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Single enantiomer free-radical chemistry—Lewis acid-mediated reductions of racemic halides using chiral non-racemic stannanes

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Abstract—Additions of one to two equivalents of Lewis acids that include magnesium salts to free-radical reduction reactions involving ester functionalized radicals and (1*R*,2*S*,5*R*)-menthyldiphenyltin hydride **4**, bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride **5**, tris((1*R*,2*S*,5*R*)-menthyl)tin hydride **6**, bis((1*R*,2*S*,5*R*)-menthyl)-[8-(*N*,*N*-dimethylamino)naphthyl]tin hydride **12**, bis((1*R*,2*S*,5*R*)-menthyl)-[1-((*S*)-*N*,*N*-dimethylaminoethyl)phenyl]tin hydride **13** or 3α-dimethylstannyl-5α-cholestane **14** result in remarkable enantioselectivities. Examples include (*S*)-naproxen ethyl ester **16**, produced in 74% yield and greater than 99% ee at −78°C from the bromide and **5** in the presence of $MgBr_2$, and ethyl (*R*)-*N*-trifluoroacetyl-D-phenylglycinate **18**, obtained in 78% yield and 99% ee under identical conditions. Kinetic and computational studies provide insight into the origins of these observations.

1. Introduction

The synthetic chemists' toolbox is filled with well-established techniques that have matured over time to the extent that impressive regio- and stereochemical outcomes are routinely possible for a wide cross-section of transformation types. The large majority of these techniques are based on ionic chemistry that often require a suite of protection protocols in order to achieve the desired outcome, indeed 'protecting group chemistry' is in itself a mature discipline. In contrast, free-radical chemistry, with its inherent tolerance of a variety of functional groups, has until recently, existed largely under the shadow of its older, more mature sibling. It is fair to say that during the 20 year period 1970–1990, radical chemistry underwent a series of remarkable transformations that effectively drew to a close the era in which free radicals were considered to give rise only to intractable tars or polymers. While this period revolutionized synthetic chemists' attitudes toward free-radicals,[1] only the polymer industry has, to date, enthusiastically embraced the large-scale use of radical technology for the preparation of a wide cross-section of useful products. While this chemistry is now commonplace for the construction of niche ring systems, the ability to control the stereochemical outcomes of free-radical reactions has presented a more difficult problem. Despite advances made in the control of diastereoselectivity by the late eighties, only low levels of enantiocontrol had been achieved by the mid-nineties.

The importance of single-enantiomer outcomes in synthesis cannot be overstated. In 1999, 33% of all dosage form drug sales were single enantiomer formulations; this had risen to 40% in 2001. In addition, 80% of new drugs entering development are enantiomerically pure, a consequence of the pharmacological importance of chirality and the ever-tightening restrictions on the composition of pharmaceutical preparations imposed by regulatory authorities. It is not surprising therefore, that the design of reagents for achieving high enantioselectivities during free-radical transformations is an objective that continues to occupy several research groups around the world.[2]

Chiral stannanes on their own have generally been ineffective in providing synthetically useful outcomes,[3–6] primarily, we believe, because of the large (ca. 3.5 Å) tin–carbon separation in the transition state for delivery of hydrogen atom from the stannane to the carbon-centered radical in question.[7] Thus, menthyl-substituted stannanes examined by us,[3] the chiral, nitrogen-coordinated stannanes **1** of Metzger,[4] and the C_2-symmetric

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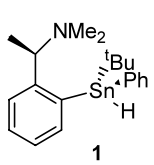
reagents **2** reported independently by Curran[5] and Metzger[6] provide enantioselectivities of up to 52% in their reactions with a series of simple pro-chiral radicals.



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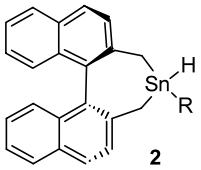

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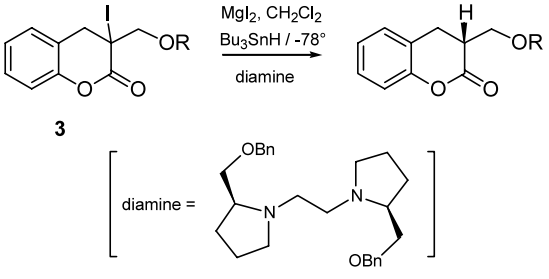
Recently, we demonstrated that steric interactions are largely responsible for the subtle changes in rate constant observed during the delivery of a hydrogen atom from a series of alkyldiphenylstannanes to primary alkyl radicals.[8] With this in mind, we reasoned that increases in steric bulk on either the substrate or reagent involved in enantioselective free-radical reductions may well lead to improvements in enantioselectivity. In particular, addition of Lewis acids to reactions in which the carbon-centred radical involved contains a binding site for that Lewis acid may achieve the required objective.

Several workers report the use of chiral Lewis acid catalysts to achieve enantioselective outcomes in free radical reduction chemistry,[2,9] the most successful of these being the group of Hoshino who achieved 61% ee during the reduction of coumarin **3** with Bu_3SnH in the presence of a chiral Lewis acid (Scheme 1).[10] The work described herein differs in that the source of chiral recognition is the chiral stannane itself. We now report that addition of a wide cross-section of Lewis acid types to low-temperature reductions of radicals bearing ester functionalities by simple chiral non-racemic stannanes, such as bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride, routinely proceed with enantioselectivities in excess of 90%.[11] Examples include naproxen, ibuprofen and natural and unnatural amino acids which are routinely prepared in greater than 99%ee by this method.



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Scheme 1.

