140.9, 136.0, 128.9, 118.7, 115.2, 110.2, 39.9, 33.9, 22.3, 21.1; IR (CCl_4, cm^{-1}) 3613, 2937, 1615, 1513, 1438, 1257, 1171, 1104, 892, 828; MS (EI, 70 eV) m/z 214 (M^+, 100), 186 (68), 169 (13), 157 (39), 107 (11), 91 (11), 77 (9); HRMS for $C_{14}H_{14}O_2$ calcd 214.0994, found 214.0992.

***trans*-1-(4-Hydroxyphenyl)-2-isopropylcyclohexane (67).** A rapidly stirred solution of phenol **42** (80.8 mg, 0.248 mmol) and CH_2Cl_2 (25 mL) was cooled to -78 °C, and $EtAlCl_2$ (8.70 mL, 8.7 mmol, 1.0 M in hexane) was added dropwise at a rate to keep the temperature below -76 °C. After the solution was stirred for 10 min, aqueous workup ($NaHCO_3$, ether) afforded 45.5 mg of crude product (5:1 mixture of diastereomers, ^1H NMR). HPLC (8 μm silica gel column, i.d. 1 cm, 15% ethyl acetate/hexane, 0.5 mL/min, retention time 17.25 min) afforded 42.2 mg (78%) of **67** as a white solid, mp 102.0-109.0 °C. The minor diastereomer (^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (t, J = 6.7 Hz, 1 H, ArC*H*)) was not isolated. Major diastereomer (>20:1 mixture of diastereomers, ^1H NMR): purity by GC 99.53% (11.62 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.76 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.80 (b s, 1 H, OH), 2.32 (dt, J = 11.2, 3.0 Hz, 1 H, ArC*H*), 1.85-1.01 (m, 10 H, $ArCH(CH_2)_4CHCH(CH_3)_2$), 0.79 (d, J = 6.8 Hz, 3 H, CH_3CHCH_3), 0.67 (d, J = 6.8 Hz, 3 H, CH_3CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 139.1, 128.4, 115.1, 48.1, 47.4, 36.8, 27.5, 27.1, 26.7, 24.8, 21.4, 15.3; IR (CCl_4, cm^{-1}) 3613, 3480, 2929, 1614, 827, 798; MS (EI, 20 eV) m/z 218 (M^+, 82), 133 (100), 107 (84), 91 (5); HRMS for $C_{15}H_{22}O$ calcd 218.1671, found 218.1675.

Acknowledgment. We thank Dr. Richard Kondrat and Mr. Ronald New for obtaining the mass spectra and Mr. Christopher Tegley for expert technical assistance. This research was supported by a grant from the National Institutes of Health (GM 39354).

Supplementary Material Available: Full spectral data for 1-(4-hydroxyphenyl)-1-[[(methoxyethoxy)methyl]oxy]-3-[[(4-methylphenyl)sulfonyl]oxy]propane, methyl 7-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-7-[[(methoxyethoxy)methyl]oxy]-3-oxoheptanoate, 8-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-8-[[(methoxyethoxy)methyl]oxy]-2-methyloct-2-ene, 1-[4-[(*tert*-butyldimethylsilyl]oxy]phenyl]-4-furan-3-yl-1-[[(methoxyethoxy)-methyl]oxy]butane and copies of the ^1H and ^{13}C NMR for compounds lacking combustion data (40 pages). Ordering information is given on any current masthead page.

Homolytic Acylation of Protonated Pyridines and Pyrazines with α-Keto Acids: The Problem of Monoacylation

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The silver-catalyzed decarboxylation of α-keto acids by persulfate leads to acyl radicals, which can effect the selective homolytic acylation of pyridine and pyrazine derivatives. Compared with the previously developed source of acyl radicals by hydrogen abstraction from aldehydes, this procedure is more effective in monoacylation when multiple positions of high nucleophilic reactivity are available in the heterocyclic ring. Although the introduction of an acyl group strongly activates the heterocyclic ring toward further substitution, monoacylation can be achieved by taking advantage of the difference in basicity and lipophilicity between the starting base and the monoacylation products in a two-phase system.

