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ASYMMETRIC SYNTHESIS *via* CHIRAL ACETAL TEMPLATES. 8.[1] REACTIONS WITH ORGANOMETALLIC REAGENTS

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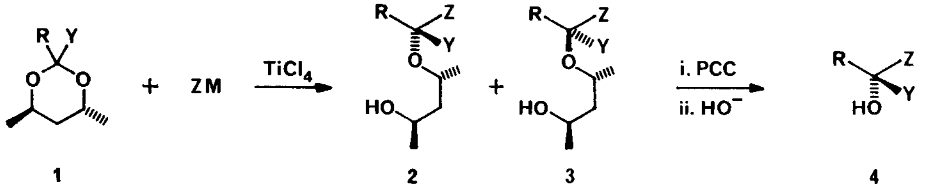
ABSTRACT: *The titanium tetrachloride catalyzed coupling of organometallic reagents with chiral acetals 1 is shown to provide a convenient route for the preparation of a variety of chiral alcohols 4 of high optical purity.*

Recent studies have shown that the Lewis acid promoted coupling of chiral acetals 1 (Y = H) with various nucleophilic organosilicon reagents proceeds in a highly diastereoselective manner, ultimately providing a route for generating chiral secondary hydroxy compounds in high chemical and optical yields.[1,2] As part of a program aimed at expanding the generality of this reaction we now report on the results of the $TiCl_4$-catalyzed coupling of the acetals 1a-1e and the ketal 1f with various organometallic compounds (ZM) (Scheme, Table).[3,4]

The yield and diastereoselectivity of this reaction were found to be variously affected depending on the structures of the acetal 1 and organometallic reagent ZM, and on the nature of the solvent system. However, through the judicious choice of reaction conditions[5] and reagents the desired product 2 was obtained in high yield and with good to excellent diastereoisomeric purity (Table). As previously noted[2a,b] the diastereoisomers 2 and 3 were in all cases separable using standard chromatographic methods,[6] thus providing a route to material of optical purity equal to that of the chiral auxiliary, i.e., >97%.[4]

The products 2a-2f were converted to the alcohols 4a-4f, respectively, in >85% overall yields[7] by the previously described oxidation/β-elimination procedure.[2a] The absolute configurations of these alcohols were established by comparison of the signs of their optical rotations with reported values for these or closely related compounds.[8] The optical purity of alcohols 4a-4e as determined *via* their (+)-MTPA esters,[9a] and of 4f as determined using a chiral shift reagent,[9b] agreed well (after correction for the % ee of the chiral auxiliary[4]) with the ratios obtained for the coupling products 2/3.[10] The (+)-MTPA ester of (2R)-decanol (4d) was identical (GC coinjection and ^{1}H NMR) with the (+)-MTPA ester of a sample of the same compound isolated from the defense secretions of the East African Nasute Termite *Trinervitermes bettonianus*.[11] This provides an unequivocal confirmation of the absolute configuration of this simple chiral pheromone, which had previously been assigned on the basis of empirical ^{1}H NMR data.[11a]

Scheme



a R = m-$C_6H_5OC_6H_4$, Y = H, Z = CH_3
b enantio-a
c R = n-C_8H_{17}, Y = H, Z = CH_3
d enantio-c
e R = cyclohexyl, Y = H, Z = n-C_4H_9
f R = $(CH_3)_2C=CHCH_2CH_2$, Y = CH_3, Z = C_2H_5
g R = n-C_8H_{17}, Y = H, Z = n-C_4H_9
h R = n-C_8H_{17}, Y = H, Z = $CH_2=CHCH_2$

TABLE

Results of the Transformations Shown in the Scheme

	Acetal 1[4]	ZM[4]	Coupling Product 2/3			Alcohol 4			
Entry	case	(molarity)	case	% yield[7]	ratio[10]	case	$[\alpha]_D$ (c)	% ee[9]	config.
1[a]	1a[c]	MeMgCl (2.8)[d]	2a/3a[c]	97	98:2	4a[c]	-26.2°(1.1)[i]	93	S[8a]
2[a]	1a	MeLi (1.2)[e]	2a/3a	83	98:2				
3[a]	1b[l]	MeMgCl (2.8)[d]	2b/3b	97	98:2	4b	+27.1°(1.1)[i]	96	R[8a]
4[a]	1c[2a]	MeMgBr (2.8)[e]	2c/3c	76[g]	96:4				
5[b]	1c	MeMgBr (2.8)[e]	2c/3c[c]	90	96:4	4c[c]	+6.3°(4.2)[i]	89	S[8b]
6[a]	1c	Me_2CuLi (0.5)[e]	2c/3c	15[g]	70:30				
7[b]	1d	MeMgBr (2.8)[e]	2d/3d	89	96:4	4d	-6.5°(4.1)[i]	91	R[8b]
8[a]	1e[2a]	*n*-BuMgCl (2.0)[e]	2e/3e	36[h]	92:8				
9[a]	1e	*n*-BuLi (1.6)[f]	2e/3e[c]	74	87:13	4e[c]	-10.9°(1.8)[i]	72	S[8c]
10[a]	1f[c]	EtMgBr (2.8)[e]	2f/3f	46[g]	70:30				
11[a]	1f	Et_2CuMg (0.8)[e]	2f/3f	80	89:11	4f[c]	-1.9°(1.8)[i]	72	S[8d]
12[b]	1c	*n*-BuLi (1.6)[f]	2g/3g[c]	82	87:13				S[k]
13[b]	1c	AllylMgBr (1.0)[e]	2h/3h[2a]	93	97:3	4h[2a]	+10.6°(4.9)[j]		R[2a]