2. Results and discussion

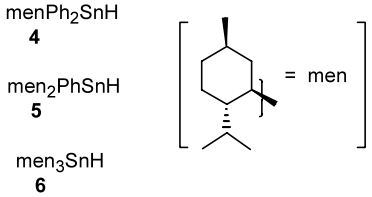
2.1. Reactions with simple substrates

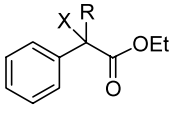
(1*R*,2*S*,5*R*)-Menthyldiphenyltin hydride **4**, bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride **5** and their enantiomers have been prepared previously within our group,[12] while both enantiomers of tris((1*R*,2*S*,5*R*)-menthyl)tin hydride **6** were prepared by the method of Jousseaume.[13] Initial substrates chosen for this work include bromides **7** (X = Br) employed by Metzger et al. in their recent study and the ketone **8** used by Curran and Nanni;[5] 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 into which 1.0 equivalent of the Lewis acid (see below) of choice and 1.1 equivalents of the stannane were added in toluene at −78°C initiated using 9-BBN,[14] or triethylborane.[5,15] 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 **7** and **8** (X = H) against an internal standard (either octane or undecane). Reduced compounds **7** and **8** (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 **7** and **8** prepared and resolved following literature procedures.[16]

Table 1 lists enantioselectivity data for the model substrates **7**, **8** reacting with bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride **5** at −78°C in toluene in the absence of any additive and in the presence of one equivalent of BF_3, zirconocene dichloride **9**, (*S*,*S*)-(−)- and (*R*,*R*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalycidene)-1,2-cyclohexanediaminomanganese(III) chloride **10** and **11**.[17]

Inspection of Table 1 reveals some interesting features which aid our understanding of the factors which govern the 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 ee's. For example, addition of one equivalent of BF_3 to the reaction involving **7** (R = Et, X = Br) results in an increase in enantioselectivity from 4 to 20%.





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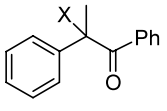

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Table 1. Enantioselectivities observed for reactions involving bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride **5** in toluene at −78°C[a]

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

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

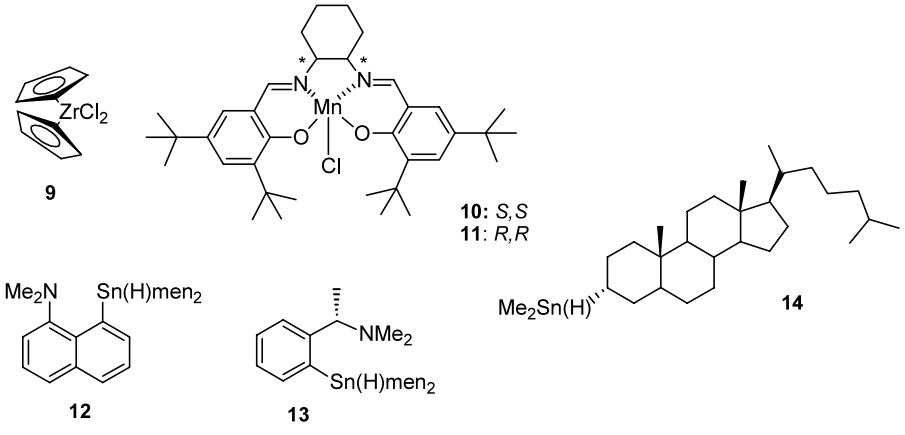
Increasing Lewis acid bulk results in further increases; 46% ee is observed with the addition of zirconocene dichloride **9**, while addition of **10** results in a remarkable improvement in ee to a value of 86%. It is interesting to note that the (*S*)-isomer of the product dominates in all of the reductions listed in Table 1. It is also important to note, when the reduction of **7** (R = Et, X = Br) was repeated with the enantiomer of **5**, bis((1*S*,2*R*,5*S*)-menthyl)phenyltin hydride, in the presence of **11**, (*R*)-**7** (R = Et, 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 **9** itself has a remarkable effect on the stereochemistry of the reactions in question. In addition, both enantiomeric forms of *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride, namely **10** and **11**, 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 **9**, **10** and (for one example) **11**. Stannanes **12**–**14** were prepared as previously described by us.[18] It is interesting to note that the achiral stannane, tributyltin hydride, reacts with **7** (R = *tert*-Bu, X = Br) in the presence of Lewis acids **9** and **10** to afford **7** (R = *tert*-Bu, X = H) with 0 and 8% ee, respectively. The former result is expected; the latter result demonstrates, once again, that chirality in the stannane is more important than that in the Lewis acid. The reader's attention is also 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.

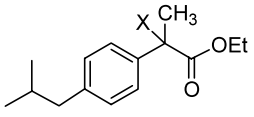
2.2. Expanding the range of Lewis acids

As discussed in the previous section, the observation that enantioselectivity during chiral radical reduction is related to the bulk of the Lewis acid additive, seems to fit well with the hypothesis that chiral recognition phenomena are the result of subtle steric interactions that manifest themselves in the transition states for delivery of a hydrogen atom from the chiral stannane to the *re* and *si* faces of the radicals involved in this chemistry. This is discussed in more detail below. We were surprised then to observe that magnesium based Lewis acids such as $MgBr_2$, MgI_2, $Mg(OAc)_2$, $Mg(ClO_4)_2$ and



$Mg(OTf)_2$ seem to outperform many bulkier Lewis acids.[19] While magnesium based additives have been used in the past to promote stereoselectivity in some free-radical transformations,[20] its application to the chemistry described in this paper, to the best of our knowledge, is novel. As is clearly evident in Table 3 (entries 1–5), reaction of the bromoester **7** (R = Me, X = Br) with bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride **5** in the presence of a wide cross-section of magnesium salts affords ethyl (*S*)-2-phenylpropionate in high yield and routinely high enantioselectivity. We speculate that the addition of magnesium salts allows for coordinated dimers to form, the result being that one ester unit provides the steric bulk that affords high selectivity during the reduction of the other unit. It is interesting to note that addition of $MgCl_2$ provided no ee in this reaction (entry 6), presumably due to poor solubility characteristics. In addition, standard lithium, beryllium and calcium salts also provided no ee, presumably for similar reasons.