The substitution of protonated heteroaromatic bases by nucleophilic alkyl and carbonyl radicals reflects many aspects of the Friedel-Crafts aromatic substitution, but with opposite reactivity and selectivity.[1] Thus, electron-withdrawing groups activate and alkyl groups deactivate the heterocyclic ring; position 2 of 4-cyanoquinoline is ~130-fold more reactive toward the benzoyl radical than the same position of 4-methylquinoline.[2] Consequently, when multiple positions of high nucleophilic reactivity (e.g., α and γ) are available in the heterocyclic ring, polysubstitution at these positions by acyl radicals occurs easily and it is difficult to arrest the reaction at the monosubstitution stage. Monosubstitution by acyl radicals is, however, of synthetic interest in many compounds that have more than one reactive position in the heterocyclic ring.

Results and Discussion

We have previously reported a method for the acylation of heteroaromatic compounds by using the t-BuOOH/Fe^{2+} redox system in the presence of aldehydes (eq 1).[3] The

$$\text{Het-H} + \text{RCHO} + t\text{-BuOOH} \xrightarrow{Fe^{2+}} \text{Het-COR} + t\text{-BuOH} + H_2O \quad (1)$$

reaction was generally carried out in aqueous acetic acid because of the low water solubility of most aldehydes. We were interested in arresting the reaction at the monosubstitution stage by using a two-phase system, taking advantage of the acid-base equilibria of the heterocyclic compounds[3] and the difference in lipophilicity between the reagents and the reaction products.[4] These attempts failed or gave poor results because the organic solvent usually extracted all of the aldehyde from the aqueous phase, preventing the generation of acyl radicals. Only the lower aliphatic aldehydes, which are slightly water soluble, gave a moderate increase in monoacylation.[5]

We now report a different and quite general source of acyl radicals that allowed us to develop a two-phase system

(1) Recent review: Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489.
(2) Caronna, T.; Fronza, G.; Minisci, F.; Porta, O.; Gardini, G. P. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1477.
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Table I. Acylation of Quinoline by RCOCOOH[a]

entry	R	solvent	acid (mol)[b]	$S_2O_8^{2-}$ (mol)	orient. of monoacyl (%)	conversion (%)	monoacyl (%)	diacyl (%)
1	Me	H_2O	H_2SO_4 (1)	1.5	2 (32) 4 (68)	48	61	39
2	Me	CH_2Cl_2/H_2O	H_2SO_4 (1)	1.5	2 (59) 4 (41)	74	74	26
3	Me	H_2O	CF_3COOH (1)	3	2 (32) 4 (68)	66	41	59
4	Me	CH_2Cl_2/H_2O	CF_3COOH (1)	3	2 (73) 4 (27)	90	57	43
5	Et	CH_2Cl_2/H_2O	CF_3COOH (1)	1.1	2 (41) 4 (59)	61	90	10
6	Pr	H_2O	H_2SO_4 (1)	1.1	2 (37) 4 (63)	45	50	50
7	Pr	H_2O	H_2SO_4 (1)	1.5	2 (47) 4 (53)	62	35	65
8	Pr	CH_2Cl_2/H_2O	CF_3COOH (1)	1.1	2 (50) 4 (50)	83	87	13
9	Ph	CH_2Cl_2/H_2O	CF_3COOH (1)	3	2 (63) 4 (27)	100	100	

[a] 3 moles of keto acid per mole of base. [b] Moles of reagent per mole of base.

suitable for monoacylation. It utilizes the silver-catalyzed oxidative decarboxylation of α-keto acids by persulfate (eq 2). Both aliphatic and aromatic α-keto acids are sufficiently water-soluble that oxidation occurs readily in a two-phase system.

