Enantioselectivity of the Transfer of Hydrogen Atoms to Acyclic Prochiral Carbon-Centred Radicals Using Chiral Tin Hydrides

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Racemic α-bromo esters 2 have been reduced via prochiral radicals 5 with low to moderate enantioselectivities using chiral tin hydrides 1 with a stereogenic tin atom containing chiral 2-[1-di dimethylaminoalkyl]phenyl ligands. The tin hydrides 1 were mixtures of diastereomers. It could be shown that the minor diastereomer of tin hydrides 1a and 1b reacts with good enantioselectivity whereas the major diastereomer reacts almost unselectively. The observed enantioselectivities are also strongly influenced by steric effects of the substituents attached to the radical core.

Introduction
The stereoselectivity of intermolecular reactions of acyclic alkyl radicals has been a subject of considerable interest[1]. Little is known about the enantioselectivity of the free-radical transfer of hydrogen atoms. The enantioselective abstraction of hydrogen atoms from racemic carboxylates by chiral amine-boryl radicals giving rise to kinetic resolution was described by Roberts et al.[2]. We have recently reported on the first examples of the enantioselective transfer of hydrogen atoms from chiral tin hydrides to prochiral α-ester radicals[3][4]. Quite recently, the first results of the enantioselective hydrogen transfer using tin hydrides containing a C2-symmetric binaphthyl moiety have been reported independently by us[5] and others[6]. We have now investigated the enantioselectivity of the free-radical reduction of some α-bromo esters using chiral tin hydrides with a stereogenic tin atom containing chiral 2-[1-dimethylaminoalkyl]phenyl ligands (DAAP). These reactions, which give the enantiomerically pure reduction products directly, are examples of a stereoselectivity in which a chiral reagent distinguishs between the enantiotopic faces of a radical in diastereomeric transition states (Figure 1) and are different from enantioselective reactions with chiral auxiliaries coordinated to the radical as described, for example, by Murakata et al.[7].

Results
Tin hydrides that contain chiral ligands are hydrogen donors which, in principle, can trap prochiral radicals enantioselectively without loss of chirality under free-radical conditions. We synthesized tin hydrides 1a–f with a chiral DAAP ligand[8], hoping that the alkyl groups linked to the tin atom might cause a strong repulsive steric interaction with the alkyl group at the stereogenic centre of the chiral DAAP ligand and lead to the formation of one favoured diastereomer. However, we obtained mixtures of diastereomers which could not be separated, comparable to the results of Schumann et al.[9]. The diastereomers are configurationally stable at the tin atom[9].

Table 1. Diastereomeric ratios of tin hydrides 1a–f

<table>
<thead>
<tr>
<th>dr</th>
<th>1a</th>
<th>1b</th>
<th>1c</th>
<th>1d</th>
<th>1f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58:42</td>
<td>80:20</td>
<td>66:34</td>
<td>51:49</td>
<td>57:43</td>
</tr>
</tbody>
</table>

Tin hydrides 1 proved to be very efficient free-radical reducing agents[10]. α-Bromo esters 2 were readily reduced without any initiator added, even at −30°C (Scheme 1). Transfer of hydrogen from tin hydride 1 to prochiral radicals 5 leads to the formation of (S)-4 and (R)-4, the ratio of which was determined by GC analysis. The reaction of α-bromo ester 2a with tin hydride 1a at −30°C led to the reduction products in a ratio of [(S)-4a]/[(R)-4a] = 55:1:44.9 (10% ee) (Table 2, entry 1). By changing the configuration...
of the DAAP ligand from tin hydride 1a to tin hydride 1b, inversion of the enantioselectivity is observed (Table 2, entries 1–3; Table 3, entry 1). Variation of the alkyl substituent R^2 of the α-bromo ester 2 shows that the stereoselectivity is strongly influenced by the steric effect of R^2. It is thus remarkable that the enantiomeric ratio of the reduction products 4 (Figure 2) decreases on going from [(S)-4]/[(R)-4] = 55.1:44.9 (R^2 = Me, Table 2, entry 1) through 54.5:45.5 (R^2 = Et, entry 4) to 51.8:48.2 (R^2 = iPr, entry 7) and is reversed and dramatically increased to 37.4:62.6 (R^2 = tBu, Table 3, entry 2). In contrast, α-bromo ester 2e is reduced unselectively (R^1 = nBu, R^2 = Me, Table 2, entry 10). We measured the temperature dependence of the enantioselectivity of the reduction of α-bromo esters 2a–d (Tables 2, 3). The enantioselectivity decreases with rising temperature. The temperature effect was found to be different for 2d > 2a > 2b > 2c.

