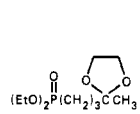
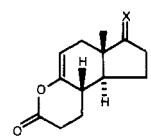
desired enone 7 in 70% yield. Only a 26% yield of 7 was obtained when 1 equiv of phosphonate 4 (and no acid) was used.[11]

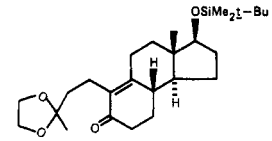


4



5 X = O

6 X = α-H, β-OSiMe$_2$t-Bu



7

It is hoped that this improved modification of the enol lactone to cyclic α,β-unsaturated ketone reaction will result in its wider use in synthesis.

Experimental Section[12]

Testosterone (3). A solution of 0.43 mL (4.0 mmol) of dimethyl methylphosphonate in 60 mL of THF at −78 °C was treated dropwise with 2.6 mL (4.08 mmol) of 1.57 M *n*-butyllithium in hexane. The resulting solution was stirred for 55 min at −78 °C and then treated dropwise with a solution of 659 mg (1.98 mmol) of enol lactone 1[2] in 8 mL of THF. The resulting gray suspension was stirred for 30 min at −78 °C, allowed to warm over 2.5 h to −20 °C, and then treated dropwise with 0.11 mL (1.92 mmol) of glacial acetic acid. The resulting solution was heated at 55 °C for 3 h, cooled to 0 °C, neutralized with 1 M aqueous hydrochloric acid, partitioned between ethyl acetate and brine, and dried ($MgSO_4$). The solvents were concentrated in vacuo to give 0.8 g of a yellow oil (TLC indicated about 1:1 testosterone to testosterone acetate) which was dissolved in 80 mL of methanol and 20 mL of water. The resulting solution was treated with 5.0 g of anhydrous potassium carbonate, stirred for 18 h at ambient temperature, treated with 10 mL of 1 M aqueous hydrochloric acid, and partitioned between brine and ethyl acetate. The organic extracts were dried (Na_2SO_4), and the solvents were removed under reduced pressure to give 570 mg (100%) of **3** as an off-white solid. Recrystallization of **3** from hot ethyl acetate and hexane gave 487 mg (85%) of pure testosterone (**3**) as a white solid: mp 153–154 °C (mixed melting point with authentic testosterone 153–154 °C); R_f 0.22 in 50% ethyl acetate in hexane (identical with authentic testosterone); NMR δ 0.80 (s, 3 H), 0.85–2.7 (m including 3 H s at δ 1.21, 23 H), 3.5–3.9 (m, 1 H), 5.78 (s, 1 H); ^{13}C NMR δ 11.07, 17.45, 20.71, 23.38, 30.46, 31.62, 32.83, 33.96, 35.77, 36.51, 38.70, 42.86, 50.57, 54.00, 81.55, 123.87, 171.12, 199.2; IR (mull) 3530, 3385, 1665, 1655, 1645, 1610, 1465, 1455, 1445, 1380, 1235, 1065, 1055, 870 cm^{-1}; mass spectrum, calcd for $C_{22}H_{36}O_2Si$ (M^+ for the trimethylsilyl derivative) *m/e* 360.2484, found *m/e* 360.2490. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.11; H, 9.91.

