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Synthesis, characterization and enantioselective free radical reductions of (1*R*,2*S*,5*R*)-menthyldiphenylgermane and its enantiomer

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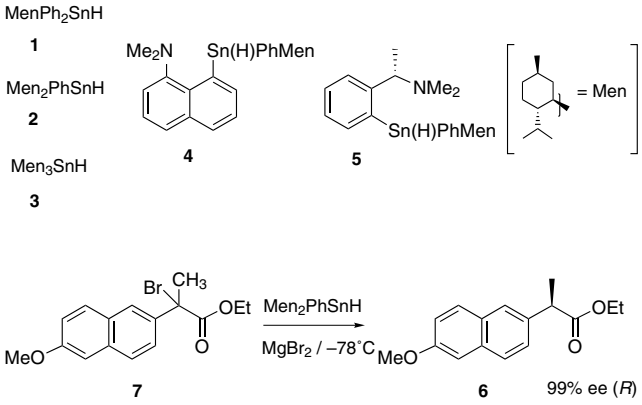
Abstract—(1*R*,2*S*,5*R*)-Menthyldiphenylgermane and its enantiomer have been prepared in a few steps from germanium tetrachloride. The initial step in this sequence, namely the reaction between germanium tetrachloride and menthylmagnesium chloride, produces menthylgermanium trichloride, which is the exclusive product of this Grignard reaction, presumably due to the bulk of the menthyl group. When used at a low temperature (−78 °C) and in conjunction with Lewis acids, such as magnesium salts, these chiral germanes are capable of reducing ester functionalized radicals in high enantioselectivity, but in low-moderate yield. For example, (*R*)-naproxen ethyl ester was obtained in 15% yield and 99% ee by reaction in toluene of 2-bromonaproxen ethyl ester with (1*R*,2*S*,5*R*)-menthyldiphenylgermane in toluene at −78 °C in the presence of magnesium bromide. At 80 °C, (1*R*,2*S*,5*R*)-menthyldiphenylgermane reacted with primary alkyl radicals with a rate constant of $1.02\times10^{6}\,M^{-1}s^{-1}$. Kinetic studies reveal the Arrhenius expression for this reaction to be: $\log(k/M^{-1}s^{-1}) = (11.1\pm0.4) - (34.6\pm3.1)/\theta$ where $\theta = 2.3RT\,kJ\,mol^{-1}$.

1. Introduction

Free-radical chemistry has benefited greatly by the introduction of chain-carrying reagents such as tributyltin hydride.[1] Indeed, the impact of tin-based reagents in this area is hard to overstate; stannanes have allowed the development of elegant syntheses of novel ring systems that in turn have led, more recently, to cascade reactions for the tandem constructions of multi-ring systems of biological interest.[1–3] While this chemistry can now be applied routinely by the synthetic practitioner, the ability to control the stereochemical outcomes of free-radical reactions has provided a greater challenge that has only recently been adequately addressed.[3–6]

Recently, we reported the preparation of chiral, non-racemic, (1*R*,2*S*,5*R*)-menthyl (Men) containing stannanes **1**–**5** for use in enantioselective free-radical reduction chemistry[7,8] and demonstrated that in conjunction with Lewis acids, these stannanes are capable of providing single enantiomer outcomes for a variety of transformations of synthetic and commercial significance.[5,6] An example of this chemistry is shown in Scheme 1, in which (*R*)-naproxen ethyl ester **6** is prepared in 99% enantioselectivity (ee) from racemic bromide **7** by reduction with bis[(1*R*,2*S*,5*R*)-menthyl]phenyltin hydride (Men_2PhSnH) **2** at −78 °C in the presence of magnesium bromide.[6]



Scheme 1.

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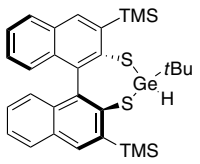
The dominance of trialkylstannanes as the reagents of choice in free radical chemistry is now being challenged. Perceived toxicity[9] and product purification[10] concerns have lead to the development of 'friendlier' reagents; tris(trimethylsilyl)silane[11–13] and tris(trimethyl)silanethiol[11,12,14] are representative of a new generation of reagents designed specifically for use in free-radical chain reactions. Improvements in synthetic flexibility resulting from the use of germanes and thiols as hydrogen donors has resulted in extensions of free-radical methodology to systems in which the primary bond-forming reaction (e.g. intramolecular addition) lies outside the acceptable range for stannane chemistry.[2] The use of trialkylgermanes, for example, with typically lower rate constants for the delivery of hydrogen atom to alkyl radicals can often lead to increased reaction yields when slow C–C bond-forming reactions are crucial in the overall synthetic strategy.[15–17]

With these considerations in mind, Curran et al. recently described the preparation of chiral germanes (e.g. **8**) based on the chiral bis(naphthalenethiol) unit and reported enantioselectivities of up to 42% in certain reductions reaction.[18]