### Scheme 1

![Scheme 1](image)

Table 2. Enantioselectivity of the reduction of α-bromo esters 2a–e with tin hydride 1a in the temperature range from −30 to 66°C.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>T °C</th>
<th>Reaction time</th>
<th>Conversion of [(S)-4]/[(R)-4] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−30</td>
<td>10</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>1</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>0.5</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>−30</td>
<td>48</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>3</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>12</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>3</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>66</td>
<td>1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>10</td>
<td>−30</td>
<td>48</td>
<td>82</td>
</tr>
</tbody>
</table>

[a] (1a)/(2) = 1.5:1; solvent: THF.

Table 3. Enantioselectivity of the reduction of α-bromo ester 2a at 20°C and of 2d in the temperature range from −30 to 66°C by tin hydride 1b[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>2</th>
<th>T °C</th>
<th>Reaction time</th>
<th>Conversion of [(S)-4]/[(R)-4] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>1.2</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>d</td>
<td>1.5:1</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>d</td>
<td>2.1</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>1.8</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>d</td>
<td>1.5:1</td>
<td>66</td>
<td>0.5</td>
</tr>
</tbody>
</table>

[a] Solvent: THF.  
[b] Tin hydride 1b was completely consumed at the end of the reaction.

The enantioselectivity of the reduction of α-bromo ester 2d (Table 3, entries 3–4) depends on the ratio of tin hydride and substrate. For example, using a substrate ratio of [1b]/[2d] = 2:1, α-bromo ester 2d was completely reduced and the enantiomeric ratio of the product was [(S)-4d]/[(R)-4d] = 53.2:46.8 at 20°C (Table 3, entry 3). However, using an excess of α-bromo ester 2d ([1b]/[2d] = 1.8) (Table 3, entry 4), tin hydride 1b was completely consumed at the end of the reaction and the enantiomeric ratio of [(S)-4d]/[(R)-4d] = 61.5:38.5 was significantly increased, which means that the major diastereomer of tin hydride 1b reacts faster and less selectively than the minor diastereomer.

We synthesized tin hydride 1d with a tBu group instead of a Me group at the stereogenic centre of the DAAP ligand to investigate the influence of this substituent on the enantioselectivity of the hydrogen transfer. Surprisingly, we found that α-bromo ester 2 was reduced almost unselectively by tin hydride 1d. The selectivity observed for the reduction of 2a at room temperature was [(S)-4a]/[(R)-4a] = 49.1:50.9 (Table 4, entry 2). Tin hydride 1e with the same DAAP ligand and the smaller nBu group at the tin centre showed improved but still low enantioselectivity for the reduction of α-bromo ester 2a, compared to tin hydride 1d [(S)-4a]/[(R)-4a] = 47.7:52.3 (Table 4, entry 1). The reversed enantioselectivity, compared to the results using tin hydride 1a (Table 2, entry 2), is most remarkable.

Table 4. Enantioselectivity of the reduction of α-bromo ester 2a by tin hydrides 1c–f at room temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>Reaction time</th>
<th>Conversion of [(S)-4]/[(R)-4] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c</td>
<td>1.5:1[a]</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>d</td>
<td>1.3:b</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>e</td>
<td>1.5:1[a]</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>f</td>
<td>1.5:b</td>
<td>2</td>
</tr>
</tbody>
</table>

[a] Solvent: THF.  
[b] Solvent: diethyl ether.

Tin hydride 1f gave low enantioselectivities as well. For example, α-bromo ester 2a was reduced at room temperature to give [(S)-4a]/[(R)-4a] = 50.4:49.6 (Table 4, entry 4). Tin hydride 1e proved to be completely unselective in the reduction of α-bromo ester 2a (Table 4, entry 3).
Discussion

The enantioselectivity of the hydrogen transfer is a result of the differentiation between the Re and Si face of the radicals 5 by the chiral tin hydride in the transition state. As can be seen from the results summarized in Tables 2–4, the observed enantioselectivities depend on the tin hydride used and on the substituents attached to the radical centre. The enantioselectivity is linearly correlated with the steric effect of the α substituent R 2 at the radical centre, decreasing with increasing steric effect of substituent R 2 going from methyl through ethyl to isopropyl and is reversed and highest for R 2 = tBu (2d) (Figure 2). This can be rationalized by considering the differences of the steric effects of the substituents R = Ph and R 2. It can be seen that with smaller differences in the steric effects between the largest substituent represented by the phenyl group (A value[11] = 1.79 kcal/mol) and the medium-sized alkyl substituent in radical 5a (R 2 = Me, A value = 1.74 kcal/mol), 5b (R 2 = Et, A value = 1.79 kcal/mol) and 5e (R 2 = iPr, A value = 2.21 kcal/mol) the observed enantioselectivities decrease. By introducing the tBu group (A value = 4.9 kcal/mol) to the radical centre in 5d, the preferred reduction product is the opposite enantiomer because in this case, the largest substituent is represented by the tBu group and the medium-sized one by the phenyl group. The COOMe (A value = 1.27 kcal/mol) group is the smallest substituent in all cases.