[3a*S*-(3aα,9aα,9bβ)]-3β-((*tert*-Butyldimethylsilyl)oxy)-3aβ-methyl-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1,2,3,3a,4,5,8,9,9a,9b-decahydro-7*H*-benz[*e*]inden-7-one (7). A solution of 385 mg (1.45 mmol) of diethyl (4-(cycloethylenedioxy)pentyl)phosphonate (**4**)[8] in 22 mL of THF at −78 °C was treated with 0.94 mL (1.49 mmol) of 1.58 M *n*-butyllithium in hexane, stirred 1 h at −78 °C, treated dropwise with 242 mg (0.72 mmol) of enol lactone 6[9] in 3 mL of THF, stirred for 1 h at −78 °C, warmed to −25 °C over 2 h, treated with 0.04 mL (0.70 mmol) of glacial acetic acid, heated at 60 °C for 6 h, cooled to 0 °C, neutralized with aqueous hydrochloric acid, and partitioned between brine and ethyl acetate. The organic extracts were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was chromatographed on silica gel eluted with 20% ethyl acetate in hexane to give 227 mg (70%) of enone **7** as a colorless oil: R_f 0.25 in 20% ethyl acetate in hexane; NMR δ 0.03 (s, 6 H), 0.9 (s, 12 H), 1.0–3.1 (m including 3 H s at δ 1.39, 21 H), 3.4–3.8 (m, 1 H), 3.98 (s, 4 H); ^{13}C NMR δ −3.25, −2.89, 10.63, 18.05, 20.13, 23.51, 23.60, 25.81, 26.62, 26.83, 30.95, 36.55, 37.07, 38.11, 39.04, 42.85, 50.52, 64.60, 81.19, 109.82, 134.16, 159.14, 198,42; IR (film) 1675, 1615, 1465, 1380, 1365, 1280, 1255, 1215, 1140, 1105, 1065, 905, 890, 850, 845, 775 cm^{-1}; mass spectrum, calcd for $C_{26}H_{44}O_4Si$ *m/e* 448.3009, found *m/e* 448.3019. Anal. Calcd for $C_{26}H_{44}O_4Si$: C, 69.59; H, 9.88. Found: C, 69.88; H, 10.01.

Registry No. 1, 1458-92-0; 2, 1045-69-8; 3, 58-22-0; 4, 1213-29-2; 5, 96038-39-0; 6, 95935-95-8; 7, 95935-96-9; dimethyl methylphosphonate, 756-79-6; *tert*-butyldimethylsilyl chloride, 18162-48-6.

(11) Attempts to effect reaction using 1 equiv of phosphonate reagent and 2 equiv of base (e.g., lithium diisopropylamide) followed by treatment with 1 equiv of the enol lactone at low temperature, warming to about 0 °C, addition of 1 equiv of glacial acetic acid, and heating at 55 °C only gave low yields of the desired product. When 2 equiv of an expensive phosphonate reagent are used, it is usually simple to recover chromatographically the excess phosphonate since it is generally much more polar than any of the reaction products.

(12) All melting points are uncorrected. Combustion analysis, IR, and mass spectra were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co., with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (crystalline samples). Mass spectra were recorded at high resolution for derivatized (Me_3Si) or underivatized compounds at 70 eV. The ^1H NMR spectra of chloroform-*d* solutions were obtained on a Varian EM-390 spectrometer operating at 90 MHz. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. ^{13}C NMR spectra were obtained of chloroform-*d* solutions on a Varian CFT-20 spectrometer operating at 20 MHz. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. Brine refers to a saturated aqueous solution of NaCl. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reactions were done under an inert atmosphere. Thin-layer chromatography (TLC) was conducted with Analtech (Uniplates) precoated with silica gel (E. Merck, 70–230 mesh).

Hexacyanoferrate-Catalyzed Oxidation of Trimethoxybenzenes to Dimethoxy-*p*-benzoquinones with Hydrogen Peroxide

Masakatsu Matsumoto* and Hisako Kobayashi

Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

Yasushi Hotta*

Research & Development Center, Daikyo Oil Co., Ltd., Inaba-cho 9-16, Yokkaichi, Mie 510, Japan

Received November 6, 1984

Hydrogen peroxide generates OH radical by the catalysis of iron salts, and their combination [Fe(II)/H_2O_2] is typically known as Fenton's reagent, which can oxidize a wide variety of organic substrates including arenes.[1,2] The reaction with arenes, however, frequently leads to results too complex for use in organic synthesis. The main reason is the high reactivity of the primary products (hydroxylated arenes) which are more easily oxidized than the starting arenes. In addition, the character of the iron salts might significantly affect the reaction; in most cases known so far, the iron salts used were those which can complex with phenols. This trend probably causes oxidation of arenes by H_2O_2/Fe salts to be all the more complicated. We report here a successful oxidation of arenes by H_2O_2 in the presence of potassium hexacyanoferrate, which has little ability to complex with ligands other than CN ion.[3]

(1) For reviews, see: (a) Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125. (b) Sheldon, R. A., Kochi, J. K., Eds. Metal-catalyzed Oxidation of Organic Compounds; Academic Press: New York, 1981.

