Remarkable Lewis acid mediated enhancement of enantioselectivity during free-radical reductions by simple chiral non-racemic stannanes

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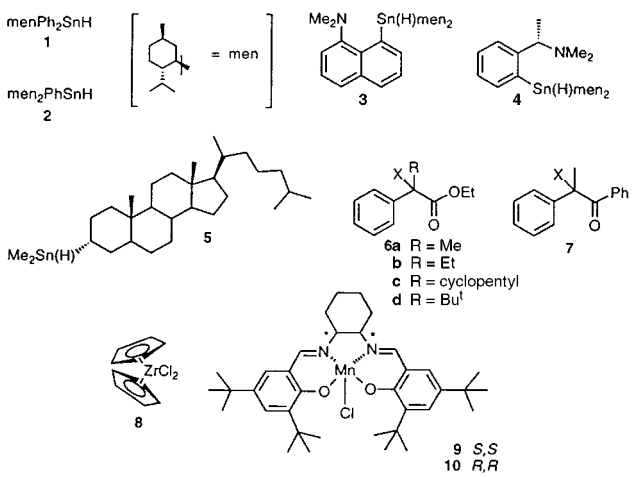
Additions of 1 equiv. of achiral and chiral Lewis acids to free-radical reduction reactions involving (1*S*,2*S*,5*R*)-menthyldiphenyltin hydride 1, bis[(1*S*,2*S*,5*R*)-menthyl]-phenyltin hydride 2, bis[1*S*,2*S*,5*R*)-menthyl][8-(*N*,*N*-dimethylamino)naphthyl]tin hydride 3, bis[(1*R*,2*S*,5*R*-menthyl]{1-(*S*)-*N*,*N*-dimethylaminoethyl]phenyl}tin hydride 4 or 3α-dimethylstannyl-5α-cholestane 5 result in remarkable increases in enantioselectivity.

Despite there being numerous reports of free-radical reactions proceeding with diastereocontrol,[1,2] there are relatively very few examples of free-radical reactions which proceed with genuine enantiocontrol.[2] The majority of examples that demonstrate enantioselective outcomes involve the use of chiral auxiliaries and, as a result, are further examples of diastereoselectivity in free-radical chemistry.[1,2] Of the remaining few reports, the introduction of asymmetry in the substrate through the use of chiral Lewis acid mediation,[3,4] and in the reagent through the use of chiral ligands on the tin atom in suitably constructed stannanes[5–8] have been the methods of choice for achieving enantioselectivity in radical chemistry.

Our approach to the development of synthetically useful chiral stannanes primarily involves the judicious choice of ligand from the multitude of compounds available in the natural chiral pool. Here we report that significant improvements in enantioselectivity during asymmetric reductions involving chiral non-racemic stannanes are achieved by the addition of Lewis acids.

(1*S*,2*S*,5*R*)-Menthyldiphenyltin hydride **1**, bis[(1*S*,2*S*,5*R*)-menthyl)phenyltin hydride **2** and 3α-dimethylstannyl-5α-cholestane **5** were prepared previously within our group.[9] The remaining hydrides **3** and **4** were prepared by reaction of the appropriate aryllithium with bis[(1*S*,2*S*,5*R*)-menthyl]phenyltin chloride followed by $LiAlH_4$ reduction.[9,10] Substrates chosen for this work include bromides **6** (X = Br) employed by Metzger and co-workers in their recent study[8] and the ketone **7** used by Curran and Nanni;[6] in this manner a direct comparison with previous work is possible.



In this study, reductions were carried out at concentrations of approximately 0.1 M of the substrate in to which 1.0 equiv. of the Lewis acid† of choice and 1.1 equiv. of the stannane were added in toluene at −78 °C, initiated using 9-BBN.[11] Reactions were carried out until TLC analysis indicated the absence of starting material (*ca.* 1–2 h) at which time the reaction mixtures 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 **6** and **7** (X = H) against an internal standard (either octane or undecane). Reduced compounds **6** and **7** (X = H) were identified by comparison of their GC retention times with those of the authentic compounds. The absolute configuration of the dominant isomer in each case was assigned by comparison with the GC retention times of the (*S*)-products **6** and **7** prepared and resolved following literature procedures.[12]

