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Communications

An Air-Stable Catalyst System for the Conversion of Esters to Alcohols

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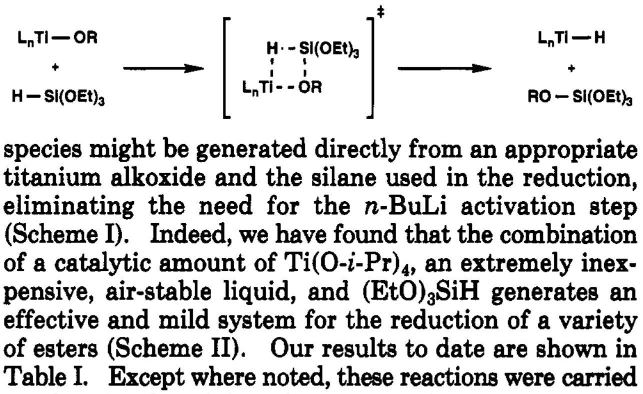
Summary: The combination of 5 mol % of $Ti(O\text{-}i\text{-}Pr)_4$ with 2.5–3.0 equiv of $(EtO)_3SiH$ cleanly hydrosilylates esters to silyl ethers at 40–55 °C, which can be converted to the corresponding primary alcohols via aqueous alkaline hydrolysis in excellent overall yield. The reaction can be carried out in the air, without solvent, and displays a high level of functional group compatibility.

We recently reported the conversion of esters to alcohols[2a] using a novel titanocene-based catalyst system in which a silane served as the stoichiometric reductant.[3] The active catalyst system was generated by the addition of 2 equiv of *n*-BuLi to Cp_2TiCl_2 under an inert atmosphere. We now report a second-generation catalyst system for ester hydrosilylation *which is self-activating, needs no added solvent, and can be generated and utilized in the air.* Moreover, this system displays an enhanced level of functional group compatibility.

A key step in the proposed catalytic cycle described in our initial report was the conversion of a titanium alkoxide into a titanium hydride by a silane via a σ-bond metathesis process.[4] We reasoned that an active titanium hydride species might be generated directly from an appropriate titanium alkoxide and the silane used in the reduction, eliminating the need for the *n*-BuLi activation step (Scheme I). Indeed, we have found that the combination of a catalytic amount of $Ti(O\text{-}i\text{-}Pr)_4$, an extremely inexpensive, air-stable liquid, and $(EtO)_3SiH$ generates an effective and mild system for the reduction of a variety of esters (Scheme II). Our results to date are shown in Table I. Except where noted, these reactions were carried out by *simply mixing the ester with 2.5–3.0 equiv of $(EtO)_3SiH$ in a test tube, adding 5 mol % of $Ti(O\text{-}i\text{-}Pr)_4$, and then heating the reaction mixture to 40–55 °C for 4–22 h.*[5a] Product isolation can be accomplished simply

Scheme I



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[1] National Science Foundation Predoctoral Fellow, 1989–92.

[2] (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Esters can be reduced using catalytic Cp_2TiCl_2 and stoichiometric *i*-PrMgBr: Sato, F.; Jinbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2175. (c) For other methods to convert esters to alcohols, see: LaRock, R. C. *Comprehensive Organic Transformations: A Guide To Functional Group Preparations*; VCH Publishers: New York, 1989 and references cited therein.

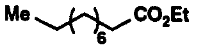
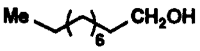
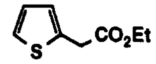
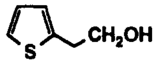
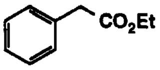
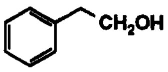
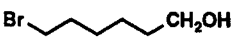
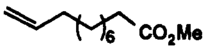
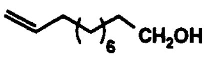
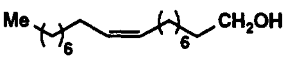
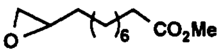
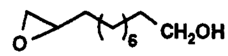
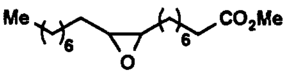
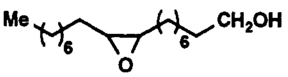
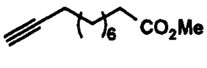
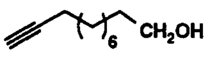
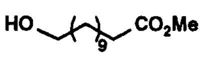
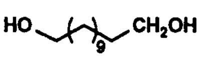
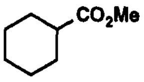
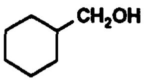
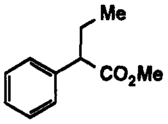
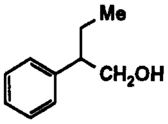
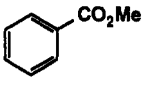
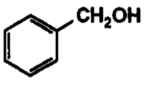
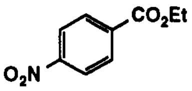
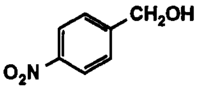
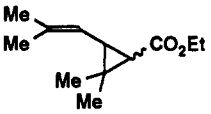
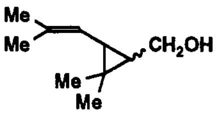
[3] For other methods to effect the hydrosilylation of esters, see: (a) Calas, R. *Pure Appl. Chem.* **1966**, *13*, 61 and references cited therein. (b) Corriu, R. J. P.; Perz, R.; Reyé, C. *Tetrahedron* **1983**, *39*, 996. (c) For a recent review of the hydrosilylation reaction, see: Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1989.