As we were interested in developing methodology for preparative application, we chose to include substrates **15** and **16** in this study with the aim of providing esters of ibuprofen **15** (X = H) and naproxen **16** (X = H).



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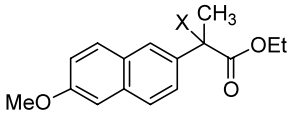

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Inspection of the data in Table 3 confirms that these targets are also effectively prepared in high enantioselectivity through the use of bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride **5** in the presence of magnesium salts, especially $MgBr_2$. It is important to note that, as expected, the enantiomeric reagent *ent*-**5** provided the opposite outcome (entry 8) and that the match between reagent and substrate is important; the C_3-symmetric,[21] tris((1*R*,2*S*,5*R*)-menthyl)tin hydride **6** providing lower selectivities under identical conditions (entries 12 and 19). In addition, boron-based additives (entries 9 and 10) and $ZnCl_2$ (entry 11) give rise to poor outcomes, while aluminium Lewis acids such as methylaluminium diphenoxide (MAD) and methyldiphenoxyaluminium (entries 17 and 18) provide good to excellent results.

Table 2. Enantioselectivities observed for reactions involving zirconocene dichloride **9** and (*S*,*S*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalycidene)-1,2-cyclohexanediaminomanganese(III) chloride **10** and its enantiomer **11** in toluene at −78°C

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

[a] GC conversion.
[b] The enantiomer of **10**.
[c] Bis((1*S*,2*R*,5*S*)-menthyl)phenyltin hydride.
[d] Isolated yield.

Table 3. Enantioselectivities observed for reactions involving substrates **7**, **15** and **16** with stannanes **5** and **6** and the expanded range of Lewis acids in toluene at −78°C

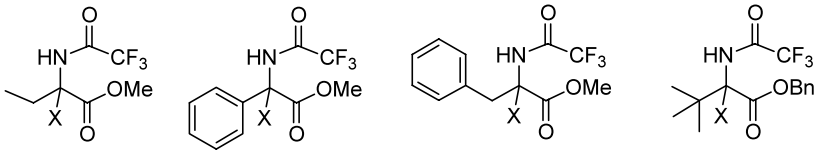
Entry	Substrate	Lewis acid[a]	Stannane	% Ee	% Yield[b]	Config.
1	**7** (R = Me)	$MgBr_2$	**5**	92	96	*S*
2		$Mg(OTf)_2$		98	quant	*S*
3		$Mg(OAc)_2$		88	72	*S*
4		$Mg(ClO_4)_2$		62	81	*S*
5		MgI_2		96	quant	*S*
6		$MgCl_2$		0	N.d.[d]	–
7	**15**	$MgBr_2$	**5**	96	55	*S*
8		$MgBr_2$	*ent*-**5**[c]	96	68	*R*
9		$(EtO)_3B$	**5**	35	N.d.[d]	*S*
10		$(i\text{-PrO})_3B$		40	N.d.[d]	*S*
11		$ZnCl_2$		15	N.d.[d]	*S*
12		$MgBr_2$	**6**	62	70	*S*
13	**16**	$MgBr_2$	**5**	>99	74	*R*
14		$Mg(OTf)_2$		62	75	*S*
15		$Mg(OAc)_2$		88	74	*R*
16		MgI_2		95	76	*S*
17		MAD		70	66	*S*
18		$MeAl(OPh)_2$		94	82	*R*
19		$MgBr_2$	**6**	30	35	*S*

[a] See Ref. 19.
[b] GC conversion.
[c] Bis((1*S*,2*R*,5*S*)-menthyl)phenyltin hydride.
[d] Not determined.

2.3. Reactions involving amino acid derivatives

Given that excellent selectivities are possible using simple Lewis acid additives together with relatively simple chiral non-racemic stannanes such as **5**, we next turned our attention to the preparation of enantiomerically pure natural and unnatural amino acids. In particular, the methodology described herein should allow for control of the configuration of the reaction product through reagent selection. In this manner, both deracemization of racemic substrates, and enantiomer switching (e.g. L→D) becomes routinely possible because the intermediate radical is prochiral. We chose to examine the representative set of amino acid derivatives **17**–**20**. As we required bromine-containing substrates (X = Br) as radical precursors, *N*-trifluoracetylation was deemed necessary as previous work by Easton and Croft had showed that free amino acids as well as other, less powerful electron-withdrawing substituents on nitrogen provide systems that cannot be selectively brominated by radical brominating agents such as *N*-bromosuccinimide (NBS).[22] Preliminary work in our laboratories confirm these observations. In addition, **19** (X = Br) was prepared by a Hell–Vollhard–Zelinski route[23] because of problems associated with benzylic bromination, while the benzyl ester **20** of *tert*-leucine was utilized because of its ease of preparation. Interestingly, **20** (X = H) appears not to become brominated in the benzylic position upon treatment with NBS under standard radical conditions.

As the data in Table 4 reveal, the chiral radical reduction chemistry developed by us is indeed amenable to the enantioselective preparation of amino acids. Apart from the 2-aminobutyric acid derivative **17**, the remaining amino acid substrates, namely methyl *N*-trifluroacetylphenylglycinate **18**, methyl *N*-trifluroacetylphenylalaninate **19**, and benzyl *N*-trifluroacetyl-*tert*-leucinate **20** are all obtained in good to excellent yield and in almost single enantiomer purity when magnesium salts are used in conjunction with stannane **5**. We attribute the poor selectivities obtained with **17** to the steric similarity of the methyl and ethyl groups attached at the prochiral carbon in the radical involved during the transformation, providing for poor facial differentiation.



