

Alkoxy-Directed Radical Reductions of Ketones Using Trichlorosilane

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The reduction of ketones with hydride reagents is a well-established two-electron transformation that has been used extensively in organic synthesis.¹ The related free-radical reduction of ketones remains a potentially valuable one-electron alternative to this reaction. Reagents used in this capacity include ⁿBu₃SnH,² SmI₂,³ and silanes;⁴ however, this reaction is not nearly as well-developed as hydride reductions. If a silane bears substituents that can react with an alcohol, an α-hydroxy ketone can be an excellent stereochemical scaffold for a free-radical ketone reduction. In this scenario, the siloxy function behaves as a steric bias for a stereoselective hydrogen atom abstraction in a one-electron reduction. Although α-alkoxy-directed reactions of ketones are now well-established with nucleophiles and hydride reagents, the related free-radical reductions have not been examined.⁵

In this paper, the reduction of simple ketones with silanes led to a new highly diastereoselective reduction of α-hydroxy ketones to *anti*-1,2-diols under neutral free radical conditions. Using the inexpensive and convenient reagent trichlorosilane, the alkoxy-directed reduction of **1** gave diastereomeric ratios up to 134:1, favoring the *anti*-1,2-diol **2**, as shown in Scheme 1.⁶ When other one-electron reagents were examined, much lower diastereomeric ratios or none of the desired products were obtained. Moreover, trichlorosilane was more stereoselective than established alcohol-directed two-electron hydride reagents such as sodium borohydride and lithium aluminum hydride, which favored **2** in lower ratios ranging from 5:1 to 20:1. A mechanistic test confirmed the free-radical nature of the reaction, which likely involves a preliminary reaction with the hydroxyl function prior to ketone reduction.

Trichlorosilane also has two additional useful benefits for the organic chemist. First, silanes in general are an appealing alternative to tin analogues, due to the environmentally and physiologically less toxic qualities of the reagents.⁷ The reagent is volatile and can be pumped away under reduced pressure; alternatively, after workup with dilute aqueous saturated NaHCO₃, trichlorosilane and its byproducts are converted to much less-harmful hydroxysilanes. Second, Cl₃SiH is a commercial and abundant byproduct of the industrial Rochow process.⁸ It is also considerably less

Scheme 1

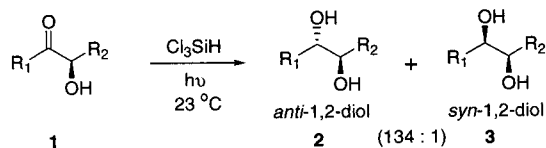
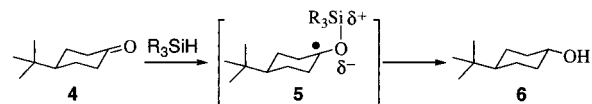


Table 1. Silane Radical Reductions of 4-*t*-Butylcyclohexanone



reducing agent	time (h)	conds	yield (%)
(Me ₃ Si) ₃ SiH	10.5	<i>hν</i>	66
Cl ₃ SiH	16	<i>hν</i>	82
Ph ₃ SiH	9	110 °C, toluene	50
Et ₃ SiH	36	<i>hν</i>	13

expensive than both tributyltin hydride and tris(trimethylsilyl)silane (TTMSS).⁹

The reduction of a simple ketone, 4-*tert*-butylcyclohexanone (**4**), was first examined using several silanes as shown in Table 1. The attachment of trimethylsilyl, halogen, and phenyl functions to the silane have been previously used to stabilize the silicon free radical that subsequently reacts with the ketone presumably via O-silyl ketyl **5**.^{4,6,10} Although the equatorial hydroxyl predominated in the *trans*-4-*tert*-butylcyclohexanol (**6**) product, a small amount of the *cis* isomer (5–20%) formed in each reaction and was included in the yield for each experiment.^{4c}

The most interesting conclusion from these data was that the yield for trichlorosilane was higher than any other silane tested. Except for triphenylsilane, the silane reducing agents were used as solvents. Most silanes except TTMSS reacted very sluggishly, and triphenylsilane did not react at all under photolytic conditions and required forcing thermal conditions at 110 °C.