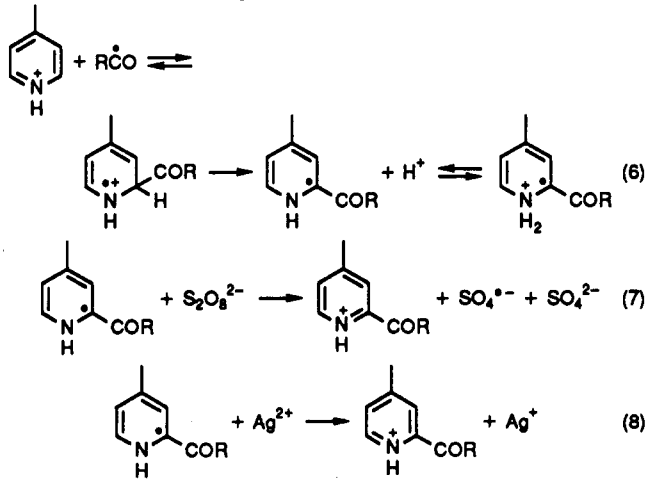
$$\text{Het-H} + \text{RCOCOOH} + S_2O_8^{2-} \xrightarrow{Ag^+} \text{Het-COR} + CO_2 + 2HSO_4^- \quad (2)$$

Acylation takes place by a redox chain process (eqs 3–8) that is generally valid for substitution of heteroaromatic bases by nucleophilic carbon-centered radicals.[1]

$$Ag^+ + S_2O_8^{2-} \longrightarrow Ag^{2+} + SO_4^{\bullet-} + SO_4^{2-} \quad (3)$$

$$Ag^+ + SO_4^{\bullet-} \longrightarrow Ag^{2+} + SO_4^{2-} \quad (4)$$

$$\text{RCOCOOH} + Ag^{2+} \longrightarrow \text{R}\dot{\text{C}}\text{O} + CO_2 + H^+ + Ag^+ \quad (5)$$



The generation of acyl radicals according to eq 5 is easier than that of alkyl radicals from the corresponding carboxylic acids. This implies that reaction 5 is not a simple outer-sphere electron-transfer process (eq 9) because the redox potential of the carboxylic group is increased by the proximity of the keto group, which should be reflected in a lower oxidation rate.

$$Ag^{2+} + \text{RCOCOOH} \rightarrow Ag^+ + H^+ + \text{RCOCOO}\cdot \rightarrow \text{RC}^{\bullet}\text{O} + CO_2 \quad (9)$$

A possible explanation is provided by an inner-sphere mechanism (eqs 10, 11) in which the breaking of the O–Ag^+ bond is either simultaneous to the breaking of the CO–CO bond or, at least, contributes in the transition state of the electron transfer.

$$\text{R-CO-COOH} + Ag^{2+} \rightleftharpoons \text{R-CO-COO-}Ag^+ + H^+ \quad (10)$$

$$\text{R-CO-COO-}Ag^+ \rightarrow \text{R-C}^{\bullet}\text{O} + CO_2 + Ag^+ \quad (11)$$

The lower energy of the CO–CO bond compared with the CH_2–CO bond would explain the faster oxidation of the α-keto acids. This fact also allows the use of mild reaction conditions (10–40 °C) that avoid decarbonylation of the acyl radicals. Conversely, primary carboxylic acids require temperatures in the range 80–100 °C, where decarbonylation of the acyl radicals (eq 12) competes with heteroaromatic substitution. The fast and selective oxidation of α-keto acids by Ag(II) salts allows the use of a wide variety of these acids: only a small concentration of the α-keto acid in the aqueous phase is needed for the reaction to proceed, permitting the use of α-keto acids that are much more soluble in the organic solvent than in water.

$$\text{R-CO} \rightarrow \text{R}^{\bullet} + \text{CO} \quad (12)$$

The reaction was mostly carried out in aqueous solution in the presence of CH_2Cl_2 at 40 °C; it was also carried out in water alone for comparison with the two-phase procedure. The results with quinoline, 4-cyanopyridine, 4-acetylpyridine, pyrazine, and quinoxaline as heteroaromatic bases and 2-oxopropanoic, 2-oxobutanoic, 2-oxopentanoic, and benzoylformic acids as sources of acyl radicals are reported in Tables I–V. Under similar conditions, monoacylation by the two-phase procedure is much more effective than in water alone. Moreover, the two-phase system gives higher conversions than the aqueous system: Table I, entries 1 and 2, 3 and 4, 6 and 7; Table III, entries 1 and 2; Table V, entries 2 and 3.