(2) Fe(III)/H_2O_2 system is also known as Ruff's reagent, which is especially effective for oxidation of sugars; for a review, see: "The Action of Hydrogen Peroxide on Carbohydrates and Related Compounds"; Moody, G. J. In "Advances in Carbohydrate Chemistry"; Wolfrom, M. L., Ed.; Academic Press: New York, 1964; Vol. 19, p 149.

(3) Ferryl ion (FeO^{2+}) and singlet oxygen were recently reported to participate in a $Fe^{II}ClO_4/H_2O_2$ system especially in nonaqueous medium: Sugimoto, H.; Sawyer, D. T. *J. Am. Chem. Soc.* **1984**, *106*, 4283. These species might, however, be scarcely generated in hexacyanoferrate system because all the six CN ligands are little exchangeable with others.

0022-3263/85/1950-1766$01.50/0

Table I. Iron-Catalyzed Oxidation of 1,2,3-Trimethoxybenzene (1) with Hydrogen Peroxide.[a]

run	catalyst	reactn time, h	conversn, %	selectivity 2 + 3, %	selectivity 2:3
1	none	120	74	20[b]	12:88
2	H_2SO_4	24	56	20[b]	
3	$Fe(SO_4)_3$	24	35	35	40:60
4	$FeSO_4$	24	39	39	48:52
5	$Fe(acac)_3$	20	33	38	31:69
6	$Fe(NO_3)_3$	24	38	30	35:65
7	$Fe(OAc)_2$	42	39	4	
8	$Fe(phen)_3Cl_2$	14	46	18	29:71
9	$Fe(phen)_2(CN)_2$	17	46	22	46:54
10	$Fe^{III}EDTA$	24	27	33	39:61
11	$K_4Fe(CN)_6$	24	69	52	70:30
12	$K_3Fe(CN)_6$	14	72	48	71:29
13	$K_3Fe(CN)_6$[c]	24	69	62	78:22
14	$K_3Fe(CN)_6$[d]	24	72	75	77:23

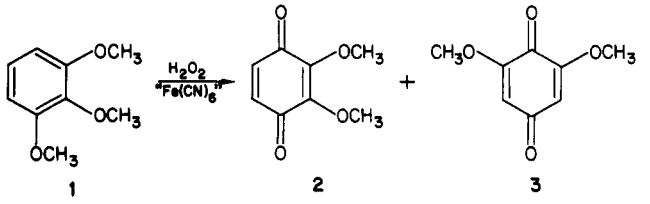
[a] Unless otherwise stated, the reaction was carried out under the following conditions: solvent, 5 mL of acetic acid, 5 mmol of 1; catalyst, 50 mg; H_2O_2, 30% aqueous solution (11 mmol); room temperature. [b] 2,3,4-Trimethoxyphenol (4) was produced as a byproduct. [c] 200 mg. [d] 800 mg.

Table II. Iron-Catalyzed Oxidation of 1,3,5-Trimethoxybenzene (6) to 2,6-Dimethoxy-*p*-benzoquinone (3) with Hydrogen Peroxide[a]

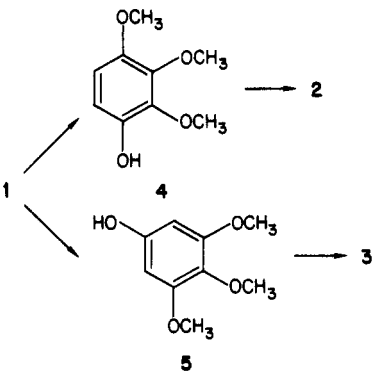
run	catalyst	solv	conversn, %	yield of 3, %
1	$FeSO_4 \cdot 7H_2O$	acetic acid	84	21
2	$Fe(phen)_3Cl_2$	acetic acid	78	26
3	$Fe(acac)_3$	acetic acid	77	12
4	$K_3Fe(CN)_6$	acetic acid	83	53
5	$K_3Fe(CN)_6$	acetonitrile	49	47
6	$K_3Fe(CN)_6$[b]	acetone/H_2O (10:1)	100	79

[a] Unless otherwise stated, the reaction was carried out under the following conditions: 6, 5 mmol; H_2O_2 (31%), 10 mmol; solvent, 5 mL; room temperature; 5–14 h. [b] Fifteen millimoles of H_2O_2 was used.