Figure 2. Correlation of the enantioselectivity of the hydrogen transfer from tin hydrides 1a and 1b to acyclic radicals RPhCOOMe 5a–d with steric substituent parameter A[11] of the alkyl substituents R (Table 2, entries 2, 5, 8); the inversed value of the enantiomeric ratio of reduction product 4d (Table 3, entry 4) was used.

Radical 5e is reduced unselectively. This can be explained by a preferred conformation of radical 5e in the transition state of hydrogen transfer. The alkyl groups are turned away from the attacking H donor. In this conformation no discrimination between the enantiotopic faces of the radical is possible (Figure 3). This also explains why radicals 5a and 5b show similar selectivities.

A remarkable and very important result is the difference in the reactivities and selectivities of the diastereomers of tin hydrides 1a and 1b. The major diastereomer reacts faster and almost unselectively. In contrast, the minor diastereomer reacts more slowly and with higher enantioselectivity. This can be rationalized considering the probable structures of the two diastereomers. The only existing X-ray structure analysis of a comparable tin hydride, tert-butyl[8-(dimethylamino)naphthyl][(−)-menthy]tin hydride, gives evidence for a very weak donor–acceptor interaction of the dimethylamino group and the tin atom trans to the tert-butyl group.[12]

Assuming the same donor–acceptor interaction in the case of tin hydrides 1[8], the configuration of the two diastereomers can be obtained as given in Figure 4 for tin hydride 1b. An inspection of the possible transition states of the hydrogen transfer to radicals 5 leads to a straightforward rationalization of the observed enantioselectivities (Figure 4). Based on steric effects in the transition state of the hydrogen transfer, in which the donor, hydrogen, and acceptor atoms assume a linear arrangement S (Sn–H–C), diastereomer (R 2,S 2)-1b should be able to distinguish between the faces of prochiral radicals such as 5d (Figure 4a). In this transition state, the small substituent S = COOMe at the radical centre is presumably oriented beneath the dimethylamino group, the medium-sized substituent M = Ph is oriented beneath the methyl group and the large substituent L = tBu is oriented in the least sterically hindered space between the tBu and the Ph ligands of the tin hydride. Based on this model, the selective formation of (S)-4d is expected upon reduction of the a-bromo ester 2d via radical 5d. In the case of the reduction of a-bromo ester 2a via radical 5a, the selective formation of (R)-4a was expected and observed. On the other hand, diastereomer (R 2,S 2)-1b should not be able to differentiate between the enantiotopic faces because the spaces between the tBu and the Ph ligands and between the tBu and the DAAP ligands are approximately equal (Figure 4b). Thus, assuming an approximately unselective reduction by the major diastereomer (R 2,S 2)-1b, the enantioselectivity of the reduction of radical 5d by the minor diastereomer (R 2,S 2)-1b can be calculated from the data in Table 3 (entries 3 and 4) to be close to 100% at 20°C. This simple steric model of the interaction of hydrogen donor and acceptor in the transition state can also explain the other experimental results, such as the almost unselective reduction of a-bromo esters 2 by tin hydride 1d. An inspection of the possible transition state of hydrogen transfer from diastereomer (S 2,R 2)-1d to radical 5a indicates that the small substituent S = COOMe is oriented beneath the tBu group, the medium-sized substituent M = Me is oriented beneath the dimethylamino group and the large substituent L = Ph is oriented in the space between the phenyl group and the tBu.
ligand (Figure 5) to give (R)-4a with low selectivity, because the steric effect of the dimethylamino group is comparable to that of the tBu group. Diastereomer (S,C,S,S)-1d is expected to react completely unselectively, comparable to (R,C,R,S)-1b (Figure 4b). The selectivities of tin hydrides 1c and 1f can be explained analogously. Tin hydride 1e, bearing two phenyl ligands, is also expected to reduce radicals 5 unselectively, comparable to the unselective diastereomer of tin hydride 1b (Figure 4b).