[a] Procedure A: (i) 2 mol eq $TiCl_4/CH_2Cl_2/-78°C$; (ii) 2 mol eq ZM instilled over 10-30 min. [b] Procedure B: as for A, but repeat steps (i) and (ii) prior to work-up. [c] A satisfactory combustion analysis was obtained for this compound. [d] THF solution. [e] Et_2O solution. [f] Hexane solution. [g] GC yield only. [h] 36% of starting acetal 1e also isolated. [i] $CHCl_3$ solution. [j] CCl_4 solution. Measured on a sample of 4h obtained from a 98:2 mixture of 2h/3h (ref. 2d). [k] Absolute configuration assigned by analogy to other products listed in Table.

The (R)-alcohol 4b was of special interest due to its close structural relationship to (S)-α-cyano-3-phenoxybenzyl alcohol,[1] certain esters of which are important as pyrethroid insecticides.[12a] One problem associated with these (S)-cyanohydrin derived pyrethroids is their tendency to undergo epimerization in the field yielding mixtures containing the inactive (R)-cyanohydrin esters. This should not occur in pyrethroids derived from 4b, and consequently the 3-methyl-2-(4-chloroanilino)butyrate esters of alcohols 4a and 4b were prepared and tested for insecticidal activity.[12] As expected the ester of 4a exhibited very low activity, while the ester of 4b exhibited twice the activity of the racemic pyrethroid. Comparison of LD$_{50}$ (μg/insect) values with those for the analogous racemic cyanohydrin derived pyrethroid,[12a] indicated that the pyrethroid derived from 4b exhibited greater activity against the common housefly *Musca domestica* (LD$_{50}$ 0.13), but had slightly lower activity against the tobacco budworm *Heliothis virescens* (LD$_{50}$ 0.085).

The results presented above indicate that the Lewis acid catalyzed reaction of chiral aliphatic or aromatic acetals with organometallic reagents provides a convenient route for the highly enantioselective preparation of a variety of secondary alcohols, in either antipodal form.[13] The method has been extended, in one case, to the preparation of a chiral tertiary alcohol with satisfactory results. The diastereoselectivity of these reactions is comparable to that observed in the coupling reactions of chiral acetals with organosilicon reagents,[1,2] and in every case the absolute configuration of the product 2 is consistent with the previously proposed S$_N$2-like mechanism,[1] in which attack of 1 by a nucleophile occurs so as to relieve a 1,3-diaxial H/Me or, in the case of ketal 1f, a Me/Me interaction.

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4. Acetals 1a-1e were prepared in >95% yield (ref. 7) and 1f was prepared in 82% yield (ref. 7) as described in ref. 1. The % ee of the 2R,4R-pentane diol (Aldrich Chem. Co.) and of the S,S-isomer (generously donated by Dr. A. Tai, Osaka University) used in the preparation of 1 were shown to be 97.5 and 99.5, respectively, by GC analysis of their bis-(+)-MTPA esters (ref. 9a). Organometallic reagents were obtained from Aldrich Chem. Co. except for dimethyl- and diethylcuprates, which were prepared by addition of MeLi and EtMgBr to purified CuI. See Johnson, C. R. and Dutra, G. A. J. Am. Chem. Soc., 1973, 95, 7777.

5. The experimental procedure is typified by the following example. TiCl$_4$ (155 µl, 1.4 mmol) was added to a cold (-78°C) stirred solution of 1a (200 mg, 0.70 mmol) in dry CH$_2$Cl$_2$ (20 ml). After 5 min a 2.8 M solution of MeMgCl in THF (500 µl, 1.4 mmol) was instilled over a 10 min period. After a further 15 min a 2:1 MeOH:pyridine mixture 6 ml) was added, and the mixture was warmed to room temperature, then poured into 1 M hydrochloric acid. GC analysis (ref. 10) of the crude, and of the chromatographed product (ref. 7) 2a/3a (204 mg, 0.68 mmol) showed two peaks in the ratio of 98:2. In the case of acetals 1c and 1d a second addition of reagents prior to work-up resulted in increased yields of products.

6. For example, the diastereoisomers 2e and 3e were completely separated upon a single pass through a DuPont 21.2 mm x 25 mm Zorbax ODS HPLC column (1:9 H$_2$O/MeOH).

7. Products were purified by low pressure column chromatography using "Merck silica-gel 60 H for thin layer chromatography." The ^{1}H NMR and IR spectra were consistent with the assigned structures.

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10. The diastereomeric ratios were determined by GC analysis (ref. 9a). In the case of the adduct 2e/3e it was necessary to prepare the *tert*-butyldiphenylsilyl ether in order to obtain a base line separation.

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