17 **18** **19** **20**

Table 4. Enantioselectivities observed for reactions involving amino acid substrates **17**–**20** with stannanes **5** and **6** and Lewis acids in toluene at −78°C

Entry	Substrate	Lewis acid[a]	Stannane	% Ee	% Yield[b]	Config.
1	**17**	None	**5**	0	N.d.[d]	–
2		$MgBr_2$		10	N.d.[d]	N.d.[d]
3		$(EtO)_3B$		10	N.d.[d]	N.d.[d]
4	**18**	None	**5**	5	70	*S*
5		$MgBr_2$		>99	78	*R*
6		$ZnCl_2$		14	N.d.[d]	*S*
7		Me_3Al		12	N.d.[d]	*S*
8		BF_3		13	N.d.[d]	*S*
9		$Ln(OTf)_3$		14	N.d.[d]	*S*
10		None	**6**	0	65	–
11		$MgBr_2$		20	60	*S*
12	**19**	None	**5**	6	N.d.[d]	*S*
13		$MgBr_2$		99	81	*R*
14	**20**	None	**5**	18	45	*S*
15		None	*ent*-**5**[c]	20	60	*R*
16		$MgBr_2$	**5**	99	(65)[e]	*S*
17		$MgBr_2$	*ent*-**5**[c]	96	58	*R*
18		$Mg(OAc)_2$	**5**	99	95	*S*
19		MgI_2		99	96	*S*
20		MAD		99	90	*S*
21		$MeAl(OPh)_2$		86	90	*S*
22		$ZnSiO_4$		99	95	*S*
23		$CaSiO_4$		99	70	*S*
24		$MgSiO_4$		99	65	*S*
25		$Al_2(SiO_4)_3$		99	52	*S*
26		None	**6**	6	N.d.[d]	*S*
27		$MgBr_2$	**6**	96	70	*S*

[a] See Ref. 19.
[b] GC conversion.
[c] Bis((1*S*,2*R*,5*S*)-menthyl)phenyltin hydride.
[d] Not determined.
[e] Isolated yield.

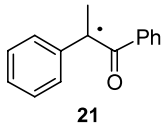
As is clearly evident from the data in Table 4, additions of magnesium salts once again provide for the best outcomes. In the case of the phenylglycine and *tert*-leucine derivatives **18** and **20**, an increased range of Lewis acids have been examined. Not unexpectedly, the aluminium species (entries 20 and 21) provide good outcomes. However, to our surprise, addition of zeolites such as zinc, calcium and magnesium silicates (entries 22–24) also result in excellent enantioselectivities. It is interesting to note that kaolinite clay ($Al_2(SiO_4)_3$, entry 25) is also an effective additive. Finally, entries 6–9 clearly demonstrate that other 'traditional' additives[20] such as $ZnCl_2$, BF_3, Me_3Al and $Ln(OTf)_3$ are all less effective in their ability to promote high enantioselectivities during the reduction reactions in this study.

2.4. Computational studies

Recently, we explored the effect of temperature on the ratio of enantiomers obtained during the reduction of ketone **8** (X = Br) with tris((1*R*,2*S*,5*R*)-menthyl)tin hydride **6** in toluene and in the absence of any Lewis acid additive and determined the relative Arrhenius expression for the reaction to be (Eq. (1)):[3]

$$\log(S/R) = (0.03\pm0.03) - (0.7\pm0.1)/2.3RT \qquad (1)$$

(where $R = 8.314\times10^{-3}$ kJ K^{-1} mol^{-1}).



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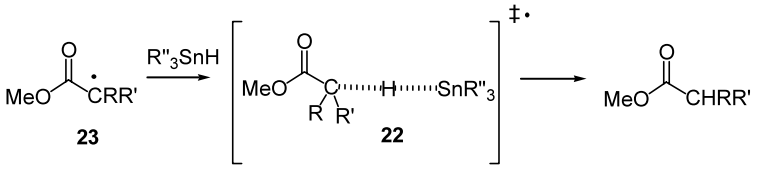
Eq. (1) reveals that the difference in activation energy ($\Delta\Delta E^{\ddagger}$) for delivery of hydrogen atom to the *si* and *re* faces of the prochiral radical **21** involved during the reduction of **8** (X = Br) is only 0.7 kJ mol^{-1}. Clearly, this value needs to be increased significantly if synthetically viable outcomes are to be achieved; values in excess of about 10 kJ mol^{-1} (preferably 15–20 kJ mol^{-1}) are desirable. These low values of $\Delta\Delta E^{\ddagger}$ ultimately have their origins in the diastereomeric transition states for

hydrogen transfer to the two faces of the prochiral radicals in question. As mentioned above, we reported recently the results of an ab initio study of the geometric requirements in the transition states involved in the delivery of hydrogen atoms from several types of stannane to a variety of alkyl radicals.[7] These calculations provided overall Sn–C distances of about 3.50 Å in these transition states that proved to be largely independent of alkyl substitution on either radical or stannane.[7] It would seem reasonable to suggest that the relatively large C_{TS}–Sn separations in these structures severely restrict the ability of the ligand on tin to impart chiral information to the prochiral radical during the reduction process resulting in poor enantioselectivities in the absence of Lewis acid additives.

How then do we improve the situation? One approach would be to construct stannanes bearing very bulky chiral substituents able to induce asymmetry across the 3.5 Å transition-state distance. This approach is somewhat limited if we choose to restrict ourselves to cheap, readily available ligands from the chiral pool. Alternatively, we might try to 'bulk up' the radical by the addition of a sterically-demanding co-reagent or catalyst capable of coordination to the reacting species.