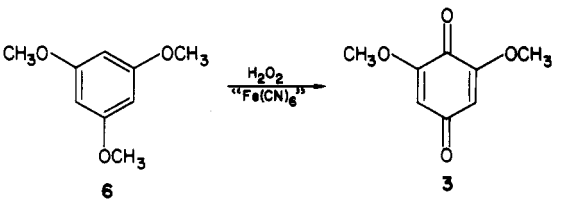
Scheme I



Scheme II



Scheme III



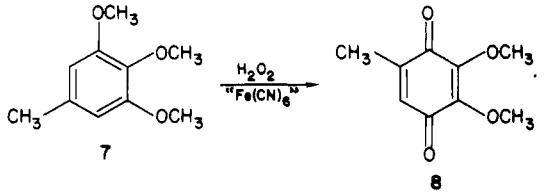
We chose trimethoxybenzenes as the substrate to be investigated, because these arenes were expected to be oxidized to trimethoxyphenols which, under the reaction conditions, would be further oxidized to dimethoxy-*p*-benzoquinones useful in organic synthesis.[4] First, we examined oxidation of 1,2,3-trimethoxybenzene (1) by H_2O_2 (30% aqueous solution) in the presence of various iron salts in acetic acid at room temperature. Table I shows the superiority of potassium hexacyanoferrate[5] to the other iron salts or complexes as the catalyst, though the major products were an isomeric mixture of dimethoxy-*p*-benzoquinones 2 and 3 irrespective of the species of iron used. The hexacyanoferrate system achieved higher conversion of the arene 1 and higher selectivity of the quinone (2 + 3) formation than the others. Another distinctive character was found in the product distribution 2:3; the hexacyanoferrate system favored the formation of 2, while the system with the other iron catalysts led mainly to the quinone 3 (Scheme I).

The oxidation yielding quinones 2 and 3 probably proceeds through the corresponding phenols 4 and 5, as expected (Scheme II). The formation of phenols 4 and 5 might be caused either by attack of OH radical generated in the Fe/H_2O_2 system or by attack of peracetic acid on arene 1. Of the two possibilities, peracetic acid was shown

(4) Among the *p*-benzoquinones with alkoxy substituents, 2,6-dimethoxy-*p*-benzoquinone is a simple naturally occurring material with biological activities: Otsuka, H.; Komiya, T.; Fujioka, S.; Goto, M.; Hiramatsu, Y.; Fujimura, H. *Yakugaku Zasshi* **1981**, *101*, 1108. 2,3-Dimethoxy-5-methyl- and 2,3-dimethoxy-*p*-benzoquinones are the key intermediate in the synthesis of Coenzyme Q and its analogues possessing antitumor activities; for a review, see: Yamada, S.; Takeshita, T.; Tanaka, J. *J. Synth. Org. Chem. Jpn.* **1982**, *40*, 268. See also: Porter, T. H.; Kishi, T.; Forkers, K. *Bioorg. Chem.* **1978**, *7*, 333.

(5) There are probably no significant differences between activity of hexacyanoferrate(II) and that of hexacyanoferrate(III) in catalytic decomposition of H_2O_2 under the present reaction conditions; for a review, see Mellor, J. W., "A Comprehensive Treatise on Inorganic and Theoretical Chemistry"; Longmans: London, 1960; Vol. 1, p 943.

Scheme IV



to scarcely participate in the present oxidation by the results of runs 1 and 2 in Table I[6] and by those in the oxidation of 1,3,5-trimethoxybenzene (vide infra). Anyhow, the first step (phenol formation) does not likely make a difference in product distribution (2:3) between the hexacyanoferrate system and other iron systems. The reaction paths from intermediary phenols **4** and **5** might be affected by the species of iron used since Fe(III) also acts as an oxidant.

Iron-catalyzed oxidation of 1,3,5-trimethoxybenzene (**6**) with H_2O_2 gave simply quinone **3** as shown in Table II, where the superiority of hexacyanoferrate over the other iron catalysts was further clearly demonstrated. The oxidation of **6** to **3** proceeded effectively not only in acetic acid but also in acetonitrile and in acetone, in which participation of peracid was not possible (Scheme III).

