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Construction of a quaternary carbon center via cyclic sulfite

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Abstract

Reaction of (*S*)-2-oxo-4-methyl-4-phenyl-1,3,2-dioxathiolane with triethylaluminum selectively took place at the tertiary carbinol center to give (*R*)-2-methyl-2-phenyl-1-butanol. Enhanced stereoselectivity was obtained in a nonpolar solvent. Similarly, a series of (*S*)-4,4-disubstituted-1,3,2-dioxathiolanes reacted with trimethylaluminum to afford the corresponding (*R*)-2-alkyl-2-phenyl-1-propanols in good yields.

Chiral quaternary carbon centers are widespread in natural products such as steroids, alkaloids and terpenes.[1,2] For the construction of the carbon framework of these compounds, a primary alcohol having a quaternary carbon atom at the C2 position would be an important building block. However, a few methods for generating this moiety in an efficient enantioselective manner have been reported.[2] As a possible approach for the construction of this class of compounds, the reaction of nucleophiles with tertiary carbon electrophiles would be conceivable. However, bimolecular nucleophilic substitution reactions at tertiary carbon atoms bearing suitable leaving groups are relatively rare processes since competing β-elimination is usually favored in such systems.

Cyclic sulfites and cyclic sulfates are considered as activated diols.[3] Thus, it was reported that the reaction of 2-oxo-4-phenyl-1,3,2-dioxathiolane (**1a**) and 2-oxo-4-(*tert*-butyldiphenylsilylmethyl)-1,3,2-dioxathiolane (**1b**) with 3 mol equivalents of Me_3Al selectively took place at the secondary carbinol center to give 2-phenyl-1-propanol (**2a**) and 3-(*tert*-butyldiphenylsilyl)-2-methylpropanol (**2b**), respectively (Scheme 1).[4] A transition state with a carbenium-like character has been proposed to explain the selectivity observed. It could, therefore, be expected that 2-oxo-4,4-disubstituted-1,3,2-dioxathiolanes react with aluminum reagents, giving the corresponding primary alcohols having a quaternary carbon atom at the C2 position.

In this communication, we wish to report the preparation of primary alcohols having quaternary centers at the C2 position by the regioselective alkylation of tertiary carbon atom of a *prim*, *tert*-diol via 1,3,2-dioxathiolane.

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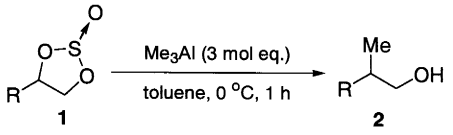
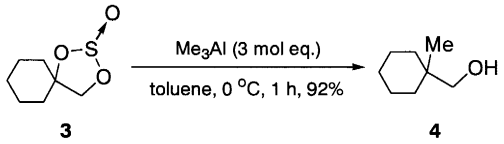


1, 2	R	Yield of 2 (%)
a	Ph	94
b	*t*-BuPh2SiCH2	93

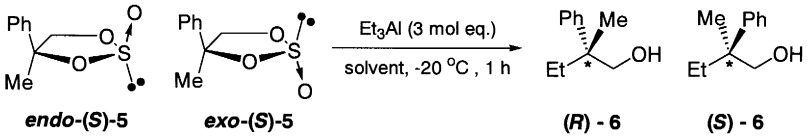
Scheme 1.

At the outset, cyclohexanespiro-4′-(2′-oxo-1′,3′,2′-dioxathiolane) (**3**)[5] reacted with 3 mol equivalents of Me_3Al in toluene at 0°C for 1 h to give 1-hydroxymethyl-1-methylcyclohexane (**4**) in 92% yield (Scheme 2).



Scheme 2.

In order to confirm the stereochemistry of the reaction, (*S*)-2-phenylpropane-1,2-diol was converted into the *exo*- and *endo*-isomers of (*S*)-2-oxo-4-methyl-4-phenyl-1,3,2-dioxathiolane [*exo*-(*S*)-**5** and *endo*-(*S*)-**5**],[5] which reacted, respectively, with Et_3Al at −20°C for 1 h (Scheme 3).



Scheme 3.

When the reaction of *exo*-(*S*)-**5** was carried out in CH_2Cl_2, a mixture of (*R*)- and (*S*)-2-methyl-2-phenyl-1-butanol [(*R*)-**6** and (*S*)-**6**] was obtained in 84% yield with (*R*)-isomer:(*S*)-isomer=1.37:1 (16% ee) (Table 1, Entry 1).

Table 1
Reaction of **5** with Et_3Al at −20°C for 1 h

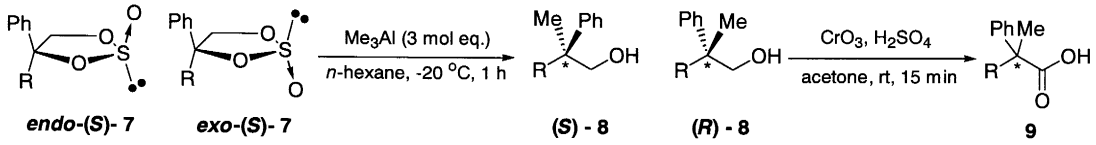
Entry	Substrate	Solvent	(*R*)-**6** + (*S*)-**6** Yield (%)	% ee*	(*R*)-**6** : (*S*)-**6**
1	*exo*-5	CH_2Cl_2	84	16	1.37 : 1
2	*endo*-5	*n*-hexane	85	56	3.59 : 1
3	*exo*-5	*n*-hexane	94	70	5.72 : 1

* Determined by HPLC (CHIRACEL OD).