In order to facilitate a useful outcome to this discussion, we needed to understand also the effect of delocalization on the transition states in question as the carbon-centred radicals in this study would be expected to interact differently with the reducing agents **4**–**6** than those in our initial ab initio study.[7] We chose to explore briefly the transition states for hydrogen atom transfer from stannanes to a series of carbonyl-substituted radicals by ab initio and other molecular orbital techniques. In particular, we examined the transition state **22** (R = R′ = R″ = H) for hydrogen transfer from stannane (SnH_4) to carbomethoxymethyl radical **23** (R = R′ = H) using ab initio techniques and AM1 calculations (Scheme 2). Critical transition state distances are displayed in Figure 1. Beckwith and Zavitsas reported the use of AM1 calculations to accurately predict the diastereomeric outcome during Bu_3SnH reduction of several dioxolanyl radicals.[24] Despite inherent deficiencies associated with the AM1 method, namely its inability to reproduce ab initio transition state energy barriers for stannane reductions,[7] it would appear to be capable of reproducing relative energy barriers and stereochemical trends.[24] It seemed reasonable, therefore, to explore the ability of AM1 to reproduce trends observed during enantioselective stannane reductions. The questions we sought answers to included whether or not AM1 would predict the correct stereochemical outcome in these transformations, whether or not it would reproduce the observed effect of Lewis acid in these reactions, and lastly, whether or not AM1 could quantitatively predict the observed enantioselectivities. While we were confident in providing insight into the first two questions, we were less confident in the ability of AM1 to accurately predict ees, mainly because of the subtle energy differences involved.

Transition states **22** for the reaction of two prototypical prochiral radicals **23** (R = Ph; R′ = Me, *tert*-Bu) with chiral stannanes **4**–**6**, in the absence of, and in the presence of BF_3 and, for one example, $B(OMe)_3$ were



Scheme 2.

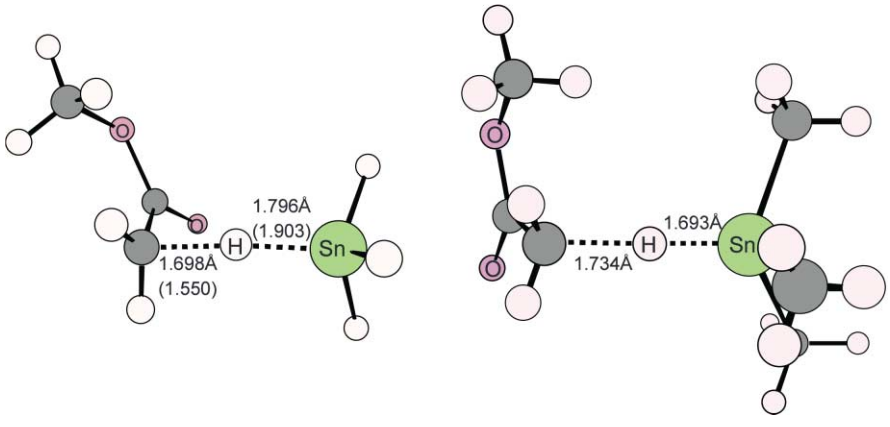


Figure 1. MP2/DZP calculated geometry[a] of **22** (R = R′ = R″ = H) (left) and AM1 calculated geometry of **22** (R = R′ = H; R″ = Me) (right). [a](UHF/DZP) data in parentheses.

optimized by AM1. In all, six transition states were determined for each reacting pair, corresponding to the three lowest-energy rotamers for the attack of **3**–**5** at each (*re* or *si*) face of **23**. Figure 2 depicts a typical transition state **22**, with, and without the inclusion of BF_3 as Lewis acid. In order to save computational cost, the critical distances in transition states **22** were fixed at those calculated by AM1 for **22** (R = R′ = H; R″ = Me), namely: r(C–H) = 1.73 Å; r(Sn–H) = 1.69 Å; θ(C–H–Sn) = 180°, and the remaining structure optimized in the usual way. Energy differences ($\Delta E^{\ddagger}_{si}$–$\Delta E^{\ddagger}_{re}$) were calculated using the optimized lowest energy conformation for the attack at the two prochiral radical faces and are listed in Table 5.[25]

The role of the Lewis acid is clearly evident in Figure 2. As expected, BF_3 is calculated to coordinate to the carbonyl oxygen of the radical. The time-averaged effect of this coordination is to increase steric discrimination between the two faces of the prochiral radical. This is clearly evident in the calculated energy differences ($\Delta E^{\ddagger}_{si}$–$\Delta E^{\ddagger}_{re}$) presented in Table 5.

The data presented clearly indicate that AM1 does indeed correctly predict the predominant isomer formed during the asymmetric radical reductions investigated in this study; in all cases for which experimental information is available the preferred configuration is calculated to be (*S*). In addition, AM1 appears to predict correctly the stereo-enhancing effect of the Lewis acid. In all cases, the inclusion of BF_3 in the calculation serves to improve enantioselectivities, in agreement with the experimental observations presented in the preceding sections. When the steric bulk of the Lewis acid is increases (entry 5, Table 5), further increases in enantioselectivity are predicted, in accord with experimental observation. Enantioselectivities were calculated using the relative Arrhenius expression:

$$\log(S/R) = \log A_{si} - \log A_{re} - (\Delta E^{\ddagger}_{si} - \Delta E^{\ddagger}_{re})/2.3RT$$

assuming that entropy contributions for attack at both faces of the radical are identical. As expected, the factors affecting the magnitude of the enantioselectivities are subtle and not easily amenable to prediction. It