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As part of our ongoing development of new reagents for stereoselective free radical chemistry, we herein report the development of both enantiomers of menthyldiphenylgermane **9**; these chiral germanes are capable of reducing ester functionalized radicals in high enantioselectivity, but in low-moderate yield. Given that a knowledge of rate constants is crucial to the design of free-radical reactions of synthetic significance, we have also determined these important parameters for our chiral germanium reagents. We also report that at 80 °C, (1*R*,2*S*,5*R*)-menthyldiphenylgermane reacts with primary alkyl radicals with a rate constant of $1.02\times 10^6\,M^{-1}s^{-1}$. Kinetic studies reveal the Arrhenius expression for this reaction to be: $\log(k/M^{-1}s^{-1}) = (11.1\pm 0.4) - (34.6\pm 3.1)/\theta$ where $\theta = 2.3RT\,kJ\,mol^{-1}$ As observed previously for related stannanes, menthyl substitution would appear to affect both energy and entropy terms of this Arrhenius expression.

2. Results and discussion

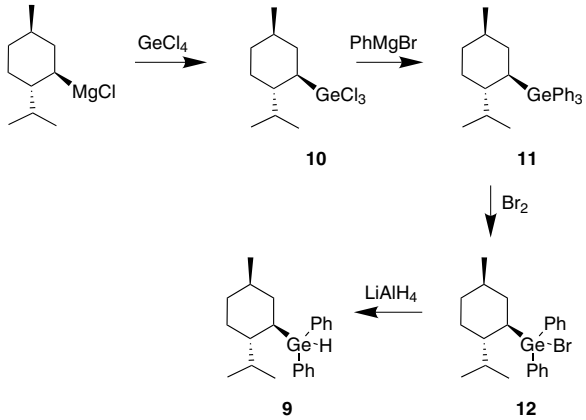
2.1. Synthesis of (1*R*,2*S*,5*R*)-menthyldiphenylgermane 9

Recently, we developed and published a synthetic methodology for the preparation of (1*R*,2*S*,5*R*)-menthyldiphenyltin hydride **1** and its related stannanes.[7] In the preparation of **1**, this methodology involves the reaction of menthylmagnesium chloride with triphenyltin chloride followed by further synthetic manipulation. It is possible to react the analogous germane, namely triphenylgermanium chloride, with Grignard reagents.[19] Despite this, triphenylgermanium chloride was inert to menthylmagnesium chloride, even after considerable experimentation with variables such as solvent, temperature and reaction time performed. It quickly became apparent that an alternative strategy would be required.

The literature suggests that Grignard reagents (RMgX) react with $GeCl_4$ to provide complex mixtures of the type R_nGeCl_{4-n} that require difficult fractional distillation techniques to separate and therefore give low yields of alkylgermanium trichloride.[20,21] Despite this, we chose to react (1*R*,2*S*,5*R*)-menthylmagnesium chloride directly with germanium tetrachloride. Surprisingly, this reaction proceeded smoothly to afford (1*R*,2*S*,5*R*)-menthylgermanium trichloride **10**, which was isolated in 50% yield after simple distillation (Scheme 2). Trichloride **10** proved to be laevorotatory, with $[\alpha]_D^{25} = -51.3$ (*c* 1, $CHCl_3$).

It is curious that this reaction should proceed so well given that the analogous tin reaction cannot be controlled to give a single 1:1 product,[22] and that $GeCl_4$ usually reacts indiscriminately or poorly with these types of reagents, as described above. We postulate that this is due to the steric environment of the menthyl substituent, which leads to the poor reactivity of the Grignard reagent with triphenylgermanium chloride and that this same steric phenomenon is responsible for the excellent selectivity observed in the reaction involving $GeCl_4$.

Further synthetic manipulation involving treatment of **10** with 3 equiv of phenylmagnesium bromide afforded (1*R*,2*S*,5*R*)-menthyltriphenylgermane **11** in excellent isolated yield (93%) (Scheme 2). Germane **11** also proved to be laevorotatory $\{[\alpha]_D^{25} = -34.8$ (*c* 1, $CHCl_3)\}$. Crystallization from hexane at 4 °C afforded germane **11** as a crystalline solid suitable for single-crystal X-ray analysis, the results of which are displayed in Figure 1.



Scheme 2.

Inspection of Figure 1 reveals **11** to be quite ordinary, with regular C–Ge bond lengths and C–Ge–C angles.