Table 1 lists enantioselectivity data for the model substrates **6** and **7** reacting with bis[(1*S*,2*S*,5*R*)-menthyl]phenyltin hydride **2** at −78 °C in toluene in the absence of any additive and in the presence of 1 equiv. of BF_3, zirconocene dichloride **8**, (*S*,*S*)-(−)- and (*R*,*R*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalycidene)-1,2-diaminocyclohexanemanganese(III) chloride **9** or **10**.[13]

Inspection of Table 1 reveals some interesting features which aid in our understanding of the factors which goven the

Table 1 Enantioselectivities observed for reactions involving bis-[(1*S*,2*S*,5*R*)-menthyl]phenyltin hydride **2** in toluene at −78 °C[a]

Entry	Substrate	Lewis acid	Ee[a] (%)	Conversion[b] (%)
1	**6a**	None	2	80
2	**6a**	BF_3	32	64
3	**6a**	**8**	36	58
4	**6a**	**9**	60	81
5	**6a**	**10**	55	59
6	**6b**	None	4	81
7	**6b**	BF_3	20	68
8	**6b**	**8**	46	52
9	**6b**	**9**	86	75 (71)[c]
10	**6b**	**10**	84	69
11	**6c**	None	9	81
12	**6c**	BF_3	30	79
13	**6c**	**8**	35	74
14	**6c**	**9**	80	82 (70)[c]
15	**6c**	**10**	78	75
16	**6d**	None	6	82
17	**6d**	BF_3	10	76
18	**6d**	**8**	60	68
19	**6d**	**9**	80	72
20	**6d**	**10**	83	52
21	**7**	None	16	81
22	**7**	BF_3	12	69
23	**7**	**8**	52	92
24	**7**	**9**	52	76
25	**7**	**10**	50	60

[a] All reductions gave the (*S*)-product. [b] GC conversion. [c] Isolated yield.

Table 2 Enantioselectivities observed for reactions involving zirconocene dichloride **8** and (*S*,*S*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalycidene)-1,2-diaminocyclohexanemanganese(III) chloride **9** and its enantiomer **10** in toluene at −78 °C

Entry	Substrate	Lewis acid	Stannane	Ee (%)	Yield[a] (%)
1	**6a**	**8**	**1**	36 (*S*)	59
2	**6a**	**8**	**3**	38 (*S*)	77
3	**6a**	**8**	**5**	60 (*S*)	82
4	**6a**	**9**	**1**	60 (*S*)	82
5	**6a**	**9**	**4**	90 (*R*)	73 (68)[e]
6	**6a**	**9**	**5**	34 (*S*)	58
7	**6b**	**8**	**1**	42 (*S*)	51
8	**6b**	**8**	**3**	52 (*S*)	79
9	**6b**	**8**	**5**	54 (*S*)	54
10	**6b**	**9**	**2**	70 (*S*)	78
11	**6b**	**9**	**4**	72 (*S*)	68
12	**6b**	**9**	**5**	62 (*S*)	67
13	**6b**	**10**[b]	*ent*-**2**[c]	86 (*R*)	72
14	**6c**	**9**	**4**	96[d] (*S*)	75 (67)[c]
15	**6d**	**8**	Bu_3SnH	0 (—)	—
16	**6d**	**8**	**1**	58 (*S*)	63
17	**6d**	**8**	**3**	62 (*S*)	87
18	**6d**	**8**	**5**	76 (*S*)	96
19	**6d**	**9**	Bu_3SnH	8 (*S*)	—
20	**6d**	**9**	**1**	72 (*S*)	74
21	**6d**	**9**	**4**	80 (*S*)	76
22	**6d**	**9**	**5**	82 (*S*)	72 (68)[e]
23	**7**	**8**	**1**	50 (*S*)	68
24	**7**	**8**	**3**	56 (*S*)	62
25	**7**	**8**	**5**	42 (*S*)	79
26	**7**	**9**	**1**	58 (*S*)	81
27	**7**	**9**	**3**	46 (*S*)	85
28	**7**	**9**	**4**	62 (*S*)	74
29	**7**	**9**	**5**	52 (*S*)	72