The higher efficiency of the two-phase procedure can be related to the fact that acyl radicals are generated according to eq 5 and that complexation of the silver salt by the heteroaromatic base can inhibit silver salt catalysis (eqs 3–5). The organic solvent extracts the small amount of unprotonated heterocyclic compound, thus preventing complexation of the silver salt in the aqueous solution.

Several factors are important in determining the effectiveness of monoacylation:

(1) Under a given set of conditions, the ratio of mono to diacylation decreases with increasing percent conversion of the heterocyclic compound. The percent conversion can be controlled by the amount of persulfate used.

Table II. Acylation of 4-Cyanopyridine by RCOCOOH[a]

entry	R	solvent	acid (mol)[b]	$S_2O_8^{2-}$ (mol)	conversion (%)	monoacyl (%)	diacyl (%)
1	Me	H_2O	H_2SO_4 (4)	3	52	75	25
2	Me	CH_2Cl_2/H_2O	H_2SO_4 (2)	1.5	48	100	
3	Et	CH_2Cl_2/H_2O	H_2SO_4 (2)	3	100	66	34
4	Pr	H_2O	H_2SO_4 (2)	3	100	33	67
5	Pr	CH_2Cl_2/H_2O	H_2SO_4 (2)	3	100	86	14
6	Pr	CH_2Cl_2/H_2O	CF_3COOH	1.5	96	94	6
7	Ph	CH_2Cl_2/H_2O	H_2SO_4 (1)	3	100	100	

[a] 3 moles of keto acid per mole of base. [b] Moles of reagent per mole of base.

Table III. Acylation of 4-Acetylpyridine by RCOCOOH[a]

entry	R	solvent	acid (mol)[b]	$S_2O_8^{2-}$ (mol)	conversion (%)	monoacyl (%)	diacyl (%)
1	Me	H_2O	H_2SO_4 (2)	1.5	30	73	27
2	Me	CH_2Cl_2/H_2O	CF_3COOH (1)	1.5	75	84	16
3	Pr	H_2O	H_2SO_4 (1)	3	100	14	86
4	Pr	CH_2Cl_2/H_2O	H_2SO_4 (2)	1.2	80	93	7
5	Ph	CH_2Cl_2/H_2O	H_2SO_4 (2)	3	100	100	

[a] 3 moles of keto acid per mole of base. [b] Moles of reagent per mole of base.

Table IV. Acylation of Pyrazine by RCOCOOH[a]

entry	R	solvent	acid (mol)[b]	$S_2O_8^{2-}$ (mol)[b]	conversion (%)	monoacyl (%)	diacyl (%)
1	Me	H_2O	H_2SO_4 (2)	1.5	100	66	34
2	Me	CH_2CL_2/H_2O	CF_3COOH (3)	1.5	54	100	
3	Pr	H_2O	H_2SO_4 (2)	3	100		100
4	Pr	CH_2Cl_2/H_2O	CF_3COOH (2)	3	100	74	26
5	Ph	CH_2Cl_2/H_2O	H_2SO_4 (1)	3	100	100	

[a] 3 moles of keto acid per mole of base. [b] Moles of reagent per mole of base.

Table V. Acylation of Quinoxaline by RCOCOOH[a]

entry	R	solvent	acid (mol)[b]	$S_2O_8^{2-}$ (mol)[b]	conversion (%)	monoacyl (%)	diacyl (%)
1	Me	CH_2Cl_2/H_2O	CF_3COOH (3)	1.5	63	94	6
2	Pr	H_2O	H_2SO_4 (2)	3	74	42	58
3	Pr	CH_2CL_2/H_2O	H_2SO_4 (2)	3	100	86	14
4	Pr	CH_2Cl_2/H_2O	H_2SO_4 (2)	1.2	75	93	7
5	Ph	CH_2Cl_2/H_2O	H_2SO_4 (2)	3	100	100	

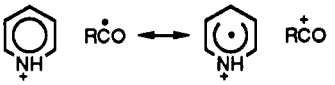
[a] 3 moles of keto acid per mole of base. [b] Moles of reagent per mole of base.