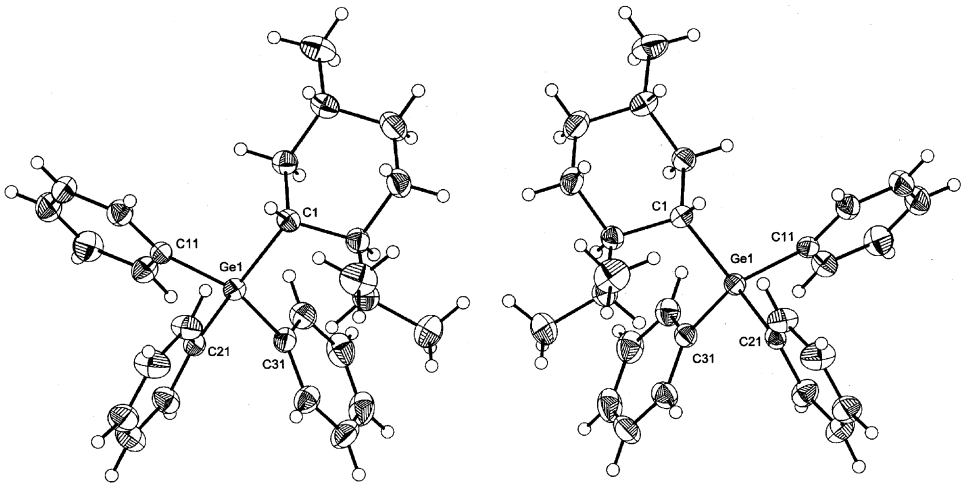


Figure 1. Perspective diagram of (1*R*,2*S*,5*R*)-(−)-menthyltriphenylgermane **11** (left), and its enantiomer *ent*-**11** (right) with key atom numbering.

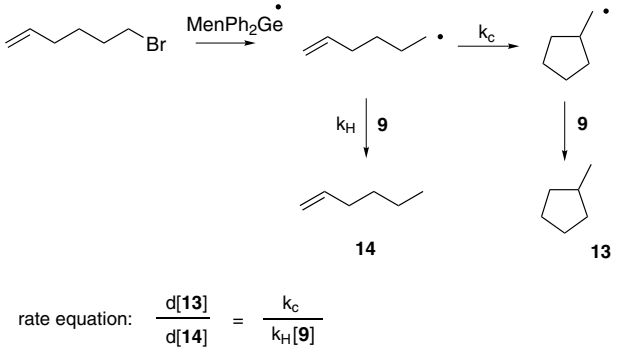
The most important information provided by the crystallographic information is confirmation that each stereogenic centre in the menthyl substituent is indeed of the correct configuration; in particular no epimerization, has occurred during the Grignard chemistry described above.

Slow addition of 1 equiv of elemental bromine to a solution of **11** gave (1*R*,2*S*,5*R*)-menthyldiphenylgermanium bromide **12**, which crystallized on standing. Germane **12** was not purified, but further reacted with lithium aluminium hydride to provide the required germane, (1*R*,2*S*,5*R*)-menthyldiphenylgermane **9** as a colourless oil in 87% yield after distillation (Scheme 2). The structure of **9** was confirmed by spectroscopic techniques and microanalytical data and also proved to be laevorotatory $\{[\alpha]_D^{22} = -32.2$ (*c* 1, toluene)$\}$.

As expected, the enantiomer of **9**, namely (1*S*,2*R*,5*S*)-menthyldiphenylgermane *ent*-**9** was prepared in an identical fashion starting from (1*S*,2*R*,5*S*)-menthyl chloride.

2.2. Determination of kinetic parameters for radical reactions of 9 with primary alkyl radicals

The absolute rate constants for the delivery of the hydrogen atom from **9** to primary alkyl radicals in *tert*-butylbenzene were determined through application of the well-established '5-hexenyl radical clock'[23] reaction as described by us (Scheme 3).[24] Provided that the 'clock' rate constant (k_c) is well established for any given temperature, then the rate equation (Scheme 3) will provide a value for the hydrogen transfer rate constant (k_H). It should be noted that several published Arrhenius parameters exist for the ring-closure of the 5-hexenyl radical.[25–32] Kinetic EPR spectroscopy and competitive experiments provide Arrhenius expressions, with values of 9.5–10.7 for $\log(A/s^{-1})$, and activation energies of 25.5–32.6 kJ mol^{-1},[30,31] with the 'best' values being 10.4 ± 0.3 and 28.7 ± 1.8.[32] In our previous work,[24] we calibrated the 'hexenyl radical clock' in *tert*-butylbenzene and determined the Arrhenius



Scheme 3.

expression in that solvent to be similar to the expressions determined in other solvents, namely:

$$\log k_c/s^{-1} = (10.13 \pm 0.42) - (27.6 \pm 2.6)/\theta \qquad (1)$$

where θ is $2.3RT$ kJ mol^{-1}. We therefore have chosen to use this expression for the 'clock reaction' throughout this work.