[a] GC conversion. [b] The enantiomer of **9**. [c] Bis[(1*R*,2*R*,5*S*)-menthyl]phenyltin hydride. [d] See footnote ¶. [e] Isolated yield.

stereochemical outcome in the reactions of interest. Firstly, a Lewis acid is crucial in obtaining reasonable enantioselectivities. Experiments carried out in the absence of these Lewis acids give significantly poorer ees. For example, addition of 1 equiv. of BF_3 to the reaction involving **6b** (X = Br) results in an increase in enantioselectivity from 4 to 20%. Increasing Lewis acid bulk results in further increases; 46% ee is observed with the addition of zirconocene dichloride **8**, while addition of **9** results in a remarkable improvement in ee to a value of 86%. It is interesting to note that the (*S*)-isomer of the product dominates in all of the reductions listed in Table 1. It is also important to note, when the reduction of **6b** (X = Br) was repeated with the enantiomer of **2**, bis[(1*R*,2*R*,5*S*)-menthyl]phenyltin hydride, in the presence of **10**, (*R*)-**6b** (X = H) was obtained with an ee of 86% under the same reaction conditions.

Despite the obvious benefit derived by the presence of the Lewis acid, chirality transfer appears to originate with the ligand on tin because the achiral Lewis acid **8** itself has a remarkable effect on the stereochemistry of the reaction in question. In addition, both enantiomeric forms of *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-diaminocyclohexanemanganese(III) chloride, namely **9** and **10**, result in enantioselectivities within a few percent of each other and with the same enantiomeric form of the reduced substrate dominating.

Table 2 lists the effect that different stannanes have on the observed enantioselectivities at −78 °C for reactions involving Lewis acids **8**, **9** and (for one example) **10**. It should be noted that the achiral stannane, tributyltin hydride, reacts with **6d** (X = Br) in the presence of Lewis acids **8** and **9** to afford **6d** (X = H) with 0 and 8% ee, respectively. The former result is expected; the latter result demonstrates, one again, that chirality in the stannane is more important than that in the Lewis acid.

The reader's attention is drawn to the numerous examples provided in Tables 1 and 2 where the observed enantioselectivity exceeds 80% and the two examples (entries 5 and 14, Table 2) of ees ⩾ 90%. These results are significant as they represent the highest-ever reported enantioselectivities in stannane reduction chemistry,[1,4,14]§ the 96% ee observed for the reaction of **6c** (X = Br) with **4** in the presence of **9** being truly remarkable; indeed, this result exceeds the highest ee achieved in any free-radical reaction.[1,15,16] We believe that, consistent with previous models proposed to account for diastereoselective outcomes in radical reactions,[1–4] the profound increases in enantioselectivity observed upon addition of the Lewis acids in this study are a result of the significant increases in steric bulk[17] associated with the ester group during coordination of the carbonyl moiety of the boron or metal centre in BF_3, **8**–**10**.

In order to explore the synthetic utility of the use of these reagents and catalysts, we repeated the reduction of several substrates in the presence of **9** (entries 9, 14 in Table 1; 5, 14, 22 in Table 2). We were delighted to isolate the reduction products **6** (X = H) in 67–71% yield after workup and chromatography; GC analysis provided ees as listed.¶

We are currently exploring immobilisation of these chiral reagents onto polymer support and the use of catalytic chiral stannane reductions. We thank the Australian Research Council for financial support.

Notes and references

† The use of less than 1.0 equiv. results in noticeably lower ees, while greater amounts provide no increases in ee.

‡ Enantioselectivities were determined by gas chromatographic analyses of the reaction mixtures using a chiral trifluoroacteylated γ-cyclodextrin (Chiraldex™ G-TA, 30 m × 0.25 mm) capillary column purchased from Alltech.

§ To the best of our knowledge, the value of 61% reported by Hoshino and co-workers represents the previous record, see ref. 1, 4, 13. Roberts has reported recently some enantioselective hydrosilation reactions which proceed with ees approaching 95%, see ref. 16.

¶ 96% ee for entry 14 in Table 2 represents a GC-determined lower limit.

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