The hexacyanoferrate-catalyzed oxidation with H_2O_2 could be applied to the conversion of 3,4,5-trimethoxytoluene (**7**) to 2,3-dimethoxy-5-methyl-*p*-benzoquinone (**8**) in a moderate yield (Scheme IV). Last, it is worth pointing out that benzene itself was oxidized to phenol with H_2O_2 by the use of potassium hexacyanoferrate as a catalyst.[7]

Experimental Section

Infrared (IR) spectra were recorded on a Jasco Model A-202 spectrometer. Mass spectra were recorded at 70 eV on a Hitachi RMU-6M mass spectrometer. A Varian XL-100 spectrometer was used to obtain ^1H nuclear magnetic resonance (NMR) spectra. 3,4,5-Trimethoxytoluene (**7**) was prepared by the published procedure.[8] All other reagents were commercial products of the highest purity obtainable.

The experiments summarized in Table I were performed according to the following general procedures.

Oxidation of 1,2,3-Trimethoxybenzene (1). Aqueous hydrogen peroxide (30%, 1.3 g, 11 mmol) was added to a solution of 1,2,3-trimethoxybenzene (**1**, 840 mg, 5 mmol) and Fe(II) or Fe(III) salt (50–800 mg) in acetic acid (5 mL). The solution was stirred at room temperature until hydrogen peroxide was consumed (KI test). The reaction mixture was diluted with CH_2Cl_2 and was successively washed with water, saturated aqueous solution of $NaHCO_3$, and brine. The organic layer was separated and was dried over $MgSO_4$. After removal of the solvent, the residue was rinsed with methanol to separate crystalline 2,6-dimethoxy-*p*-benzoquinone (**3**). The methanol solution was concentrated, and the residue was chromatographed on silica gel (Wako C-200). Elution with hexane–CH_2Cl_2 (1:1) afforded unreacted 1,2,3-trimethoxybenzene (**1**) and then 2,3-dimethoxy-*p*-benzoquinone (**2**).

2,3-Dimethoxy-*p*-benzoquinone (**2**): red needles (from hexane); mp 66–67 °C (lit.[9] 66–67 °C); NMR ($CDCl_3$) δ 4.00 (s, 6 H), 6.57 (s, 2 H); IR (KBr) 1680, 1670, 1635, 1590, 1305, 1210, 1080 cm^{-1}; mass spectrum, *m/e*, (relative intensity) 168 (M^+, 73), 153 (31), 123 (100), 82 (44), 69 (72).

2,6-Dimethoxy-*p*-benzoquinone (**3**): yellow needles (from acetic acid); mp 240–242 °C (lit.[10] 240–242 °C); NMR ($CDCl_3$) δ 3.80 (s, 6 H), 5.82 (s, 2 H); IR (KBr) 1700, 1640, 1590, 1325, 1260, 1220, 1100 cm^{-1}; mass spectrum, *m/e* (relative intensity) 168 (M^+, 50), 138 (18), 125 (13), 97 (12), 80 (35), 69 (100).

Oxidation of 1,3,5-Trimethoxybenzene (6). To a solution of potassium hexacyanoferrate (100 mg) in water (500 mg) was added a solution of 1,3,5-trimethoxybenzene (840 mg, 5 mmol) in acetone (5 g) and hydrogen peroxide (30% aqueous solution, 15 mmol) successively. After being stirred for 15 h at room temperature, the solution was diluted with CH_2Cl_2, washed with water, and dried over $MgSO_4$. The solution was concentrated, and the residue was rinsed with methanol to separate yellow crystalline 2,6-dimethoxy-*p*-benzoquinone (**3**) (660 mg, 79% yield).

The other experiments (runs 1–5) in Table II were carried out similarly to above experiment (run 6).