In order to support our experimental techniques, reactions of chiral germane **9** with 1-bromo-5-hexene were initially performed at 80 °C under 'pseudo first-order' conditions at three germane concentrations (0.05, 0.1, 0.15 M) as described in our previous work.[24] In addition to this, we also chose to examine the reaction of tributylgermane, a reagent that has been studied previously, albeit not in *tert*-butylbenzene. We expected our data for Bu_3GeH to correlate with those reported previously, providing a further test for our methodology. Application of the integrated rate equation (Scheme 3) provided the rate constant data listed in Table 1. The data presented for each entry are the average of three individual experiments. The degree of convergence between the data obtained for each system in this manner indicates that the kinetic model (Scheme 3) is correct and that we are monitoring free-radical processes, as well as supporting our experimental technique. In addition, the rate constant

Table 1. Selected rate data for the reaction of primary alkyl radicals with (1*R*,2*S*,5*R*)-menthyldiphenylgermane **9** and tributylgermanane in *tert*-butylbenzene at 80 °C

Germane	Temp (°C)	[Germane] (M)	% **13**	% **14**	k_H/k_c (M^{-1})[a]	k_H ($\times 10^6 M^{-1} s^{-1}$)
$MenPh_2GeH$ **9**	80	0.05	95.6	4.4	0.92	1.01
	80	0.10	91.5	8.5	0.93	1.02
	80	0.15	87.4	12.6	0.95	1.04
Bu_3GeH	80	0.10	97.1	2.9	0.30	0.33

[a] Average of three experiments.

(k_H) of $3.3\times10^5 M^{-1} s^{-1}$ determined for Bu_3GeH at this temperature is in excellent agreement with the literature value of $3.4\times10^5 M^{-1} s^{-1}$ determined in octane.[16]

The remaining kinetic data for reactions at temperatures other than 80 °C were also obtained under 'pseudo first-order' conditions. Systematic variations in temperature (60–120 °C) reveal a linear correlation between $\log k_H$ and reciprocal temperature for each germane. All kinetic data are averages of three experiments and errors in $\log A$ and activation energy (E_a) are expressed to 95% confidence and account for random, but not systematic errors. The Arrhenius data obtained in this manner are summarized in Table 2 together with the available data for triphenylgermane.[33]

Inspection of Table 2 reveals that the Arrhenius data obtained for the chemistry involving Bu_3GeH in *tert*-butylbenzene are in excellent agreement with those previously determined in octane,[16] indeed they are identical to within experimental error, once again supporting our experimental techniques. The data presented for the menthyl-substituted system **9** are interesting; it would appear that **9** reacts with the 5-hexenyl radical with a significantly greater $\log A$ value, as well as a significantly larger activation energy (E_a) than the analogous process involving Bu_3GeH. It is difficult to make comparisons with other germanes in this regard because so little Arrhenius data exist for these hydrides, and none, to the best of our knowledge, for systems that bear sterically demanding ligands such as menthyl.[17] However, comparisons can be made with the available data reported for related stannanes.[34] For example, menthyldiphenyltin hydride **1** has been measured to react with the 1-hexenyl radical with a value for $\log(A/M^{-1} s^{-1})$ of 9.95 ± 0.22 and an activation energy (E_a) of 19.08 ± 1.52 kJ mol^{-1}.[34] The data can be compared with values of 9.07 ± 0.24 and 15.45 ± 1.34 for $\log A$ and energy terms, respectively, for the analogous reaction involving tributyltin hydride (Bu_3SnH).[32] It appears therefore, that as was observed for reactions involving the tin-based reagents **1**–**5**, the sterically-demanding menthyl substituent also exerts an influence on both the energy and entropy of activation in reactions involving **9**. As was speculated for the tin-based reagents **1**–**5**, chiral germane **9**, with an activation energy of 34.6 kJ mol^{-1} for its reaction with the 5-hexenyl radical, some 15 kJ mol^{-1} higher than that that for the analogous reaction involving Bu_3GeH, must react with a significantly more disordered transition state than Bu_3GeH in order to achieve a faster delivery of the hydrogen atom to the primary alkyl radical than Bu_3GeH.

Table 2. Kinetic parameters for the reactions of primary alkyl radicals with (1*R*,2*S*,5*R*)-menthyldiphenylgermane **9** and tributylgermane in *tert*-butylbenzene (60–120 °C) and comparative data for triphenylgermane

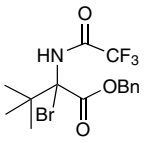
Germane	$\log A/M^{-1} s^{-1}$[a]	E_a (kJ mol^{-1})[a]	k_H (80 °C)[b] ($\times 10^6 M^{-1} s^{-1}$)
$MenPh_2GeH$ **9**	11.13 ± 0.44	34.57 ± 3.05	1.02
Bu_3GeH	8.60 ± 0.46	20.70 ± 3.21	0.34
	8.44 ± 0.47[c]	19.7 ± 1.86[c]	0.30
Ph_3GeH	—	—	3.8[d]

[a] Error limits are expressed to 95% confidence but include random and not systematic variations.
[b] Calculated from the Arrhenius parameters.
[c] Ref. 16.
[d] Ref. 33.