The reduction of α-hydroxy ketone **7a**, R = cyclohexyl, was studied next, comparing the diastereoselectivity of several silanes and ⁿBu₃SnH as free-radical reductants.¹¹ This is shown in Table 2. For comparison purposes, the diastereoselectivities for the common two-electron hydride reductants, NaBH₄ and LiAlH₄, were also obtained. Adequate separation of the diastereomeric product diols could not be achieved by capillary GC, so conversion to the acetonides was adapted, as shown in Scheme 2. This was achieved by reacting the diastereomeric diol mixture with 2,2-dimethoxypropane, acetone, and a catalytic amount of *p*-TsOH. The *syn*-**8** and *anti*-**8** diols produced the *anti*-**9** and *syn*-**9** ketals, respectively, by rotation about the carbon–carbon bond between the hydroxyl functions to accommodate the acetonide ring.

It is noteworthy that only two of the silane reagents gave diol products. Trichlorosilane gave an excellent (93%) yield of *syn*-**9a** with a ratio of 63:1. A GC trace of the crude reaction mixture shows *syn*-**9a** is 97% pure. The hydride

(9) The 1998–99 Aldrich Chemical Co. catalog lists 500 g of Cl₃SiH for \$41.60, 25 g of TTMSS for \$143.50, and 50 g of ⁿBu₃SnH for \$71.70.

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(11) Ketone **7a** was prepared by the reaction of cyclohexanecarboxaldehyde with the Grignard reagent of α-bromostyrene in THF at 0 °C. Ozonolysis of the product in dichloromethane at –78 °C, followed by dimethyl sulfide quench, gave **7a** in 85% yield for the two-step synthetic sequence.

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(5) For a review, see: Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994; p 403.

(6) For earlier work with Cl₃SiH, see: Kraus, G. A.; Liras, S. *Tetrahedron Lett.* **1990**, 31, 5265–5268.

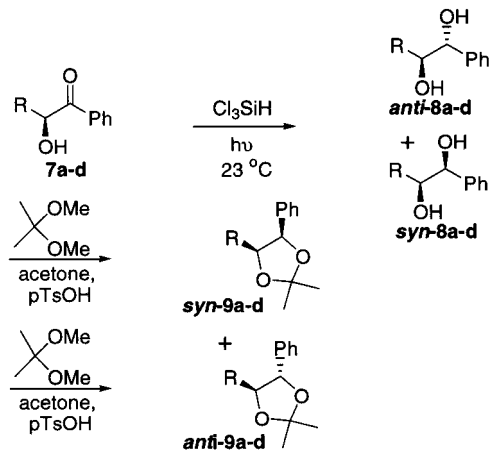
(7) Crich, D.; Sun S. *J. Org. Chem.* **1996**, 61, 7200–7201 and references therein.

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Table 2. Diastereoselective Silane Radical Reductions of α -Hydroxy Ketone **7a**

reducing agent	equiv	time (h)	condns	<i>syn</i> - 9 / <i>anti</i> - 9	yield (%)
(Me ₃ Si) ₃ SiH	1.2	16	110 °C	1:1	47 ^c
Cl ₃ SiH	4.0 ^d	16	<i>hν</i>	63:1	93 ^{a,b}
Ph ₃ SiH	2.0	72	110 °C, toluene		<i>e</i>
Et ₃ SiH	4.0 ^d	16	110 °C		<i>e</i>
NaBH ₄	1.1	1.5	EtOH	20:1	
LiAlH ₄	1.1	2.0	Et ₂ O	17:1	
Bu ₃ SnH	2.4 ^d	40	110 °C	3:1	72 ^c

^a Two step yield. ^b Crude GC shows product is 97% pure. ^c Yield reflects intermediate diol isolated and purified. ^d Used as solvent. ^e Only diketone observed.