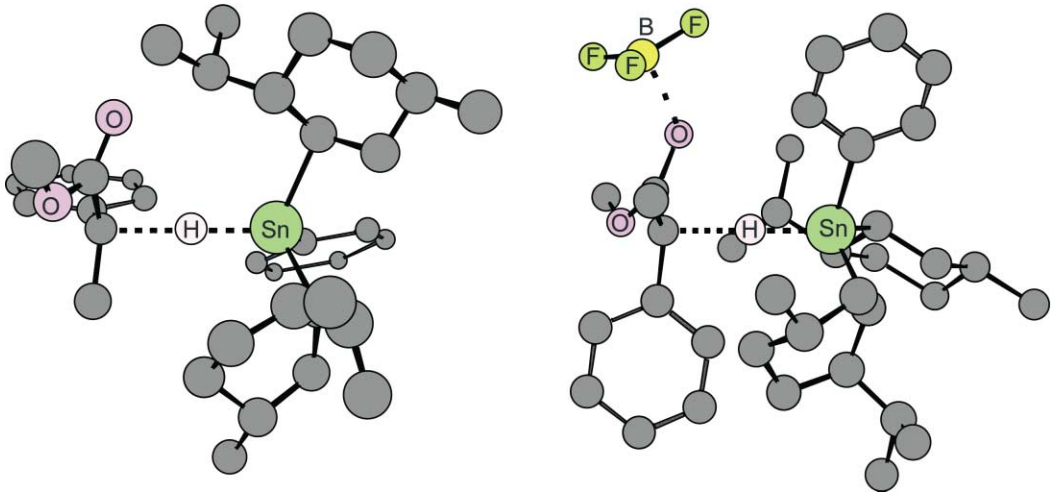


Figure 2. AM1 calculated structures (non-important hydrogen atoms removed for clarity) of typical transition states **22** involved in the reaction of **23** (R = Me; R′ = Ph) with **5**, without (left) and with (right) the inclusion of BF_3.

Table 5. AM1 calculated energy differences ($\Delta E^{\ddagger}_{si}$–$\Delta E^{\ddagger}_{re}$)[a] between the *re* and *si* transition states **22** involved in the reactions of prototypical prochiral radicals **23** (R = Ph) and associated stereochemical predictions

Entry	R′	Stannane	Lewis acid	($\Delta E^{\ddagger}_{si}$–$\Delta E^{\ddagger}_{re}$)	Configuration of product	% Ee (calcd)[b] (−78°C)	% Ee (expt)[c] (−78°C)
1	Me	**4**	None	1.1	*S*	34	4 (*S*)[d]
2		**4**	BF_3	6.8	*S*	97	–
3		**5**	None	1.7	*S*	50	2 (*S*)[d]
4		**5**	BF_3	2.8	*S*	70	32 (*S*)[d]
5		**5**	$B(OMe)_3$	8.9	*S*	99	35 (*S*)[e]
6		**6**	None	3.4	*S*	78	2 (*S*)[d]
7		**6**	BF_3	7.0	*S*	99	–
8	*tert*-Bu	**5**	None	3.5	*S*	80	6 (*S*)[d]
9		**5**	BF_3	13.1	*S*	100	10 (*S*)[d]

[a] Energies are in kJ mol^{-1}.
[b] Calculated assuming $\log(A/M^{-1}\ s^{-1})_{re}$-$\log(A/M^{-1}\ s^{-1})_{si} = 0$ (see text).
[c] Experimental data taken from Tables 1 and 2.
[d] Experiments performed on ethyl ester analogue.
[e] Experiment performed on the ibuprofen analogue **15**.

is clear that AM1, as applied in this study, seriously overestimates the magnitude of the enantioselectivity in all cases.

2.5. Kinetic studies

In this final section, we report the results of relative Arrhenius studies designed to gain experimental insight into the energetic and entropic requirements of the chemistry in this study. Accordingly, in the same manner as described previously,[3] we examined the effect of temperature on the ratio of enantiomers obtained during the reduction of esters **7** and **15** (X = Br) with bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride **5** in toluene and in the absence and presence of Lewis acid additives. The Arrhenius data from this study are displayed in Table 6.

The data in Table 6 reveal some noteworthy features. Firstly, that the Lewis acid additive primarily affects the difference in *re*/*si* activation energies, $\Delta\Delta E^{\ddagger}$. As the bulk of the Lewis acid increases (entries 1–5) so does this difference increase. Likewise, addition of $MgBr_2$ (entries 9 and 10) has a similar effect. Significantly though, the assumption used to predict enantioselectivities from AM1 energy data, namely that the log A terms for attack at both faces of the prochiral radical are identical (viz. $\log(A/M^{-1}\ s^{-1})_{si}-\log(A/M^{-1}\ s^{-1})_{re}=0$) appears not to be valid, especially with the addition of the bulkier Lewis acids. Indeed, the observed trends suggest strongly that the Lewis acid additives influence the Arrhenius pre-exponential terms of these reactions in a manner that *decreases* enantioselectivity. In doing so, these unfavourable entropic factors counteract the favourable energy effects that act to *increase* selectivity. This, in turn, perhaps, begins to shed light on the reason why the selectivities predicted in Table 5 are all overestimated. For example, application of a logA difference of only 0.5 ($\log(A/M^{-1}\ s^{-1})_{si}-\log(A/M^{-1}\ s^{-1})_{re}=0.5$) to the AM1 data for the reaction of **23** (R = Ph, R′ = Me) with **5** reduces the predicted enantioselectivity from 70% at −78°, to 28%, in much closer agreement with the experimental data. What is clear from the computational and kinetic studies in this work is that while the magnitude of the enantioselectivity is not reliably predicted by AM1, its apparent ability to provide the correct stereochemical outcome and to predict the effect of additives makes it a qualitatively useful tool. We are further exploring computational techniques in this regard. In addition, we note that we have achieved the previously set requirement that values of $\Delta\Delta E^{\ddagger}$ should exceed about 10 kJ mol^{-1} for synthetically useful outcomes (see above). Indeed we have shown that this requirement can be met and in systems that achieve 99%ee, this difference is about 20 kJ mol^{-1}.