2.3. Enantioselective reactions of 9 with selected prochiral radicals

In our previous work, we described how appropriately chosen Lewis acid additives can enhance enantioselectivities (ees) during reductions involving chiral stannanes and radicals, which contain proximate Lewis acid binding sites, such as ester functionalized systems. It was also demonstrated that magnesium salts such as $MgBr_2$ were especially effective in this regard. We have speculated 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'.[6] Other workers have used chiral Lewis acids to engender high enantiopurity in free-radical reduction and C–C bond formation chemistry, as well as diastereoselective processes.[3,4] With this in mind, we set out to determine firstly, whether or not chiral germanes such as **9** could provide superior results to their tin counterparts in the absence of any additive, and secondly, whether or not Lewis acid additives had the same enhancing effect in the germanium chemistry described herein. Preliminary enantioselectivity testing of (1*R*,2*S*,5*R*)-menthyldiphenylgermane **9** and its enantiomer *ent*-**9** against selected substrates **7**, **15**–**18** was preformed in toluene at −78 °C according to our previously-published protocol, the results of which are listed in Table 3.[6] The substrates chosen for this investigation are representative of those previously used by us and serve as appropriate benchmarks.

Inspection of Table 3 reveals that chiral germanes appear to behave in a very similar manner to their tin counterparts in that poor enantioselectivities are observed in the absence of a Lewis acid, in this case $MgBr_2$. In every entry, the addition of the magnesium salt had a



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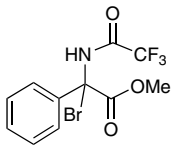

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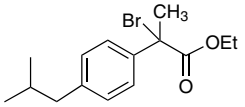

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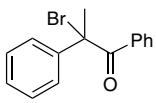

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dramatic effect on the observed ee. For example, entry 1 demonstrates that in the absence of $MgBr_2$, 2-bromonaproxen ester **7** affords the reduced product, naproxen ester **6** in 30% conversion with only 10% ee. While the addition of $MgBr_2$ appears not to improve the reaction yield, it does have the same dramatic increase on the reaction's ee as has been observed previously in chiral stannane chemistry,[6] with **6** being produced in 99% ee. Importantly, as is clearly evident in Table 3, the two enantiomeric germanes **9** and *ent*-**9** provided opposite stereochemical outcomes for each substrate, as expected. The data obtained in this work can be compared with those of Curran and co-workers, who reported ees of up to 42% using chiral germane **8**, albeit in the absence of Lewis acid additives.[18] While the selectivities reported herein are high in the presence of $MgBr_2$, the ees reported by Curran exceed those obtained in this study in the absence of Lewis acid additives, suggesting that the chiral environment provided by structures such as **8** is more effective in imparting chiral recognition than that provided by **9**.

Table 3. Enantioselectivities observed for reductions of substrates **7**, **15**–**18** with (1*R*,2*S*,5*R*)-menthyldiphenyl-germane **9** and its enantiomer *ent*-**9** in toluene at −78 °C

Entry	Substrate	Lewis acid[a]	Germane	% Ee	% Yield[b]	Config
1	**7**	None	**9**	10	30	*S*
2		$MgBr_2$		99	30	*S*
3		None	*ent*-**9**	5	20	*R*
4		$MgBr_2$		99	15[c]	*R*
5	**15**	None	**9**	10	20	*S*
6		$MgBr_2$		80	20	*S*
7		None	*ent*-**9**	5	15	*R*
8		$MgBr_2$		90	20[c]	*R*
9	**16**	None	**9**	0	20	—
10		$MgBr_2$		99	40	*S*
11		$MgBr_2$	*ent*-**9**	99	50	*R*
12	**17**	None	**9**	10	30	*S*
13		$MgBr_2$		99	30	*S*
14	**18**	None	**9**	10	35	*S*
15		$MgBr_2$		99	30	*S*

[a] See Ref. 35.
[b] GC conversion.
[c] Isolated yield.

Finally, the low to moderate reaction yields and conversions deserve mention. Despite our efforts to improve the yield through modification of reaction conditions, we were never able to achieve outcomes that exceeded about 50%. We speculate that poor radical chain propagation due to slow germane hydrogen transfer rate constants at low temperature (compared to their tin counterparts) may be partly responsible for this observation.[36] Indeed, low-temperature reductions involving **9** required repeated re-initiation. It should be noted that **8** provides yields up to 97%, but is some 15 times more reactive that **9** with a reported rate constant of about $1.4\times10^7\ M^{-1}\ s^{-1}$ at 80 °C for reaction with primary alkyl radicals.[18]

3. Experimental

Substrates **7**, **15**–**18** and reduction standards were prepared following our previously published protocols.[6] ^1H and ^{13}C NMR spectra were obtained using a Jeol GX 270, Varian 300 MHz Unity Plus, or Jeol Eclipse Plus 400 NMR spectrometer. Chemical shifts (δ) are given in ppm and are referenced against tetramethylsilane (TMS). Gas chromatographic analyses were performed using a chiral trifluoroacetylated γ-cyclodextrin (ChiraldexTM G–TA, 30 m×0.25 mm) capillary column purchased from Alltech. HPLC analyses were carried out using a Regis (*S*,*S*) *Whelk-O 1* (25 cm×4.5 mm ID) column.