Figure 4. Probable transition-state structures of the hydrogen transfer to radical 5d from (a) the minor diastereomer (R,C,S,S)-1b, which is expected to occur selectively, and (b) the major diastereomer of tin hydride (R,C,R,S)-1b, which is expected to occur unselectively.

Figure 5. Probable transition-state structure of the hydrogen transfer to radical 5a from diastereomer (S,C,R,S)-1d of tin hydride 1d, which is expected to reduce with very low selectivity.

Conclusion

With the increasing use of radical reactions in organic chemistry, a more detailed understanding of the selectivities is of great importance. Especially important is the knowledge of the enantioselectivity of hydrogen transfer and the possibility of controlling it, since this step is frequently the decisive product-forming step in radical reactions. It has been shown that the enantioselectivity of hydrogen transfer from chiral tin hydrides to prochiral radicals is determined by steric interactions between the hydrogen donors and the prochiral radicals. The observed selectivities are strongly influenced by the steric effects of the substituents attached to the radical centre. The selectivities for the minor diastereomers of tin hydrides 1a and 1b are shown to be good. This shows that we have to focus on the synthesis of enantioomerically pure tin hydrides.

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Experimental Section

Melting points: Laboratory Devices Mel-Temp. – 1H (300.1 MHz) and 13C (75.47 MHz) NMR: Bruker AM 300, tetramethylsilane (TMS) as internal standard for 1H NMR, solvent signals for 13C NMR. – MS: Finnigan MAT 212; MAT 95 for HRMS. – Elemental analysis: FA 1108 CHNS-O Fisons Instr. or Mikroanalytisches Labor Beller, D-37004 Göttingen, Germany. – Analytical GC: Carlo Erba HRGC with FID detector and 25-m capillary column and heptakis(2,6-di-O-methyl-3-O-pentyl)-β-cyclodextrine phase diluted in 50% of OV-1701. Products were identified by comparison to retention times of independently synthesized reference compounds. – Tin hydrides 1 were synthesized as described[10]. All reactions with organometallic compounds were carried out using standard Schlenk techniques under dry, oxygen-free argon.

Methyl rac-2-Bromo-2-phenylpropanoate (2a): 2-Phenylpropionic acid (1.34 g, 8.9 mmol) and 0.89 g (10 mmol) of NBS were dissolved in 20 ml of dry CCL4. This suspension was irradiated with a 300-W sun lamp. After a short time, the reaction mixture started to reflux. The reaction was monitored by GC analysis. After complete conversion of the starting compound, the reaction mixture was cooled to 0°C and stirred for 20 min. The solid was filtered off and washed with small portions of CCL4. The solvent was removed from the filtrate at reduced pressure. For esterification, diazomethane was added to the residue. After removal of the solvent the product was distilled at reduced pressure yielding 1.7 g (79%) of 2a, b.p. 119–121°C/3 Torr[14a][14b]. – nD20 = 1.5396.

Methyl rac-2-Bromo-2-phenylbutanoate (2b): In a 100-ml conical flask with reflux condenser and drying tube, 8.2 g (50 mmol) of 2-phenylbutanoic acid and 4.7 ml (13.5 g, 50 mmol) of phosphorous tribromide were heated at 60°C for 1 h. After cooling to room temperature, the lower layer was removed. Then 3.2 ml (10 g, 62.5 mmol) of bromine was added carefully through the condenser and the resulting mixture was heated at 100°C for 6 h. Small portions of bromine were added during this time until the colour of the bromine did not disappear. After completion of the reaction, the solution was cooled to 0°C and 25 ml of dry methanol was added. After the addition, the resulting solution was stirred for 1 h and was decolorized by addition of Na2CO3. Filtration and removal of the solvent gave the crude product which was distilled at reduced pressure yielding 8.61g (67%) of 2b, b.p. 117°C/3 Torr[14a][14b]. – nD20 = 1.5409. – 1H NMR (CDCl3): δ = 2.7 (m, 2 H, 3-H), 1.11 [d, 3 H, 4-H], 3.79 (s, 3 H, OCH3), 2.5 (m, 2 H, 3-H), 1.0 (t, 3 H, 4-H). – 13C NMR (CDCl3): δ = 171.04 (C=O), 139.69, 128.32, 128.17, 126.96, 69.97 (C-Br), 53.34 (OCH3), 35.62 (C-3), 10.46 (C-4).