[4] (a) Woo, H.-G.; Tilley, T. D. *J. Am. Chem. Soc.* **1989**, *111*, 3757. Woo, H.-G.; Tilley, T. D. *J. Am. Chem. Soc.* **1989**, *111*, 8043. (b) We note that Nicolaou has recently described the reduction of an oxime *O*-benzyl ether to a hydroxylamine *O*-benzyl ether using an excess of both $Ti(O\text{-}i\text{-}Pr)_4$ and Ph_2SiH_2: Nicolaou, K. C.; Screiner, E. P.; Stahl, W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 585.

[5] (a) **Typical Procedure.** Triethoxysilane (1.7 mL, 9 mmol) and methyl 10-undecenoate (594 mg, 3 mmol) were added to a test tube. Titanium(IV) isopropoxide (45 μL, 0.15 mmol) was then added, and the test tube was fitted with a drying tube packed with DrieRite to exclude excess moisture. The vessel was then heated in an oil bath at 50 °C. After being stirred for 16 h, the reaction mixture was washed into a 100-mL round-bottom flask with 10 mL of THF. Then, 20 mL of 1 N NaOH was added slowly with stirring. **NOTE:** Vigorous bubbling was observed. After 4 h, the mixture was added to 50 mL each of ether and water. After shaking, the layers were separated, and the aqueous layer was extracted with an additional 50 mL of ether. The combined organic extracts were then washed with two 50-mL portions of 1 N HCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 443 mg (87% yield) of 10-undecen-1-ol as a clear oil. The product was >95% pure as determined by GC and ^1H NMR analysis. **CAUTION!!!** Suitable eye protection is required for handling triethoxysilane (vapors can cause blindness); cf. *Silicon Compounds: Register and Review*; Anderson, R., Larson, G. L., Smith, C., Eds.; Hüls America, Inc.; Piscataway, NJ, 1991; pp 5, 190. In the absence of substrate and under an inert atmosphere, $(EtO)_3SiH$ is disproportionated by $Ti(O\text{-}i\text{-}Pr)_4$ to form SiH_4, a pyrophoric gas. For a discussion of another titanium-catalyzed disproportionation of $(EtO)_3SiH$, see: Xin, S.; Aikten, C.; Harrod, J. F.; Mu, Y.; Samuel, E. *Can. J. Chem.* **1990**, *68*, 471. (b) An extra equivalent of $(EtO)_3SiH$ is required.

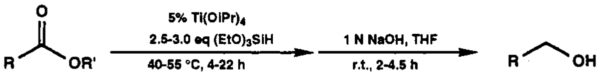
0022-3263/92/1957-3751$03.00/0

Table I. $Ti(O\text{-}i\text{-}Pr)_4$ Catalyzed Reduction of Esters

entry	ester	time (h)	alcohol	yield[a] (%)
1		10		95
2		4		93[b]
3		4		89
4		6		88
5		16		87
6		5		92
7		21		83[c]
8		18		87[c]
9		18		70[c]
10		7		88[d]
11		16		88
12		14		87
13		10		75[e,f]
14		20		75[c,f]
15		22		80[c,f]

[a] All products were >95% pure and were characterized by GLC, ^1H NMR, and IR spectroscopy. They are all known compounds. [b] 50 mmol scale. [c] Purified by flash chromatography or recrystallization. [d] Using 3.75 equiv of $HSi(OEt)_3$. [e] 37 mmol scale, distilled yield. [f] 1.3 equiv of $HSi(OEt)_3$ and 1.4 equiv of H_3SiPh are required for complete conversion.

Scheme II



by adding the reaction mixture to a small amount of THF and 1 N NaOH and stirring (2–4.5 h). Conventional workup generally provides the alcohol in >95% purity; the bulk of the silicon- and titanium-containing species go into the aqueous layer or remain at the boundary between the aqueous and organic layers and are easily separated from the product. In the case of epoxides, flash chromatography or recrystallization may be employed to remove traces (less than 5%) of ring-opened products.[6]

The tolerance to other functional groups exhibited by this catalyst system is noteworthy. Halides, olefins, epoxides, alcohols,[5b] and an alkyne (about 5% triple-bond reduction is observed) all survive the reduction protocol. In particular, for entries 4, 5, and 7, the yields are 10–25% better than realized with our previous catalyst system.[2a]

While the simple protocol described above works in many instances, the reduction of aromatic and cyclopropyl

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[6] The reaction with methyl 10,11-epoxyundecanoate gave 1% isolated yield of a product whose ^1H NMR spectrum is consistent with its formulation as 1,2,11-undecanetriol.

esters stops short of completion. Since methyl cyclohexanecarboxylate (entry 11) and methyl 2-phenylbutyrate (entry 12) react smoothly under the given conditions, this effect cannot be adequately explained by steric factors. However, for these substrates, complete conversion is achieved by the addition of $PhSiH_3$, presumably due to its smaller size and more reactive Si–H bonds.[7] Several other limitations of this method have been discovered to date. For instance, α,β-unsaturated esters react to give mixtures of 1,2 reduction and fully saturated products. In addition, α-bromo esters and ω-cyano esters have not been successfully converted to the desired products.