(1R,2S,5R)-(−)-Menthylgermanium trichloride **10**: A solution of freshly-prepared (1*R*,2*S*,5*R*)-menthylmagnesium chloride, prepared from (1*R*,2*S*,5*R*)-menthyl chloride (8.15 g, 46.6 mmol) and magnesium (1.25 g, 51.3 mmol) in THF (50 mL) was added via cannula to a cooled (−20 °C) stirred solution of germanium tetrachloride (10.0 g, 46.6 mmol) in ether (100 mL). The reaction mixture was allowed to warm to room temperature and stirred overnight. After removal of the precipitate by filtration and removal of the solvent in vacuo, distillation (94 °C, 5 Pa) gave the title compound as a colourless oil (7.4 g, 50% yield). $[\alpha]_D^{25} = -51.3$ (*c* 1, $CHCl_3$). ^1H NMR (299.98 MHz, $CDCl_3$): δ 0.87 (d, 3H, CH_3), 0.96 (d, 3H, CH_3), 0.99 (d, 3H, CH_3), 1.00–1.26 (m, 2H), 1.14–1.24 (m, 1H), 1.62–1.86 (m, 4H), 1.96–2.08 (m, 1H), 2.13–2.23 (m, 1H), 2.38–2.50 (m, 1H); $^{13}C\{^1H\}$ NMR (75.44 MHz, $CDCl_3$): δ 15.33 (CH_3), 21.51 (CH_3), 22.30 (CH_3), 25.30 (CH_2), 31.36 (CH), 34.07 (CH), 34.24 (CH_2), 36.34 (CH_2), 44.70 (CH), 50.54 (CH); ESMS (+ve) 341.0 $(M+Na)^+$. Anal. Calcd for $C_{10}H_{19}GeCl_3$ (318.23): C 37.74, H 6.02; found: C 37.80%, H 6.00%.

(1R,2S,5R)-(−)-Menthyltriphenylgermane **11**: A solution of phenylmagnesium bromide, was prepared from bromobenzene (29.6 g, 188.5 mmol) and magnesium (4.58 g, 188.5 mmol) in THF (200 mL). The solution was filtered into a second flask, through a sintered glass frit under nitrogen, while hot, to remove unreacted magnesium. (1*R*,2*S*,5*R*)-(−)-Menthylgermanium trichloride **10** (10.0 g, 31.4 mmol) in THF (20 mL) was added dropwise at room temperature to the filtered solution. The reaction mixture was stirred overnight before being

carefully quenched with water. The solvent was removed in vacuo and ether (200 mL) and water (100 mL) added. After filtration and separation, the organic layer was dried over Na_2SO_4, and the solvent removed in vacuo. Crystallization from hexane at 4 °C gave the title compound as a colourless solid (13.0 g, 93% yield). Mp 97–98 °C. $[\alpha]_D^{25} = -34.8$ (*c* 1, $CHCl_3$). ^1H NMR (299.98 MHz, $CDCl_3$): δ 0.77 (d, 3H, CH_3), 0.82 (d, 3H, CH_3), 0.97 (d, 3H, CH_3), 1.00–1.15 (m, 2H), 1.20–1.35 (m, 2H), 1.40–1.55 (m, 1H), 1.55–1.65 (m, 1H), 1.75–2.05 (m, 3H), 2.10–2.30 (m, 1H), 7.40–7.60 (m, 9H, Ph), 7.65–7.85 (m, 6H, Ph); $^{13}C\{^1H\}$ NMR (75.44 MHz, $CDCl_3$): δ 16.36 (CH_3), 21.58 (CH_3), 22.65 (CH_3), 26.37 (CH_2), 30.81 (CH), 31.47 (CH), 34.66 (CH), 35.21 (CH_2), 39.68 (CH_2), 45.21 (CH), 127.92 (Ph_m), 128.37 (Ph_p), 135.29 (Ph_o), 137.87 (Ph_i); Anal. Calcd for $C_{28}H_{34}Ge$ (443.19): C 75.88%, H 7.73%; found: C 75.80%, H 7.81%.

(1R,2S,5R)-(−)-Menthyldiphenylgermanium bromide **12**: Bromine (5.06 g, 31.63 mmol) was added dropwise to a solution of (1*R*,2*S*,5*R*)-(−)-menthyltriphenylgermane **11** (14.02 g, 31.63 mmol) in dibromoethane (50 mL). The solution was stirred overnight at reflux, after which the solvent removed in vacuo to give the title bromide as a pale yellow oil, which solidified on standing and used without further purification (13.8 g, 98%). Mp 51–52 °C. $[\alpha]_D^{20} = -44.9$ (*c* 1, $CHCl_3$). ^1H NMR (270.17 MHz, $CDCl_3$): δ 0.64 (d, 3H, CH_3), 0.79 (d, 3H, CH_3), 0.89 (d, 3H, CH_3), 0.90–1.30 (m, 3H), 1.30–1.50 (m, 1H), 1.50–1.65 (m, 1H), 1.65–1.90 (m, 3H), 2.00–2.25 (m, 2H), 7.30–7.80 (m, 10H, Ph); $^{13}C\{^1H\}$ NMR (67.94 MHz, $CDCl_3$): δ 15.68 (CH_3), 21.51 (CH_3), 22.48 (CH_3), 25.83 (CH_2), 30.96 (CH), 34.33 (CH), 34.89 (CH_2), 36.16 (CH), 38.51 (CH_2), 45.13 (CH), 128.26/128.34 (Ph_m), 129.68 (Ph_p), 133.70/133.81 (Ph_o), 137.14/136.04 (Ph_i).