2.6. Computational chemistry

All ab initio molecular orbital calculations were carried out using the Gaussian 98 program.[26] Geometry optimisations were performed using standard gradient techniques at the SCF and MP2 levels of theory using UHF and UMP2 methods. Vibrational frequencies were calculated on each ab initio calculated structure. All ab initio calculations were performed using the previously published DZP basis set[27] as described by us.[7] AM1 calculations were performed within Gaussian 98 or AMPAC 5.0.[28]

3. Experimental

Ibuprofen, naproxen, 2-aminobutyric acid, phenylglycine, phenylalanine and *tert*-leucine were sourced from Aldrich. Stannanes **4**–**6** and **12**–**14** were prepared as previously described.[11,13,18] Esters **7**, **15** and **16** (X = H) were prepared by standard thionyl chloride/ethanol chemistry as described previously.[29] The hydrochlorides of the amino acid esters **17**–**19** were prepared as described previously.[30] Bromides **7**, **8**, **15**–**18** and **20** (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

Table 6. Relative Arrhenius parameters (*si*–*re*) for the reactions of bromides **7**, **8** and **15** (X = Br) (−78 to 0°C) with stannanes **5** and **6**

Entry	Substrate	Stannane/additive	$\Delta(\log A/M^{-1}\ s^{-1})$[a]	$\Delta\Delta E^{\ddagger}$[a] (kJ mol^{-1})[a]
1	**7** (R = Me)	**5**/**11**	1.3±0.1	7.2±0.6
2	**7** (R = Et)	**5**/none	0.2±0.1	1.2±0.4
3		**5**/BF_3	1.0±0.3	5.9±1.5
4		**5**/**9**	1.3±0.3	7.7±1.2
5		**5**/**10**	2.1±0.5	11.5±2.0
6		*ent*-**5**/**10**	−3.4±0.8	−13.1±3.6
7	**7** (R = *c*-Pen)	**5**/**10**	0.9±0.3	5.8±1.5
8	**7** (R = *t*-Bu)	**5**/**10**	1.6±0.6	9.4±2.8
9	**8**	**6**/none	0.03±0.03[b]	−0.7±0.1[b]
10		**5**/**10**	0.9±0.2	5.3±0.8
11	**15**	**5**/none	1.6±0.3	2.8±1.1
12		**5**/BF_3	2.4±0.3	7.1±1.5
13		**5**/$MgBr_2$	4.8±0.7	19.5±3.0

[a] Error limits are expressed to 95% confidence but include random and not systematic variations.
[b] Ref. 3.

the literature.[3,5,29] Gas chromatographic analyses were performed using a chiral trifluoroacteylated γ-cyclodextrin (Chiraldex™ G-TA, 30 m×0.25 mm) capillary column purchased from Alltech.

3.1. General procedure for preparation of *N*-TFA-amino acid methyl esters 17–19 (X=H)

Dry triethyl amine (1.1 equiv.) was added to a stirred mixture of the amino acid methyl ester hydrochloride **17**–**19** (X=H) followed by methyl trifluoroacetate (1.5 equiv.) in dry methanol (10 mL). The reaction was allowed to reflux for 12 h, after which the excess solvent was removed and the resulting mixture re-dissolved in ether (20 ml), washed with sat. NH_4Cl, the separated organic layer dried with $MgSO_4$ and the solvent removed in vacuo to obtain the corresponding *N*-TFA-amino acid methyl ester sufficiently pure for further use.

3.2. Benzyl *N*-trifluoroacetyl-*tert*-leucinate 20 (X=H)

tert-Leucine (200 mg, 1.5 mmol) and triethylamine (0.3 mL) were dissolved in methanol (0.5 mL). Methyl trifluoroacetate (0.16 mL) was added and the mixture stirred at rt for 15 h. The solvent was removed in vacuo and the residue dissolved in DMF (0.5 mL). Triethylamine (0.14 mL) and benzyl chloride (350 mg, 2.7 mmol) were added and the mixture stirred at rt for 40 h. The mixture was poured into ethyl acetate, washed with water, 5% HCl and satd. $NaHCO_3$, and finally with satd. NaCl. The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to afford a pale yellow oil that was purified by flash chromatography (24:1 hexane:ethyl acetate) to afford the title compound as a pale oil (360 mg, 65%). ^{1}H (NMR) $CDCl_3$: δ 7.6 (1H, s(br)), 7.2 (5H, m), 5.3 (2H, q, *J* 8 Hz), 4.5 (1H, d, *J* 8 Hz), 1.0 (9H, s). ^{13}C NMR $CDCl_3$: δ 170.0, 156.8 (q, J_{CF} 37 Hz), 134.6, 128.68, 128.63, 128.61, 128.52, 115.7 (q, J_{CF} 288 Hz), 67.6, 60.3, 35.5, 26.3.

3.3. General procedure for the preparation of bromides 7, 15–18 and 20 (X=Br)

Methyl 2-bromo-2-phenylpropanoate **7** (X=Me). *N*-Bromosuccinimide (360 mg, 2.0 mmol) was added to a solution of methyl 2-phenylpropanoate (300 mg, 1.8 mmol) in carbon tetrachloride (5 mL). 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.

