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PREVENTION OF CHELATION BY AN OXYGEN FUNCTION THROUGH PROTECTION WITH A TRIISOPROPYL SILYL GROUP

Stephen V. Frye and Ernest L. Eliel*

William R. Kenan, Jr. Laboratories of Chemistry
University of North Carolina, Chapel Hill, NC 27514 USA

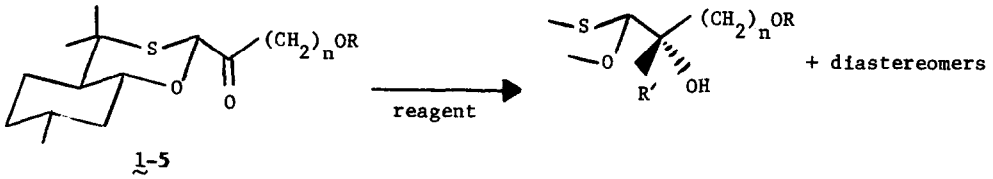
Summary. In contrast to other α- and ß-alkoxy substituents the triisopropylsilyloxy group does not depress the high diastereomer excess normally realized in nucleophilic addition to 2-acyl-1,3-oxathianes.

Since the pioneering work of Cram[1], chelation control has developed into an important method for achieving diastereofacially selective addition of organometallics to the carbonyl function of chiral α- and ß-alkoxyketones.[2,3,4] The asymmetric synthesis of highly enantiomerically pure tertiary and secondary α-hydroxyaldehydes from chiral 1,3-oxathianylketones[4,5] is an example where the chelate model has been used to explain and predict the stereochemical outcome of addition to the diastereotopic faces of a chiral α-alkoxyketone. The usefulness of this synthesis would be enhanced if oxygen containing functions in the side chain of the ketone (cf. Table 1, top) could be tolerated. However, such functions might competitively interfere with the chelation by the oxathiane oxygen. To investigate the effect of α- and ß-oxygen substitution on the diastereoselectivity of reactions of organometallics with oxathianylketones[6], and to gather further evidence regarding the importance of chelation in asymmetric syntheses based upon chiral 1,3-oxathianes, compounds 1-4 (Table 1) were prepared and allowed to react with CH_3MgBr, L-Selectride® and DIBAL.

The results of this investigation are presented in Table 1. α- and ß-benzyl ether functions in the side chain of the ketone greatly depress the stereoselectivity of Grignard addition (entries 1, 4); even with more remote benzyloxy functions, stereoselectivity is diminished.[5e] Replacement of benzyl by trityl in the ß-alkoxy case (entry 13) improves matters, but stereoselectivity remains considerably below the customary[5] 90-99%. L-Selectride® reduction when n = 2 (entry 5) is almost completely unselective.

In contrast, the triisopylsilyl (TIPS) substituent, previously used as a bulky protective group for both NH[7] and OH[8] functions, proved extremely effective (much more so than trityl) in preventing competing chelation of α- and ß-oxygen functions. In Grignard addition (entries 7,

Table 1



1-5

#	cpd.	n	R	Reagent	d.e.*
1	1	1	Bz	CH_3MgBr[a]	33
2		1	Bz	L-Selectride®[b]	72
3		1	Bz	DIBAL[c]	57
4	2	2	Bz	CH_3MgBr	17
5		2	Bz	L-Selectride®	9
6		2	Bz	DIBAL	-66‡
7	3	1	TIPS[d]	CH_3MgBr	95
8		1	TIPS	L-Selectride®	33
9		1	TIPS	DIBAL	-60‡
10	4	2	TIPS	CH_3MgBr	95
11		2	TIPS	L-Selectride®	76
12		2	TIPS	DIBAL	-77‡
13	5	2	trityl	CH_3MgBr	72
14	6	2	$Si(CH_3)_3$	L-Selectride®	33
15	7	2	$Si(CH_3)_2$t-Bu	L-Selectride®	13

* d.e. determined by integration of the signals for the axial proton in the 2-position of the oxathiane ring.

‡ The negative sign indicates that the diastereomer in excess is epimeric to the diastereomer obtained in the reduction with L-Selectride®.