Methyl rac-2-Bromo-3-phenylpropanoate (2c): Analogously to the preparation of 2b, 1 g (15.62 mmol) of 3-methyl-2-phenylbutanoic acid was treated with PBr3/Br2 followed by the addition of methanol. The product was obtained after distillation at reduced pressure yielding 1.99 g (47%) of 2c, b.p. 105–107°C/1.5 Torr. – nD20 = 1.5496. – 1H NMR (CDCl3): δ = 7.4–7.5 (5 H, aromatic H), 3.7 (s, 3 H, OCH3), 2.72 (m, 1 H, 3-H), 1.11 [d, 3 J(CH2CH3) = 6.47 Hz, 3 H, CH3], 0.848 [d, 3 J(CH2CH3) = 6.61 Hz, 3 H, CH3]. – 13C NMR (CDCl3): δ = 170.85 (C=O), 138.16, 128.44, 128.02, 127.84, 58.46.

Enantioselectivity of the Transfer of Hydrogen Atoms

Methyl rac-2-Bromo-3,3-dimethyl-2-phenylbutanoate (2d): Analogously to the preparation of 2a, 4.2 g (20.4 mmol) of methyl 3,3-dimethyl-2-phenylbutanoate was treated with 5.5 g (61.2 mmol) of NBS for 24 h. The product was purified by column chromatography and distillation at reduced pressure. The product solidified after standing at room temperature, yielding 3.9 g (67%) of 2d, m.p. 52–54°C (methanol), b.p. 145–147°C/3 Torr. – 1H NMR (CDCl3): δ = 7.39–7.47 (m, 2 H, aromatic H), 7.35–7.26 (m, 3 H, aromatic H), 3.74 (s, 3 H, OCH3), 2.11 (m, 2 H, 5-H), [10] E. Vedejs, S. M. Duncan, A. R. Haight, J. Org. Chem. 1993, 58, 4046–4050. – 13C NMR (CDCl3): δ = 170.76 (C=O), 137.53, 128.35, 127.79, 126.92 (aromatic C), 57.98 (CBr), 52.62 (OCH3), 40.59 [C(CH3)3], 27.53 [br., C(CH3)3] – MS/CI (isobutane); m/z (%): 285/283 (14/15) [MH+] , 205 (100) [M+ – Br] – MS/EI (70 eV); m/z (%): 230 (54), 228 (56), 198 (31) [C12H15BrO2], 196 (31) [C12H15OBr], 91 (56) [C12H7], 73 (44) [C12H12O2], 73 (100) [C12H12], – C13H17BrO2: calcd. C 45.58, H 7.23, found 45.66, H 6.31.

Methyl rac-2-Bromo-2-ethyl-hexanoate (2e): Analogously to the preparation of 2h, 10 g (69.8 mmol) of 2-ethylhexanoic acid was treated with PBr3/Br2 followed by esterification with methanol. The crude product was distilled at 1 Torr with a 30-cm Vigreux column yielding 13.6 g (83%) of 2e, b.p. 88°C/1 Torr. – 1H NMR (CDCl3): δ = 3.74 (s, 3 H, OCH3), 2.11 (m, 2 H, 5-H), 2.04 (m, 2 H, 4-H), 1.31 (m, 2 H, 3-H), 1.29 (m, 2 H, CH2CH3), 0.94 (t, J = 7.31 Hz, 3 H, CH3), 0.88 (t, J = 6.99 Hz, 3 H, 6-H). – 13C NMR (CDCl3): δ = 171.38 (C=O), 68.77 (CBr), 52.82 (OCH3), 39.32 (CH2CH3), 32.93 (C-3), 27.63 (C-4), 22.46 (C-5), 13.75 (CH2CH3), 9.92 (C-6). – MS/CI (isobutane); m/z (%): 239/237 (89/100) [MH]+, 157 (34) [M+ – Br] – MS/EI (70 eV); m/z (%): 182/180 (25/23) [M+ – C2H5], 157 (57) [M+ – Br], 125 (26) [C8H12O2], 97 (100) [C10H14]+, 87 (21) [C10H12O2], 73 (24) [C10H10O2], 56 (92) [C10H6]. – C13H17BrO2 (237.1): calcd. C 45.58, H 7.23; found C 45.69, H 7.23.

Reduction of α-Bromo Esters 2: A typical reduction experiment was performed as follows: To a solution of 0.1–1 mmol of the α-bromo ester 2 in 1–10 ml of THF, a corresponding amount of tin hydride was added (see Tables 2–4). The reaction was monitored by GC analysis. The solvent was removed in vacuo and the residue was treated with pentane. A white solid formed which was filtered off. The pentane solution was filtered through a short column of silica gel and the products were eluted with pentane/diethyl ether (20:1). The enantiomeric ratio was determined by GC analysis. The products were identified by comparison to retention times of independently synthesized reference compounds.

Dedicated to Professor Manfred Weidenbruch on the occasion of his 60th birthday.