Methyl 2-Bromophenylalaninate **19** (X=Br) Phenylalanine (1.0 g, 6.05 mmol) and bromine (1.058 g, 1.1 equiv., 6.65 mmol) were heated to 65–70°C and PBr_3 (1.686 g, 1.03 equiv., 6.23 mmol) slowly added to the reaction mixture. The mixture was then heated at 65–70°C until the evolution of HBr had completely ceased (ca. 3 h). Reaction mixture was then distilled of residual HBr gas and low boiling point impurities. A 1:1 mixture of methanol/dichloromethane (10 ml) was slowly added with cat. amount of H_2SO_4 and the reaction mixture refluxed for a further 2 h. Excess solvent was removed in vacuo to obtain **19** (X=Br) of sufficient purity for further use (0.66 g, 45%) ^{1}H (NMR) $CDCl_3$: δ 7.0–7.2 (5H, m, Ar-H), 3.67 (3H, s, 0-CH_3), 3.62 (2H, s, Ph-CH_2).

3.4. Standard procedure for small-scale 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 or decane, 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.

3.5. Standard procedure for preparative-scale low-temperature stannane reductions. Reduction of benzyl *N*-trifluoroacetyl-2-bromo-*tert*-leucinate 20 (X=Br)

Magnesium bromide etherate ($MgBr_2{\cdot}Et_2O$) (120 mg, 0.478 mmol) was added to dry toluene (0.2 mL) and the mixture allowed to stir for 20 min under N_2. The bromoester **20** (X=Br) (0.08 g, 0.234 mmol) in dry toluene (0.1 mL) was added slowly to a reaction mixture which was allowed to stir at rt for further 10 min prior to cooling to −78°C. After stirring at −78°C for a further 45 min, bis((1*R*,2*S*,5*R*)-menthyl)phenyltin hydride **5** (0.2 g, 0.42 mmol) in toluene (0.25 mL) was added slowly, followed by triethylborane (0.1 mL of 1 M solution in THF) and oxygen was introduced. The reaction mixture was stirred at this temperature for a further 4 h. The mixture was quenched with water (5 mL) and extracted with ether (2×). The organic layer was dried ($MgSO_4$) and excess solvent removed in vacuo to afford the crude product as light yellow oil. Further purification of the product (flash chromatography, 96:4 hexane/ethyl acetate) yielded benzyl (*S*)-*N*-trifluoroacetyl-*tert*-leucinate **20** (X=H) as a colourless oil (65%) and with identical properties to that prepared from an authentic sample of (*S*)-*tert*-leucine. ^{1}H (NMR) $CDCl_3$: δ 7.2 (5H, m), 7.6 (1H, s(br)), 5.3 (2H, m), 4.5 (1H, d, *J* 8 Hz), 1.0 (9H, s), $[\alpha]_D^{13.7}=+9.2$ (*c* 0.4, $CHCl_3$) 99%ee (GC). Anal. calcd for $C_{14}H_{18}F_3NO_3$: C, 56.8; H, 5.7; N, 4.4. Found: C, 56.8; H, 5.8; N, 4.4.

3.6. Reduction of methyl *N*-trifluoroacetyl-2-bromo-phenylglycinate 18 (X=Br)

Following the standard procedure, methyl (*R*)-*N*-trifluoroacetylphenylglycinate **18** (X=H) was obtained as colourless oil (78%) and with identical properties to that prepared from an authentic sample of (*R*)-phenylglycine. ^{1}H (NMR) $CDCl_3$: δ 7.4 (6H, m), 5.6 (1H, d, *J* 6.5 Hz), 3.8 (3H, s), $[\alpha]_D^{12}=-21.6$ (*c* 0.15, $CHCl_3$) 99%ee (GC).

3.7. Reduction of 2-bromonaproxen ethyl ester 16 (X= Br)

Following the standard procedure, (*S*)-naproxen ethyl ester **16** (X = H) was obtained as colourless oil (74%) and with identical properties to that prepared from an authentic sample of (*S*)-naproxen. ^{1}H (NMR) $CDCl_3$: δ 7.0–7.5 (6H, m), 4.1 (2H, m), 3.9 (3H, s), 3.8 (1H, q, *J* 9 Hz), 1.5 (3H, m), 1.2 (3H, m), $[\alpha]_D^{10} = +32.6$ (*c* 0.12, $CHCl_3$) 99%ee (GC).

3.8. Reduction of 2-bromoibuprofen ethyl ester 15 (X= Br)

Following the standard procedure, (*S*)-ibuprofen ethyl ester (**15**, X = H) was obtained as colourless oil (55%) and with identical properties to that prepared from an authentic sample of (*S*)-ibuprofen. ^{1}H (NMR) $CDCl_3$: δ 7.1–7.6 (4H, m), 4.2 (2H, m), 3.6 (1H, m), 2.6 (2H, d, *J* 8 Hz), 2.4 (1H, m), 1.5 (3H, m), 1.1 (3H, m), 0.9 (6H, m), $[\alpha]_D^{10} = +38.0$ (*c* 0.8, $CHCl_3$) 99% ee (GC).

3.9. Reduction of ethyl 2-bromo-2-cyclopentyl-2-phenyl acetate 7 (R = *cyclo*-Pen, X = Br)

Following the standard procedure, ethyl (*S*)-2-cyclopentyl-2-phenyl acetate **7** (R = *cyclo*-Pen, X = H) was obtained as colourless oil (55%) and with identical properties to an authentic sample.[31] ^{1}H (NMR) $CDCl_3$: δ 7.2 (5H, m), 4.1 (2H, m), 3.2 (1H, d, *J* 7.5 Hz), 2.6 (1H, m), 1.0–2.0 (11H, m), $\alpha_D^{26} = +26.4$ (*c* 1.0, $CHCl_3$) 96%ee (GC).

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