We are at present unsure as to the nature of the active catalyst in this system. One possibility is that this is a simple Lewis acid-catalyzed hydrosilylation.[3a] However, we have determined that the conversion of ethyl decanoate to decanol is unaffected, in terms of either rate of formation or yield of product, by the addition of 20 equiv (relative to catalyst) of Lewis bases such as pyridine, THF, or PMe_3. A radical mechanism is unlikely since no rearrangement products are found in the reduction of a vinylcyclopropyl ester (Table I, entry 15).[8] An alternate scenario is that the active species in this system is an anionic pentavalent silicon hydride.[9] These species are also known to be electron donors toward organic halides, forming reductive coupling products. However, under our described conditions, ethyl 6-bromohexanoate is converted cleanly to the alcohol with no traces of reductive dimerization (Table I, entry 4). Also, in a control experiment where 1 equiv each of $Ti(O\text{-}i\text{-}Pr)_4$, $(EtO)_3SiH$, and benzyl bromide were combined, and the mixture was heated at 45 °C, no bibenzyl was detected after 2 days. Finally, our working hypothesis involves the initial formation of a titanium hydride species, as we believe occurs in the Cp_2TiCl_2/2 n-BuLi system. Yet we have found that carrying out the reduction procedure in the presence of 20 equiv of MeI has no effect on the rate or yield of the reaction.[10] A detailed mechanistic study of this intriguing new process is clearly necessary.

In summary, we have developed a new, air-stable catalyst system for the conversion of esters into primary alcohols. The experimental simplicity and mild reaction conditions of this procedure should make it useful to synthetic chemists. We are currently investigating the mechanism of this novel catalyst system and its action on other carbonyl groups and related functionality.

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Supplementary Material Available: Detailed experimental procedures for the preparation of and spectroscopic characterization of the products given in Table I (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(8) Kochi, J.; Krusic, P. J.; Eaton, D. R. *J. Am. Chem. Soc.* **1969**, *91*, 1877.

(9) Corriu, J. P.; Guérin, C.; Henner, B.; Wang, Q. *Organometallics* **1991**, *10*, 2297, 3200, and 3574.

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Why Are Isoxazoles Unreactive in Diels–Alder Reactions? An ab Initio Computational Study

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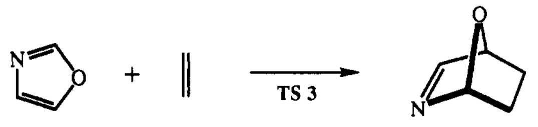
Summary: Ab initio calculations show why isoxazole Diels–Alder reactions have high activation energies and are generally not observed.

One of the most intriguing unsolved problems in heterocyclic chemistry is the different ability of oxazole and isoxazole rings to participate in Diels–Alder reactions. Diels–Alder reactions of oxazoles, 1, have been widely exploited because of their synthetic versatility. Reactions with alkenes lead to pyridines, including Vitamin B_6, pyridoxine analogs, and condensed pyridines such as ellipticine,[1] while acetylenic dienophiles give furans.[1,2] Oxazoles also react readily with a variety of heterodienophiles.[3] Amazingly, however, there are no reports on Diels–Alder reactions of simple isoxazoles, 2.[4]



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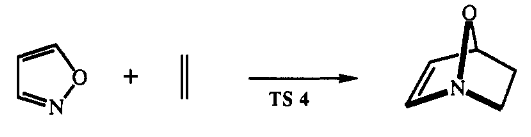

2 6

We report here the results of a theoretical study of the Diels–Alder reactions of both oxazole and isoxazole, using ab initio molecular orbital theory. The geometries of the reactants, oxazole, 1, and isoxazole, 2, the transition structures for the parent reactions of 1 and 2 with ethylene,

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[‡] Princeton University.

[§] University of California, Los Angeles.

(1) For a recent review, see: Maryanoff, B. E. In Oxazoles; Turchi, I. J., Ed.; The Chemistry of Heterocyclic Compounds series; Weissberger, A., Taylor, E. C., Eds.; Wiley-Interscience: New York, 1986; Vol. 45, p 963.

(2) (a) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *Tetrahedron Lett.* **1989**, *30*, 7173 and references cited therein. (b) Whitney, S. C.; Rickborn, B. *J. Org. Chem.* **1988**, *53*, 5595.

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