[a] -78°, THF, 2eq reagent

[b] -78°, Toluene, large excess reagent, KOH/H_2O_2 work-up

[c] -78°, Toluene, large excess reagent

[d] Triisopropylsilyl

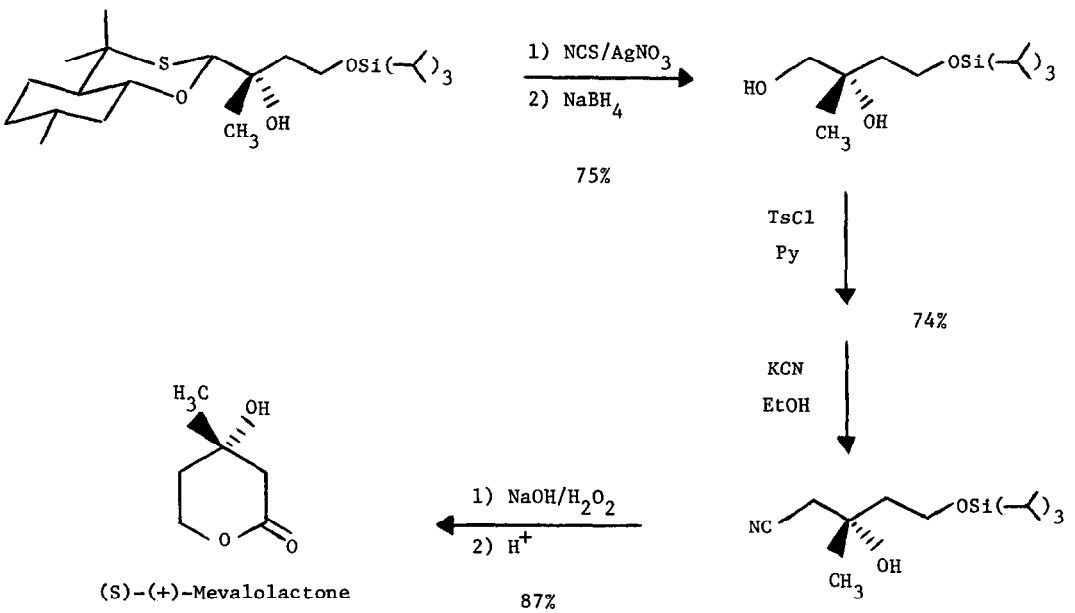
10), stereoselectivity was restored to the 95% level and with Selectride - intrinsically somewhat less selective[5c] - it rose to 76% when n = 2 (entry 11). Evidently the very bulky TIPS group prevents chelation by the adjacent oxygen in TIPS ethers.

We questioned at first if this effect was steric or if it involved some electronic aspect of the R_3SiO group. However, the failure of Me_3Si (entry 14) and t-$BuMe_2Si$ (entry 15) to inhibit the deleterious competing chelation confirms that the salient effect with TIPS is indeed steric.

Reductions with DIBAL (cf. entry 6) have previously been found[5c] to proceed with stereochemistry opposite to that with hydrides, presumably because DIBAL does not chelate and its stereoselectivity rests on other grounds (e.g. dipolar factors). Accordingly, the TIPS group does not appreciably affect selectivity in DIBAL reductions (compare entries 3 and 6 with 9 and 12).

The high selectivity of L-Selectride® with the α-benzyloxy ether (#2) and the identical stereochemical course of Selectride and DIBAL reductions in the case where n = 1 (compare entries 2 and 3) is somewhat anamolous but cannot be properly interpreted until the relative and absolute configuration of the products corresponding to entries 2, 3, 8 and 9 is elucidated. In all other cases it is clear that TIPS enhances stereoselectivity in Grignard additions and Selectride reductions of α- and ß-oxy substituted 2-acyl-1,3-oxathianes - presumably by inhibiting competing chelation sterically - but is ineffective in DIBAL reductions which presumably do not involve chelation in the first place.

The absolute configuration of the product of addition of CH_3MgBr to ketone 4 has been established by conversion to (S)-(+)-mevalolactone (Scheme 1)[9] and is consistent with the



Scheme 1

chelate rule.[1] A previous reported nine-step asymmetric synthesis of mevalolactone from an oxathianyl ketone[5d] depended upon the oxidation of a phenyl group to -COOH to introduce the necessary functionality in the molecule. The synthesis reported here reduces the number of steps in the synthesis by four at the expense of lowering the enantiomeric excess from >98 to 94%.

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9. cf. Ref. 5d and earlier references there cited.

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