(2) The proportion of monoacylation increases with decreasing basicity of the heterocyclic compound because the introduction of an acyl group further decreases basicity and facilitates extraction of the reaction product by the organic solvent. Thus, it is relatively more difficult to obtain monosubstitution on quinoline, which is the most basic among the investigated substrates.

(3) For the same reason, the ratio of mono- to diacylation increases with decreasing acidity of the medium.

(4) Other conditions being equal, the proportion of monoacylation increases with increasing lipophilicity of the heteroaromatic base and the acyl derivative. The ratios of mono- to diacylation are therefore higher with quinoxaline than with pyrazine and increase in the acyl series acetyl < propionyl < butyryl < benzoyl.

These factors not only affect the efficiency of substitution and the chemoselectivity (ratio of mono- to diacylation), but they also influence the regioselectivity between the 2- and 4-substituted isomers of quinoline (Table I). Such an effect has also been observed in homolytic alkylation.[6] We postulate that the HSAB (hard and soft acids and bases) principle can be extended to free-radical reactions when the polar effect is dominant. Thus, the softness (relatively low ionization potential) of the acyl radicals in polar solvents would promote increased attack at position 4, which is softer than position 2. Moreover, base catalysis and the solvation of polar transition states (eq 13) would influence the reversibility and regioselectivity of reactions described by eq 6 in most polar solvents.



(13)

In quinoline, quinaldine, lepidine, 4-cyanoquinoline, pyrazine, and quinoxaline, only the α and γ positions are attacked by acyl radicals, whereas in 4-cyano- and 4-acetylpyridine monosubstitution occurs mainly at position 2 with minor amounts of acylation at position 3. Diacylation occurs predominantly at positions 2 and 6, although significant amounts of the 2,5 isomers and lesser amounts of the 2,3 isomers are also formed. In these reactions, acylation probably occurs in part on the unprotonated base. The presence of two electron-withdrawing groups in the heterocyclic ring reduces basicity but activates the heterocyclic ring, thus allowing nucleophilic radical attack in the absence of protonation. The polar effect of cyano or acyl groups is much smaller than that of the protonated heterocyclic nitrogen ($\sigma_p \approx 4$),[7] but

(6) Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* **1987**, *52*, 730.

(7) Jaffè, H. H. *J. Am. Chem. Soc.* **1955**, *77*, 4445.

it is of the same order of magnitude as the unprotonated heterocyclic nitrogen ($\sigma_p \approx 0.9$)[8] and the overall regioselectivity is lower in the latter case.

Compared with alkylation,[9] in which monosubstitution is due to polar deactivation and increased lipophilicity of the alkylated product, monoacylation is favored in a two-phase system by the combination of decreased basicity and increased lipophilicity of the acylated product, with elimination or minimization of the effects of polar activation.

In comparison with the method we had previously[3] developed using aldehydes as the source of acyl radicals, this process must be considered the method of choice for the selective acylation of heteroaromatic bases.

Experimental Section

The heteroaromatic bases and the α-keto acids were commercial products. All reaction products were identified by comparison (GLC, NMR, MS, IR) with authentic samples.[3]

General Acylation Procedure. A mixture of heteroaromatic base (2.5 mmol), α-keto acid (7.5 mmol), $AgNO_3$ (0.2 mmol), $NH_4S_2O_8$, and CF_3COOH or H_2SO_4 in the amounts given in Tables I–V in 25 mL of water and 25 mL of CH_2Cl_2 was stirred for 2 h at 40 °C. The aqueous solution was made basic with NaOH, the organic solvent was separated, and the aqueous solution was further extracted with CH_2Cl_2. The extract was analyzed by GLC by the procedure previously reported.[3] The reaction products were isolated by flash chromatography (eluant hexane:ethyl acetate = 5:1).

