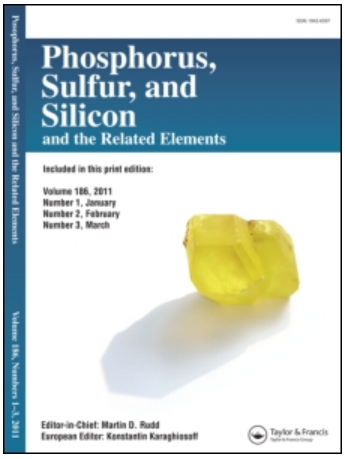

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Enantioselectivity Testing of Chiral Stannanes Derived from Menthol

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(1R,2S,5R)-Menthyldiphenyltin hydride (**1**), bis[(*1R,2S,5R*)-menthyl]phenyltin hydride (**2**) and tris[(*1R,2S,5R*)-menthyl]tin hydride (**3**) were tested as enantioselective free-radical reducing agents against a series of racemic halogen-containing organic compounds, including methyl 2-bromo-3,3-dimethyl-2-phenylbutanoate (**6f**) and 2-bromo-1,2-diphenylpropanone (**6g**). Enantioselectivities of between 2 and 16% were recorded at –78°.

Keywords: stannane; enantioselectivity; free-radical; chiral; menthol

INTRODUCTION

As part of an ongoing study targeted at the development of chiral, non-racemic stannanes for use in free-radical syntheses, we has cause to investigate the effectiveness of the (*1R, 5S, 6R*)-menthyl substituent as a stereodirecting ligand during free-radical reductions. Accordingly, (*1R,2S,5R*)-menthyldiphenyltin hydride (**1**), bis[(*1R,2S,5R*)-menthyl]phenyltin hydride (**2**) and tris[(*1R,2S,5R*)-menthyl]tin hydride (**3**), prepared by Dakternieks and Dunn,[1] were reacted with a series of racemic organic substrates (**4** – **6**) at –78°, 0° and 80°, in toluene or benzene under standard radical conditions. We now report that stannanes (**1** – **3**) induce only low levels of enantioselectivity during their reduction reactions with the halides in this study; the maximum enantioselectivity recorded being 16% for the reaction of

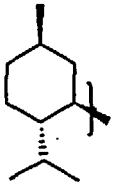
tris[(*1R,2S,5R*)-menthyl]tin hydride (**3**) with 2-bromo-1,2-diphenylpropanone (**6g**) in toluene at –78°.

RESULTS AND DISCUSSION

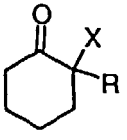
RPh_2SnH R_2PhSnH R_3SnH

1 **2** **3**

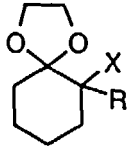
R =



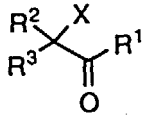
Substrates (**4** – **6**; X = Cl, Br) in this study represent a cross-section of structural types and include esters (**6d** – **f**) employed by Metzger and coworkers[2] in their recent study involving nitrogen-coordinated stannanes (**7**) and the ketone (**6g**) used by Curran and Nanni[3] to test their C_2-symmetric binaphthyl-substituted stannane (**8**).



4a: R = Me
b: R = *tert*-Bu



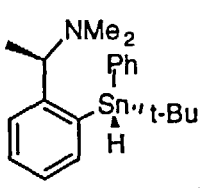
5a: R = Me
b: R = *tert*-Bu



6a: R^1= OEt, R^2= Me, R^3= Et
b: R^1= OMe, R^2= NHTFA, R^3= Et
c: R^1= OEt, R^2= Me, R^3= C(O)Me
d: R^1= OMe, R^2= Me, R^3= Ph
e: R^1= OMe, R^2= Et, R^3= Ph
f: R^1= OMe, R^2= *tert*-Bu, R^3= Ph
g: R = Ph, R^2= Me, R^3= Ph