Scheme 2**Table 3. Diastereoselective Reductions of α -Hydroxyketones **7a–d** with C₃SiH**

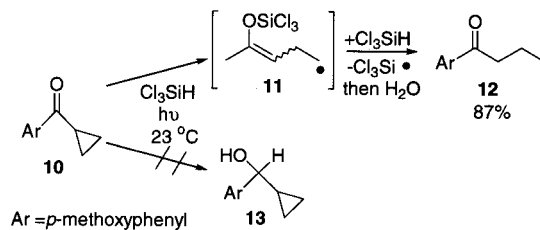
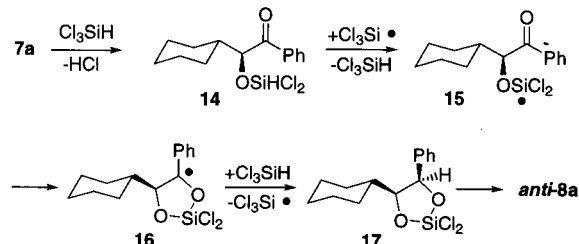
substrate	Cl ₃ SiH (equiv)	time (h)	<i>syn</i> - 9 / <i>anti</i> - 9 ^b	yield ^a (%)
7a , R = cyclohexyl	4	16	63:1 (20:1)	93
7b , R = phenyl	2	5 d	38:1	80
7c , R = 1-naphthyl	2	48	134:1 (7:1)	64
7d , R = CH ₂ CH(CH ₃) ₂	2	4	21:1 (5:1)	75

^a Two-step yield. ^b Ratios in parentheses are for conversion with NaBH₄.

reagents, NaBH₄ and LiAlH₄, gave reasonable ratios of 20:1 and 17:1, respectively, likely because of chelation-controlled delivery of the hydride via the alcohol.¹² Tributyltin hydride and TTMSS produced low distereoselectivities of 3:1 and 1:1, respectively. Triphenyl- and triethylsilane did not produce any diol products by crude ¹H NMR, and interestingly, we observed (<25%) the diketone of **7a** in each case, along with numerous byproducts.

Several other α -hydroxy ketones **7a–d** were cleanly reduced to their corresponding vicinal diols **8a–d** by employing 2–4 equiv of Cl₃SiH, as shown in Table 3. In each case, the crude mixture of diol products was converted to the respective acetonide derivatives *syn*-**9** and *anti*-**9**. The overall ratios in these examples were excellent, and in the case of **9c**, R = 1-naphthyl, the ratio was found to be as high as 134:1, demonstrating that the *syn*-**9c** acetonide derivative is highly favored via the *erythro*-diol (*anti*-**8c**). In three examples, we compared the lower chelation-controlled ratio from NaBH₄. This observation was useful in our mechanistic interpretation below.

(12) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653–2656.

Scheme 3**Scheme 4**

An experiment shown in Scheme 3 was next adopted to determine whether trichlorosilane is reacting as a free-radical reducing agent (**10** → **11** → **12**) or as a hydride donor (**10** → **13**) toward a ketone under the same conditions of our reactions. The reaction of cyclopropyl-4-methoxyphenyl ketone (**10**) with trichlorosilane should distinguish between the one- and two-electron reduction by the production of **12** or **13**, respectively. Under photochemical conditions, ketone **12** was formed in 87% yield, with no trace of alcohol **13** observed by GC.¹³

We propose the mechanism shown in Scheme 4 to account for the high diastereoselectivity seen in the radical reductions of **7a–d**. Although a chelation-controlled mechanism is possible, the higher diastereoselectivities are more consistent with the covalently bonded α -silyl ether ketone intermediate **14**.^{14,15} Due to the remaining chlorine substituents, the hydrogen atom abstraction forms an electrophilic silyl radical **15**. This facilitates the formation of the cyclic bis-silyl ether **16** by silyl radical attack at the electron-rich oxygen of the ketone. The five-membered ring incorporating the *O*-silyl ketyl radical provides a steric bias for stereoselective H-atom abstraction to produce **17**. Workup gave the *anti*-**8a** diol and subsequent acetonide formation leads to the *syn*-**9a** isopropylidene derivative.

In summary, a method to reduce α -hydroxy ketones to 1,2-diols using trichlorosilane was investigated. High diastereoselectivities of 134:1 favor the *anti*-1,2-diol via a mechanism that appears to first involve the reaction of trichlorosilane with the α -hydroxyl, followed by ketyl formation with the adjacent ketone. This reduction provides a stereoselective, mild, one-electron alternative to the established two-electron methods that use hydride reagents.

Acknowledgment. We gratefully acknowledge support by the National Science Foundation (Grant CHE-9708139) for this work.

Supporting Information Available: A general procedure and spectral data for compounds **7–9**.

JO981763W

(13) For a similar mechanistic analysis using TTMSS, see ref 4c.
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