(1R,2S,5R)-(−)-Menthyldiphenylgermane **9**: A solution of crude (1*R*,2*S*,5*R*)-menthyldiphenylgermanium bromide **12** (10.0 g, 22.4 mmol) in ether (50 mL) was added dropwise to a suspension of lithium aluminiumhydride (0.43 g, 11.2 mmol) in ether (50 mL). The reaction mixture was stirred at room temperature for 1 h and then quenched with water (50 mL) (ice cooling bath). After filtration, the organic layer was collected and the aqueous layer extracted with ether (50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed in vacuo. Distillation (140 °C, 1 Pa) (Kügelrohr) gave the title germane as a colourless oil (7.1 g, 87% yield). $[\alpha]_D^{22} = -32.2$ (*c* 1, toluene). ^1H NMR (299.98 MHz, C_6D_6): δ 0.73 (d, 3H, CH_3), 0.75 (d, 3H, CH_3), 0.78 (d, 3H, CH_3), 0.82–1.04 (m, 2H), 1.08–1.24 (m, 2H), 1.32–1.44 (m, 1H), 1.50–1.76 (m, 3H), 1.88–1.98 (m, 1H), 1.98–2.14 (m, 1H), 5.31 (s, 1H, GeH), 7.08–7.20 (m, 6H, Ph), 7.52–7.60 (m, 4H, Ph); $^{13}C\{^1H\}$ NMR (75.44 MHz, C_6D_6): δ 15.82 (CH_3), 21.91 (CH_3), 22.81 (CH_3), 26.32 (CH_2), 31.11 (CH), 31.90 (CH), 34.85 (CH), 35.57 (CH_2), 39.86 (CH_2), 45.84 (CH), 128.56/128.61 (Ph_m), 129.04/129.07 (Ph_p), 135.58/135.71 (Ph_o), 136.85/136.93 (Ph_i). Anal. Calcd for $C_{22}H_{30}Ge$ (367.08): C 71.98%, H 8.24%; found: C 71.93%, H 8.39%.

*(1S,2R,5S)-(+)-Menthylgermanium trichloride ent-***10** was prepared as described above from (1*S*,2*R*,5*S*)-menthyl chloride in 60% yield). $[\alpha]_D^{25} = +45.9$ (*c* 1, $CHCl_3$).

*(1S,2R,5S)-(+)-Menthyltriphenylgermane ent-***11** was prepared as described above from (1*S*,2*R*,5*S*)-(+)-menthylgermanium trichloride *ent*-**10** in 90% yield. Mp 101–102 °C. $[\alpha]_D^{20} = +37.1$ (*c* 1, $CHCl_3$).

*(1S,2R,5S)-(+)-Menthyldiphenylgermanium bromide ent-***12** was prepared as described above from (1*S*,2*R*,5*S*)-(+)-menthyltriphenylgermane *ent*-**11** in quantitative yield as a viscous oil. $[\alpha]_D^{21} = +43.5$ (*c* 1, $CHCl_3$).

*(1S,2R,5S)-(+)-Menthyldiphenylgermane ent-***9** was prepared as described above from (1*S*,2*R*,5*S*)-(+)-menthyldiphenylgermanium bromide *ent*-**12** in 88% yield. $[\alpha]_D^{21} = +30.0$ (*c* 1, toluene).

Typical kinetic experiment: Following our previously described procedure,[34] an aliquot (100 μL) of a standard solution (0.05–0.15 M) of germane (**9** or Bu_3GeH) in *tert*-butylbenzene was placed in a small Pyrex tube, at which point 1-bromo-5-hexene (ca. 0.1 equiv) and AIBN (ca. 1 crystal) were added and the solution degassed by the usual freeze-thaw technique, before being sealed under vacuum. After being thermolyzed in an oil bath at the required temperature, the solution was analyzed by GC.

Standard procedure for small-scale low-temperature germane reductions: Following our previously described procedure,[6] a flask fitted with a septum was charged 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 chiral germane (**9** or *ent*-**9**) (0.11 mmol) in toluene (0.5 mL) added. The reaction mixture was stirred at the required temperature for 8 h, with an additional amount of triethylborane (0.05 mL of a 1 M solution in THF) added every 2 h. The solution was warmed to room temperature and analyzed directly by GC or HPLC.