In this study, reductions were carried out at concentrations of approximately 0.1M of the substrate in benzene (80°) or toluene (0° or –78°) to which 1.1 equivalents of the stannane was added. Reactions

carried out at 80° were initiated using AIBN, while 9-BBN[4] was used as initiator in the lower temperature reductions. Reactions were carried out until TLC analysis indicated the absence of starting material (ca. 1 h) at which time the solutions were examined by chiral-phase gas-chromatography (GC) and the percentage conversion and enantiomeric ratios determined by integration of the signals corresponding to the mixture of reduced compounds (**4 – 6**; X = H) against an internal standard (either octane, decane or pinacolone). Reduced compounds (**4 – 6**; X = H) were identified by comparison of their GC retention times with those of the authentic racemic mixture. As the enantiomeric excesses determined in this manner never exceeded 16% (*vide infra*), no attempt was made to determine the absolute configuration of the stereogenic centre in the isomers produced during reduction.



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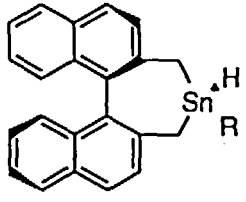


8

In all reactions carried out in this study, conversions always exceeded 60% and mostly exceeded 80%. In the reactions carried out at 80°in benzene, all reactions gave no enantioselectivity, while in the reactions performed at the lower temperatures enantiomeric ratios as listed in Table 1 were determined.

Inspection of Table 1 reveals that all three reagents perform relatively poorly across all substrates in their ability to effect stereoselective reduction. It is interesting to note that each menthyl-substituted stannane (**1 – 3**) proved to be most effective against substrates (**6d –g**; X = Br), the same substrates employed by Metzger and Curran in separate studies.[2,3] While the reagents in this study were not able to achieve the same levels of enantioselectivity reported for reactions involving the few other chiral stannanes (eg. **7**, **8**) available, it is noteworthy that in these previous studies phenyl substitution on the radical centre also proved to be important in maximizing enantioselectivity.[2,3]

Previous work in our laboratories has demonstrated that the steric bulk of the alkyl substituent on the tin centre during free-radical reduction correlates well with the activation energy for the transfer of

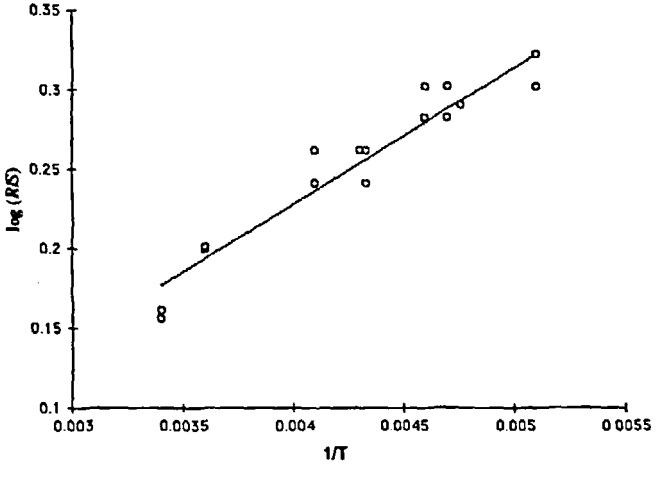
TABLE 1. Ratio of enantiomers (**4 – 6**; X = H) produced during reactions of substrates (**4 – 6**; X = Cl, Br) with stannanes (**1 – 3**) in toluene at 0° and –78°.

Substrate		1	2	3
4a	(-78°)	54:46	53:47	53:47
	(0°)	51:49	51:49	51:49
4b	(-78°)	53:47	53:47	52:48
	(0°)	52:48	51:49	51:49
5a	(-78°)	53:47	53:47	53:47
	(0°)	52:48	51:49	51:49
5b	(-78°)	54:46	54:46	54:46
	(0°)	51:49	51:49	51:49
6a	(-78°)	52:48	51:49	51:49
	(0°)	52:48	51:49	51:49
6b	(-78°)	54:46	53:47	53:47
	(0°)	51:49	51:49	51:49
6c	(-78°)	53:47	53:47	54:46
	(0°)	51:49	51:49	51:49
6d	(-78°)	50:50	51:49	53:47
	(0°)	50:50	51:49	52:48
6e	(-78°)	51:49	52:48	54:46
	(0°)	50:50	50:50	52:48
6f	(-78°)	52:48	53:47	55:45
	(0°)	50:50	51:49	53:47
6g	(-78°)	52:48	57:43	58:42
	(0°)	51:49	53:47	55:45

hydrogen atom from tin to carbon.[5] In addition, high-level ab initio calculations indicate that the distance between the tin and carbon centres in the transition state for the delivery of hydrogen atom from tin to carbon is about 3.5Å.[6]