Oxidation of 3,4,5-Trimethoxytoluene (7). A solution of 3,4,5-trimethoxytoluene (**7**, 377 mg, 2.07 mmol) in acetonitrile (2 g) and hydrogen peroxide (30% aqueous solution, 480 mg, 4.24 mmol) were added to a solution of potasium hexacyanoferrate(III) (20 mg) in water (200 mg). After being stirred for 42 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with water, and then dried over $MgSO_4$. The CH_2Cl_2 solution was concentrated, and the residue was chromatographed on silica gel (Wako C-200). Elution with CH_2Cl_2 gave unreacted **7** (170 mg) and 2,3-dimethoxy-5-methyl-*p*-benzoquinone (**8**, 89 mg).

2,3-Dimethoxy-5-methyl-*p*-benzoquinone (**8**): red needles (from hexane); mp 58–59 °C (lit.[8] 59 °C); NMR ($CDCl_3$) δ 2.05 (d, J = 1.5 Hz, 3 H), 4.02 (s, 3 H), 4.04 (s, 3 H), 6.46 (q, J = 1.5 Hz, 1 H); IR (KBr) 1680, 1660, 1640, 1605, 1285, 1240, 1130 cm^{-1}; mass spectrum, *m/e*, (relative intensity) 182 (M^+, 59), 167 (33), 137 (100), 83 (79), 69 (36), 68 (44).

Registry No. 1, 634-36-6; **2**, 3117-02-0; **3**, 530-55-2; **4**, 19676-64-3; **6**, 621-23-8; **7**, 6443-69-2; **8**, 605-94-7; H_2SO_4, 7664-93-9; $Fe_2(SO_4)_3$, 10028-22-5; $FeSO_4$, 7720-78-7; $Fe(acac)_3$, 14024-18-1; $Fe(NO_3)_3$, 10421-48-4; $Fe(OAc)_2$, 3094-87-9; $Fe(phen)_3Cl_2$, 14978-15-5; $Fe(phen)_2(CN)_2$, 14768-11-7; Fe(III)EDTA, 15275-07-7; $K_4Fe(CN)_6$, 13943-58-3; $K_3Fe(CN)_6$, 13746-66-2; benzene, 71-43-2; phenol, 108-95-2.

(6) Peracetic acid or perbenzoic acid has been reported to oxidize arene **1** to afford quinone **3** in a poor yield: (a) Friess, S. U.; Soloway, A. H.; Morse, B. K.; Ingersoll, W. C. *J. Am. Chem. Soc.* **1952**, *74*, 1305. (b) Davidge, H.; Davies, A. G.; Kenyon, J.; Mason, R. F. *J. Chem. Soc.* **1958**, 4569. However, reexamination of oxidation of **1** with a peracid gave different result from the previous works. When **1** was treated with an equimolar amount of *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature for 3 h, no quinone **3** but 2,3,4-trimethoxyphenol (**4**) was obtained in a 26% yield (selectivity 50%). On the other hand, quinone **3** was more stable than its isomer **2** under the oxidation conditions. These facts suggest that arene **1** is attacked more easily at 4-position (leading to **4**) than at 5-position (leading to **5**) by electrophilic oxidant such as peracid and OH radical.

(7) The reaction was carried out in two-phase system (benzene/H_2O–H_2O_2–$K_3Fe(CN)_6$), and the reaction mixture was qualitatively analyzed.

(8) Sugihara, H.; Watanabe, H.; Kawamatsu, Y.; Morimoto, H. *Justus Liebigs Ann. Chem.* **1972**, *763*, 109.

(9) Baker, W.; Smith, H. A. *J. Chem. Soc.*, **1931**, 2542.

(10) Baker, W. *J. Chem. Soc.* **1941**, 662.

Contrasting Directed-Aldol Reactivity of a Pair of Epimeric Trimethylsilyl Enol Ethers

Robert A. Galemmo, Jr. and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received August 2, 1984

As a general reaction type, directed aldol condensations constitute a most useful group of processes that have many obvious applications in organic synthesis.[1,2] The variant involving trimethylsilyl enol ethers and acetals or ketals under the influence of titanium tetrachloride holds particular advantage because of its high regio- and chemoselectivity and its operation under mild conditions (−78 °C).

(1) Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203.

(2) Heathcock, C. H. In "Asymmetric Synthesis, Volume 3, Part B", Morrison, J. D., Ed.; Academic Press: New York, 1984; Chapter 2.

0022-3263/85/1950-1768$01.50/0