Reduction of 2-bromonaproxen ethyl ester **7** *with (1S,2R,5S)-menthyldiphenylgermane ent-***9**: Magnesium bromide etherate ($MgBr_2{\cdot}Et_2O$) (0.36 g, 1.38 mmol) was added to dry toluene (3 mL) and the mixture allowed to stir for 30 min under N_2. Bromoester **7** (0.246 g, 0.690 mmol) in dry toluene (0.2 mL) was added slowly to the reaction mixture, which was allowed to stir at rt for a further 10 min prior to cooling to −78 °C. After stirring at −78 °C for a further 45 min, (1*R*,2*S*,5*R*)-menthyldiphenylgermane *ent*-**9** (0.36 g, 0.715 mmol) in toluene (3 mL) was slowly added, followed by triethylborane (0.2 mL of 1 M solution in THF) and oxygen introduced. The reaction mixture was stirred at this temperature for a further 8 h. Additional triethylborane (0.2 mL of 1 M solution in THF) was added to the reaction mixture every 2 h. After 8 h there was no further change as evidenced by TLC. The mixture was quenched

with water (2 mL) and extracted with ether (2×). The organic layer was dried over $MgSO_4$ 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 (*R*)-naproxen ethyl ester as a colourless oil (0.027 g, 15% yield, 99% ee). ^{1}H (NMR) $CDCl_3$: δ 7.8–7.1 (6H, m), 4.1 (2H, m), 3.9 (3H, s), 3.8 (1H, q), 1.6 (3H, d), 1.4 (3H, t). $[\alpha]_D^{14} = -32.6$ (*c* 0.12, $CHCl_3$). The sample was identical to that prepared previously.[6]

Reduction of benzyl N-trifluoroacetyl-2-bromo-tert-leucinate **15** *with (1S,2R,5S)-menthyldiphenylgermane ent-***9**: Following the protocol described above, bromoester **15** afforded benzyl (*R*)-*N*-trifluoroacetyl-*tert*-leucinate as a colourless oil (20%) with identical properties to those prepared previously.[6] ^{1}H NMR $CDCl_3$: δ 7.2 (5H, m), 7.6 (1H, br s), 5.3 (2H, m), 4.5 (1H, d, *J* 8 Hz), 1.0 (9H, s). $[\alpha]_D^{14} = +8.3$ (*c* 0.4, $CHCl_3$).

Crystallographic studies: Single crystals of (1*R*,2*S*,5*R*)-(−)-menthyltriphenylgermane **11** and its enantiomer *ent*-**11** suitable for X-ray crystallography were obtained from hexane at room temperature. Crystal data and structure solutions at $T = 293(2)$ K: **11** $C_{28}H_{34}Ge$, $M_r = 443.14$, orthorhombic, $P2_12_12_1$, $a = 9.3345(6)$, $b = 12.5991(8)$, $c = 20.6109(12)$ Å, $V = 2424.0(3)$ Å^3, $Z = 4$, $D_x = 1.214$ Mg/m^3, $F(000) = 936$, $\lambda(\text{MoK}\alpha) = 0.71073$ Å, $\mu = 1.274$ mm^{-1} and *ent*-**11** $C_{28}H_{34}Ge$, $M_r = 443.14$, orthorhombic, $P2_12_12_1$, $a = 9.3103(7)$, $b = 12.5683(9)$, $c = 20.5599(15)$ Å, $V = 2405.8(3)$ Å^3, $Z = 4$, $D_x = 1.223$ Mg/m^3, $F(000) = 936$, $\lambda(\text{MoK}\alpha) = 0.71073$ Å, $\mu = 1.284$ mm^{-1}. The data were collected to a maximum $\theta = 27.49°$ **11** and 27.49° *ent*-**11** with 3 sets at different κ-angles and 362 frames via ω-rotation ($D/\omega = 1°$) at two times 10 s per frame on a Nonius Kappa CCD diffractometer with a completeness of 99.8% (**11**) and 99.8% *ent*-**11** (θ_{max}). The structures were solved by direct methods using SHELXS-97[37] and refined by full-matrix least-squares calculations using all measured F^2 data and SHELXL-97.[38] All non-H atoms were refined anisotropically. The H atoms were placed in geometrically calculated positions using a riding model. Atomic scattering factors for neutral atoms and real and imaginary dispersion terms were taken from International Tables for X-ray Crystallography.[39] The figures were created by DIAMOND.[40] $R_1 = 0.0393$ for 5161 [$I > 2\sigma(I)$] and $wR_2 = 0.0857$ for 5533 independent reflections **11** and $R_1 = 0.0499$ for 4814 [$I > 2\sigma(I)$] and $wR_2 = 0.0982$ for 5503 independent reflections *ent*-**11**. The max. and min. residual electron densities were 0.598/−0.226 e Å^{-3} for **11** and 0.631/−0.449 e Å^{-3} for *ent*-**11**. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 240940 and 24094.

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