The data presented in Table 1 suggest that the steric influence of menthyl substitution on tin may not be significant enough for chiral recognition during stannane reduction especially considering the transition state distance of 3.5Å. It is noteworthy that the introduction of phenyl substitution on the radical centre serves to increase the enantioselectivity somewhat. This is consistent with the discussion presented above in which spin delocalization due to the presence of the aromatic ring requires a shortening of the carbon-tin separation in the transition state for reduction in order to maintain sufficient orbital overlap; this reduction in distance manefests itself in an increase in chiral recognition and hence enantioselectivity.

FIGURE 1. Relative Arrhenius relationship for the reduction of ketone **6g** with **3** in Toluene.



Finally, in order to quantify the thermodynamic parameters associated with the enantioselectivity data obtained in this study, we examined closely the effect of temperature on the ratio of enantiomers obtained during the reduction of bromide (**6g**; X = Br) with

trimenthyltin hydride (3). The data are displayed graphically in Figure 1 where log(*R/S*) is plotted as a function of 1/T. The relatively good correlation observed in Figure 4 allow the following (relative) Arrhenius expression to be extracted (eqn 1):

$$\log(R/S) = (0.03 \pm 0.03) - (0.7 \pm 0.1) / 2.3RT \qquad .....(1)$$

(where R = 8.314 x 10^{-3} kJ.K^{-1}.mol^{-1}).

Inspection of equation 1 reveals that, at least for this system, the dominant influence on enantioselectivity would appear to be activation energy of reaction rather than entropic factors; a small difference in activation energies for attack at the two faces of the prochiral radical (**6g**; X = dot) of only 0.7 kJ.mol^{-1} is observed, while the difference in logA (entropy) terms is essentially zero. Clearly then, in designing future reagents to effect enantioselective free-radical reduction, close attention will need to be given to strategies for increasing the difference in activation energies for attack at the two faces of prochiral radicals through well engineered chiral ligands of appropriate steric bulk.

EXPERIMENTAL

Ketones **4a** (X = Cl), **4b** (X = Br) and **6c** (X = Cl) were prepared following literature procedures.[6-8] Bromides **6a, b, d, e, g** (X = Br) were prepared by NBS bromination of the parent ester or ketone as outlined below and exhibited identical spectroscopic properties to those reported in the literature.[2,10-12] We thank Professor J. O. Meztger for kindly providing a sample of bromide **6f**. Gas chromatographic analyses were performed using a chiral trifluoroacteylated γ-cyclodextrin (Chiraldex™ G-TA, 30m x 0.25mm) capillary column purchased from Alltech.

General procedure for the preparation of bromides (**6a, b, d, e, e**). Methyl 2-bromo-2-phenylpropanoate (**6d**).

N-Bromosuccinimide (360mg, 2.0 mmol) was added to a solution of methyl 2-phenylpropanoate (300mg, 1.8 mmol) in carbon tetrachloride (5mL). The solution was irradiated (under reflux) by a 250W tungsten lamp for 45 min. The solid was removed by filtration and the solvent removed *in vacuo* to afford the title compound in quantitative yield and of sufficient purity for further use.

General procedure for low-temperature stannane reductions.

A flask fitted with a septum was charge with a solution of the required bromide (0.1 mmol) and internal standard (octane, decane or pinacolone, 0.1 mmol) in toluene (0.5 mL) and 9-BBN (a few crystals) added. The solution was cooled to the required temperature, the flask purged with nitrogen and the required stannane (0.11 mmol) in toluene (0.5 mL) added. The reaction mixture was stirred at the required temperature until TLC analysis indicated the absence of starting halide (ca. 1-2 h). The solution was warmed to room temperature and analyzed directly by GC .

ACKNOWLEDGMENTS

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