The stereoselectivity was significantly improved when the reaction was carried out in *n*-hexane. Thus, under the same conditions, except for changing the solvent from CH_2Cl_2 to *n*-hexane, both *endo*-(*S*)-**5** and *exo*-(*S*)-**5** gave (*R*)-**6** in 56% ee (85% yield) and 70% ee (94% yield), respectively (Table 1, Entries 2 and 3). The configuration of the main isomers of these reactions was assigned to be (*R*) by comparison of the $[\alpha]_D$ of the mixture of the enantiomers obtained with reported $[\alpha]_D$ (−5.95 for (*R*)-2-methyl-2-phenyl-1-butanol).[6]

As can be seen from Table 1, enhanced stereoselectivity was obtained in *n*-hexane. This result would be explained by assuming a carbenium-ionic character of the transition state. The lower stereoselectivity observed in *endo*-**5** than that in *exo*-**5** would be rationalized by the formation of a transition state with extensive bond-breaking (S_N1-type transition state) to release the compression energy exerted between the phenyl group and the complexed S→O group.[4]

Next, the reaction of *endo*- and *exo*-isomers of 2-oxo-4-phenyl-1,3,2-dioxathiolane, having a series of alkyl groups in the C4 position [*endo*-(*S*)-**7** and *exo*-(*S*)-**7**][5] with Me_3Al at −20°C for 1 h in *n*-hexane, was examined (Scheme 4). When the *endo*-isomer of 2-oxo-4-phenyl-4-propyl-1,3,2-dioxathiolane [*endo*-(*S*)-**7a**] was treated with Me_3Al, 2-methyl-2-phenylpentanol [(*S*)-**8a**] was obtained in 45% ee (97% yield) (Table 1, Entry 1). The reaction of the *exo*-isomer [*exo*-(*S*)-**7a**] gave (*S*)-**8a** in 48% ee (93% yield) (Table 2, Entry 2). Similarly, the reaction of the *endo*- and *exo*-isomers of 2-oxo-4-butyl-4-phenyl-1,3,2-dioxathiolane [*endo*-(*S*)-**7b** and *exo*-(*S*)-**7b**] and 2-oxo-4-isopropyl-4-phenyl-1,3,2-dioxathiolane [*endo*-(*S*)-**7c** and *exo*-(*S*)-**7c**] with Me_3Al resulted in the formation of (*S*)-**8b** and (*S*)-**8c** as main products in 95–98% yields with 35–79% ee (Table 2, Entries 3–6). The effects of the isopropyl group at the C4 position on stereoselectivity have not yet been elucidated.



Scheme 4.

Table 2
Reaction of **7** with Me_3Al at −20°C for 1 h

Entry	Substrate	R	(*S*)-**8** + (*R*)-**8** Yield (%)	% ee*	(*S*)-**8** : (*R*)-**8**	Yield **9** (%)
1	*endo*-**7a**	*n*-Pr	97 (**8a**)	45	2.63 : 1	80
2	*exo*-**7a**	*n*-Pr	93 (**8a**)	48	2.83 : 1	87
3	*endo*-**7b**	*n*-Bu	98 (**8b**)	35	2.26 : 1	30
4	*exo*-**7b**	*n*-Bu	96 (**8b**)	47	2.78 : 1	70
5	*endo*-**7c**	*i*-Pr	96 (**8c**)	79	8.63 : 1	60
6	*exo*-**7c**	*i*-Pr	95 (**8c**)	77	7.79 : 1	30

* Determined by HPLC (CHIRACEL OD).

The stereochemical assignment of the major product was made by converting the enantiomer mixture isolated into the corresponding carboxylic acid with known configration.[7] Thus, a 2.83:1 mixture of (*S*)-**8a** and (*R*)-**8a** (48% ee) was subjected to Jones oxidation to afford 2-methyl-2-phenylpentanoic acid **9** in 87% yield with $[\alpha]_D$ +3.8 (*c* 2.13, MeOH). The specific rotation observed indicates the major isomer has (*S*)-configuration. In a similar way, the stereogenic center of all major products was determined to be (*S*), indicating that stereochemical inversion took place in the substitution reaction.

In summary, the reaction of (*S*)-2-oxo-4-methyl-4-phenyl-1,3,2-dioxathiolane [*endo*-(*S*)-**5** and *exo*-(*S*)-**5**] with Et_3Al regioselectively took place at the C4 position to afford (*R*)-2-methyl-2-phenyl-1-butanol (**6**) and its (*S*)-isomer, with the former predominant. Enhanced stereoselectivity was obtained in a nonpolar solvent. Similarly, a series of (*S*)-4,4-disubstituted-1,3,2-dioxathiolanes reacted with Me_3Al to afford the corresponding (*S*)-2-alkyl-2-phenyl-1-propanols [(*S*)-**8**] as the major product in good yields, but the stereoselectivity was moderate (35–79% ee). Although the stereoselectivity of the reaction remains to be improved, the results described in this paper suggest interesting possibilities for further work.

Acknowledgements

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