The same procedure was used for reactions in the absence in CH_2Cl_2. The results are reported in Tables I–V.

Lepidine, quinaldine, and 4-cyanoquinoline were acylated under the conditions of Table I, entry 9. Conversions were complete, and only the products of monoacylation at positions 2 and 4 were observed by GLC when using pyruvic and benzoylformic acids as sources of acetyl and benzoyl radicals. The products were isolated by flash chromatography (80–90% yield) and identified by comparison with authentic samples.

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Selective Transformations of *threo*-2,3-Dihydroxy Esters

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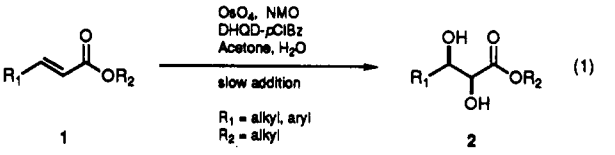
Two highly regio- and stereoselective transformations of *threo*-2,3-dihydroxy esters have been developed. In the first reaction, the α-hydroxy group is converted into a sulfonate group (tosylate or nosylate); the α-tosylates and α-nosylates are then subjected to basic conditions (K_2CO_3/ROH) to give erythro glycidic esters in high yield. The α-nosylates are also suitable electrophiles for azides, giving access to *erythro*-α-azido-β-hydroxy esters. The second reaction involves conversion of the diol esters to acetoxy bromo esters. The β-substituent plays a key role in determining the regiochemistry since cases with β-alkyl substituents afford β-acetoxy-α-bromo esters exclusively, whereas a β-phenyl substituent directs formation of the α-acetoxy-β-bromo ester. The acetoxy bromo esters can subsequently be converted to the threo glycidic esters (via the bromohydrin esters); selective hydrogenolysis of the bromine substituent can also be achieved.

Introduction

The catalytic asymmetric dihydroxylation (ADH) of olefins allows access to a wide variety of vicinal diols of high enantiomeric purity.[1] Efforts in our laboratories have been directed toward the synthetic elaboration of these optically pure diols. Previous work has shown that cyclic sulfates derived from diols are good epoxide-like synthons.[2]

The α,β-unsaturated esters are good substrates for the ADH process, with enantiomeric excesses (ee's) ranging from 67 to 86%.[3] They are easily prepared in high yield by using our catalytic system employing OsO_4, dihydroquinidine *p*-chlorobenzoate (DHQD–*p*ClBz) as the chiral auxiliary and *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant (eq 1). As with any synthetic methodology, its value is largely determined by the utility



(1)

of the products. The goal of this study was to determine to what extent the diol esters could be transformed selectively into synthetically advanced and useful intermediates.

Results and Discussion

The first selective reaction attempted was the conversion of one hydroxyl group into a leaving group (sulfonate). Probably because of the difference in acidity of the two hydroxyl groups, selective sulfonylation can be performed; the more acidic α-hydroxyl group reacts preferentially to form the monosulfonate.[4] Diol esters were regioselectively

(1) (a) Lohray, B. B.; Kalantar, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041. (b) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G. Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123. (c) Kwong, H.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999.
(2) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2632. (c) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655.
(3) The ee's range from 73 to 91% using potassium ferricyanide as the stoichiometric oxidant (see ref 1c).
(4) (a) The effect of a neighboring carbonyl group on the acidity of an alcohol can be quite dramatic, as α-hydroxy ketones have pK_a values of 11–12 and are readily titrated in water (Masamune S., private communication). (b) An example of this selective sulfonylation has recently been reported by Greene and co-workers. Denis, J.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957. (c) During the preparation of this manuscript another selective sulfonylation appeared in the literature. Watson, K. G.; Fung, Y. M.; Gredley, M.; Bird, G. J.; Jackson, W. R.; Gountzos, H.; Matthews, B. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1018.

0022-3263/91/1956-2869$02.50/0