-nonanedicarboxylate (260 mg, 1.0 mmol) and PMHS (180 mg, 3.0 mmol) were mixed according to method 1; Ti(O^{i}Pr)$_4$ (0.300 mL, 1.0 mmol) was added, and the reaction was carried out at 40 °C. After stirring 5.5 h, TLC showed complete disappearance of starting material. The reaction mixture was cooled to room temperature, hydrolyzed (12 h) and worked up according to method 1 to afford the crude product. Flash column chromatography (3:1 hexane/ethyl acetate) afforded the product as well as 8 mg of *tert*-butyl isopropyl 1,9-nonanedicarboxylate. The product was a clear colorless oil, 129 mg, 56%; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.63 (t, 2 H, J = 6.6 Hz), 2.20 (t, 2 H, J = 7.4 Hz), 1.58 (m, 5 H), 1.44 (s, 9 H), 1.32 (m, 8 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.3, 79.9, 62.9, 35.5, 32.7, 29.2, 28.9, 28.1, 25.6, 25.0; IR (neat) (cm^{-1}) 3363, 2977, 2931, 2856, 1732, 1457, 1419, 1392, 1367,

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(23) *Catalog/Handbook of Fine Chemicals;* Aldrich Chemical Company, Inc.: Milwaukee, WI, 1994.

(24) *The Aldrich Library of NMR Spectra*, 2nd ed.; Pochert, C. J., Ed.; Aldrich Chemical Company, Inc.: Milwaukee, WI, 1983.

(25) Buijs, W.; van Elburg, P.; van der Gen; A. *Synth. Commun.* **1983**, *13*, 387.

1256, 1156, 1107, 1056. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.81; H, 11.13.

Compound 3o. 2-(2-Thiophene-yl)ethan-1-ol. Methyl (2-thiophene-yl)acetate (589 mg, 3.0 mmol) and PMHS (450 mg, 7.5 mmol) were mixed according to method 1; $Ti(O^iPr)_4$ (0.223 mL, 0.75 mmol) was added, and the reaction was carried out at 65 °C. After stirring 23 h, the reaction mixture was cooled to room temperature, hydrolyzed (12 h), and worked up according to method 1 to afford the crude product. Flash column chromatography (4:1 hexane/ethyl acetate) afforded the product, as well as 38 mg of the allylic alcohol **4** (identified on the basis of it's ^1H and ^{13}C NMR spectra). The product 2-(2-thiophene-yl)ethan-1-ol was a clear colorless oil, 32 mg, 8%. The ^1H NMR spectrum was consistent with the published spectrum.[6b]

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