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Diisopropoxytitanium(III) Tetrahydroborate: A Highly Useful Reagent for the Remarkably Selective 1,2-Reduction of α,β-Unsaturated Carbonyl Compounds

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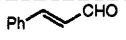
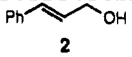
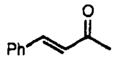
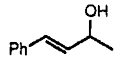
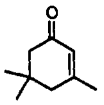
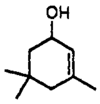
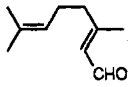
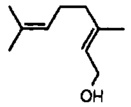
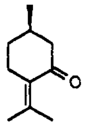
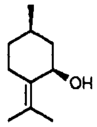
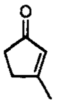
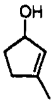
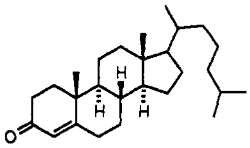
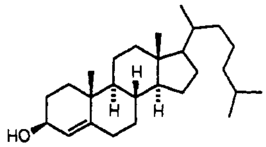
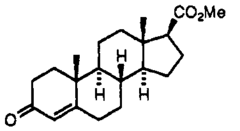
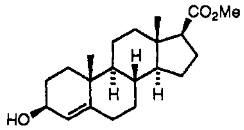
Diisopropoxytitanium(III) tetrahydroborate formed by the reaction of diisopropoxytitanium dichloride and benzyltriethylammonium borohydride (1:2) reacts with a variety of α,β-unsaturated carbonyl compounds in dichloromethane (−20 °C) very readily to yield exclusively the corresponding allylic alcohols in excellent yields.

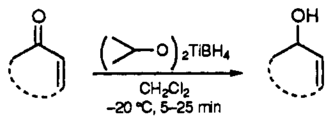
Reduction of an α,β-unsaturated carbonyl compound by metal hydride can follow two pathways: addition to the carbonyl group (1,2-addition) to give the allylic alcohol or addition to the conjugated double bond (1,4-addition) followed by 1,2-addition to the carbonyl group to give the saturated alcohol. In spite of substantial evidence, the tendency for sodium borohydride to reduce enones in a conjugate sense is often ignored but the need for reduction to the corresponding allylic alcohols has led to the development of several new specific reagents.[1,2] The most widely accepted of these involves sodium borohydride in the presence of cerium chloride which has been optimized to give excellent selectivity under mild conditions.[2] The success of this reagent has been explained by considering the active species as an alkoxy borohydride in combination with a hard cerium cation which coordinates to the carbonyl to enhance 1,2-selectivity. There is a report on the moderately selective reduction of α,β-unsaturated carbonyl compounds catalyzed by zirconocene and hafnocene complexes but interestingly titanocene complexes were found to be ineffective.[3]

Recently, we reported an unusual anti-Markovnikov hydration of alkenes with titanium(III) tetrahydroborates.[4] In order to explore the scope and utility of this reagent, we studied the reduction of α,β-unsaturated carbonyl compounds with this reagent system and found that this transition metal borohydride produces the corresponding allylic alcohols in about 90% selectivity.

Table I

entry	substrate	time (min)	product	yield (%)
1	 1	5	 2	90
2	 3	5	 4	97
3	 5	25	 6	94
4	 7	5	 8	95
5	 9	20	 10	75
6	 11	15	 12	81
7	 13	25	 14	89
8	 15	30	 16	82

We now report that diisopropoxytitanium(III) tetrahydroborate derived from diisopropoxytitanium dichloride[5] and benzyl triethylammonium borohydride[6] (1:2) effects a facile and smooth reduction of α,β-unsaturated carbonyl compounds in dichloromethane (−20 °C, 5–25 min) to produce exclusively the corresponding allylic alcohols (selectivity >99%) in excellent yields. The results of this



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remarkably selective reduction are summarized in Table I. Citral (**7**) undergoes selective reduction readily to give the allylic alcohol **8** in almost quantitative yield without affecting the isolated carbon–carbon double bond even though a similar titanium(III) tetrahydroborate has been shown earlier to effect hydration of the double bond.[4] (+)-Pulegone (**9**) under the same conditions yields only *cis*-pulegol (**10**). Cyclopentenone is intrinsically more prone to conjugate reduction than cyclohexenone and is thus a good substrate on which to test new 1,2-selective reagents.[7] Accordingly, when 3-methyl-2-cyclopentenone (**11**) is treated with diisopropoxytitanium borohydride, the corresponding allylic alcohol **12** is formed exclusively in high yield, attesting to the efficacy of this methodology.

It is interesting to note that in the reduction of steroidal enones **13** and **15** that only the equatorial allylic alcohols **14** and **16**, respectively, are obtained in very good yields. Ahn[8] has suggested that the stereoselectivity of the reduction is related to the hardness of the hydride reagent; the harder the reagent, the more favored the axial attack of cyclohexenones. The highly selective 1,2-reduction induced by diisopropoxytitanium borohydride reported herein confirms this hypothesis.

Since the reagent system is very easy to prepare and since it yields exclusively the allylic alcohols from α,β-unsaturated carbonyl compounds in excellent yields under mild conditions, this novel reduction methodology should find widespread use in organic synthesis.

Experimental Section

General Remarks. ^{1}H NMR spectra were recorded at 90 MHz in $CDCl_3$. TLC were performed on 0.25-mm E. Merck precoated silica plates (60F-254). All the products were purified by flash column chromatography on silica gel. The melting points reported are uncorrected. All starting α,β-unsaturated carbonyl compounds were commercially available and used without further purification. A stock solution of diisopropoxytitanium dichloride in dry CH_2Cl_2 (11.8% w/v) was used.[5]

Representative Procedure. Reduction of benzylideneacetone (**3**). To a solution of diisopropoxytitanium dichloride (2 mL, 1 mmol) was slowly added benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dry CH_2Cl_2 (4 mL) under N_2 at −20 °C, and the reaction mixture was stirred for 30 min. The enone **3** (0.146 g, 1 mmol) in dry CH_2Cl_2 (2 mL) was added into the reaction mixture and it was stirred for 5 min at −20 °C. A solution of 10% aqueous K_2CO_3 was added and stirred for an additional 15 min (25 °C). The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and it was washed with brine and dried (Na_2SO_4). Removal of solvent afforded a liquid which on flash chromatography [ethyl acetate–petroleum ether (1:19)] afforded the allylic alcohol **4**[9] as an oil (0.144 g, 97%): IR (thin film) ν 3358, 3028, 2968, 1140, 1059, 966, 942, 747, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3 (d, J = 6.4 Hz, 3H), 1.76 (br, s, exchangeable 1H), 4.48 (d of q J = 8 Hz, J = 6 Hz, 1H), 6.24 (dd, J = 6.4 and 14 Hz, 1H), 6.56 (d, J = 14 Hz), 7.2–7.4 (m, 5H); MS m/z 148 (M$^+$).

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Supplementary Material Available: Spectral data of compounds **2**, **6**, **8**, **10**, **12**, **14**, and **16** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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