

Synthesis and Asymmetric Hydrogermylation Reactions of Dithiogermanium Hydrides Derived from C2-Symmetric Dithiols

Dennis P. Curran, Giovanna Gualtieri

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA15260, USA

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Dedicated to Prof. Ryoji Noyori for his enduring contributions to stereoselective synthesis.

Abstract: Two members of a new class of dithiogermanium hydrides have been prepared in racemic and enantiopure form. Reaction of 2,2'-dithiobinap and 3,3'-bis-trimethylsilyl-2,2'-dithiobinap with BuGeCl_3 followed by reduction provides the corresponding germanium hydrides. Hydrogermylation of methyl methacrylate occurs with low selectivity ($<3/1$) for the former substrate but high selectivity ($>10/1$) for the latter.

Key words: hydrogermylation, germanium hydrides, stereoselectivity

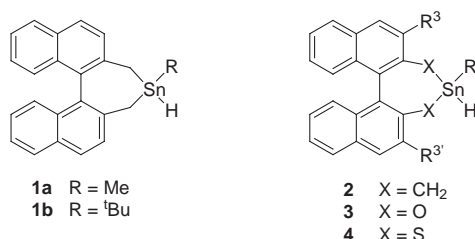


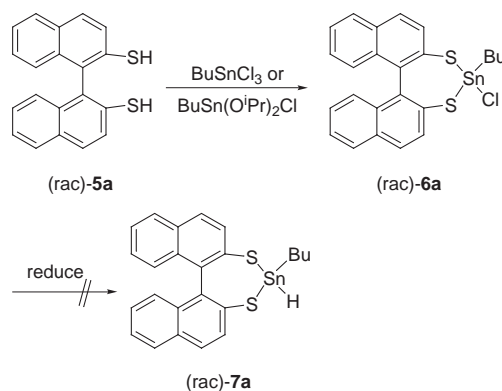
Figure 1

Despite the fast pace of advances in enantioselective radical reactions,¹ asymmetric reactions of chiral tin hydrides² still present a significant challenge. In 1996, we introduced the first enantiopure tin hydride **1a** fashioned from the popular C2-symmetric binaphthyl motif (Figure 1).³ Radical reductions with this tin hydride gave products with low to moderate ees (up to 40%). In independent work, Metzger and coworkers reported the *t*-butyl analog **1b**, which gave somewhat better ees (up to 50%).⁴ This level has since been passed by Schiesser⁵ and Hoshino⁶ by using tin hydrides in conjunction with Lewis acids.⁷ However, it is still of interest to develop asymmetric reactions that are controlled by the tin hydride alone. In this regard, we envisioned that it might be interesting to build a tin hydride inside a cleft that could better influence the geometry of an approaching radical. We report herein preliminary results that led us to synthesize two dithiogermanium hydrides **9a** and **9b** as alternatives for the traditional tin hydride. Hydrogermylation of methyl methacrylate with one of the germanium hydrides occurs with high selectivity.

Inspired by the work of Yamamoto,⁸ Wulff,⁹ and others, we envisioned that addition of substituents at C3 and C3' on the binap ring would influence the approach of radicals to the hydrogen atom of a tin hydride, and we evaluated a number of approaches to make molecules like **2** (Figure 1). Analogs **2** with the CH_2 bridge are the direct descendants of **1**, but these might not be straightforward to make. We spent some time trying to make analogs **3** ($\text{R}^3, \text{R}^{3'} = \text{H}$) with an oxygen bridge, but the Sn–O bonds in these molecules seemed too labile. Recognizing that tin–sulfur bonds are more robust,¹⁰ we next moved to the sulfur analogs **4** ($\text{R}^3, \text{R}^{3'} = \text{H}$).

Reaction of the racemic dithiobinap¹¹ (rac)-**5a** with either BuSnCl_3 or $\text{BuSn}(\text{O}i\text{Pr})_2\text{Cl}$ produced dithiotin chloride (rac)-**6a** (eq 1). As hoped, this proved to be quite stable in

the solid state. Unfortunately, we were not able to reduce **6a** to the corresponding tin hydride (rac)-**7a**, despite extensive effort. A few reducing agents (for example AlH_3 and Bu_3SnH) returned unreacted starting material, but most (for example, LiAlH_4 and DIBAL) disassembled **6a** to return the starting dithiol **5a**. Presumably, the Sn–S bonds were reduced along with the Sn–Cl bond by these reductants.

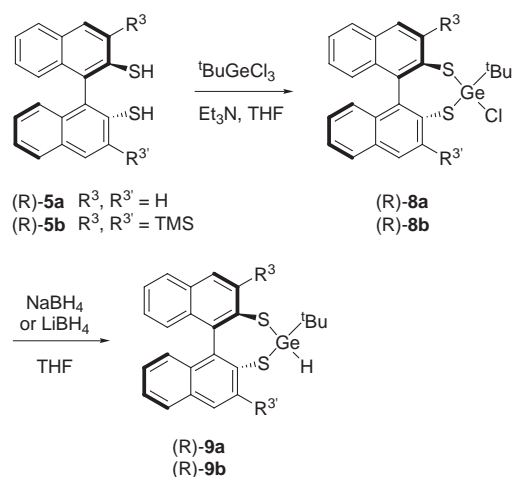


Equation 1

To strengthen the bond to sulfur, we then explored the nuclear substitution of tin by germanium. Germanium hydrides are well known if rarely used alternatives to tin hydrides in radical reactions.¹² Trialkylgermanium hydrides are poorer hydrogen donors than related tin hydrides; however, there is reason to expect that this rate-retarding effect could be offset by an activating effect of the two thio substituents.¹³ Thio-substituted germanium

hydrides are a relatively rare class of molecules¹⁴ whose members have not to our knowledge been previously used for radical chain reactions. Only a few chiral germanium hydrides are known,¹⁵ and chiral dithiogermanium hydrides are unknown.

Reaction of racemic dithiol **5a** with ^tBuGeCl₃ in THF provided the crystalline germanium chloride (rac)-**8a** in over 95% yield (eq 2; note, eq 2 shows single enantiomers only). This was a relatively stable molecule as a solid and in solution and it could be handled without any special precautions. But it slowly hydrolyzed to the germanium hydroxide in the presence of moisture. Reduction of the germanium chloride (rac)-**8a** to the hydride (rac)-**9a** again proved problematic, but could be accomplished under carefully controlled conditions. Reduction in THF with sodium borohydride followed by standard extractive workup with a base wash gave germanium hydride (rac)-**9a** contaminated with <2% of the dithiol (rac)-**5a** and trac-



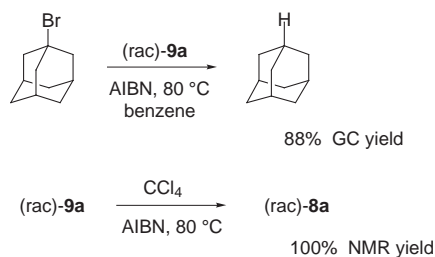
Note: Eq 2 shows single enantiomers. Racemates (rac)-**5a/b**, (rac)-**7a/b** and (rac)-**8a/b** were also made.

Equation 2

es of another unidentified impurity. This could be further purified by chromatography at the expense of extensive material loss (30–40%), and it was generally used in crude form.

Two simple reactions demonstrated that (rac)-**9a** moderates radical chain reductions. Reduction of adamantyl bromide under standard condition provided adamantane in 88% GC yield. To assess the germanium product, we reacted (rac)-**9a** in CCl₄ (solvent), and showed in an NMR experiment that germanium chloride (rac)-**8a** was formed in quantitative yield. The enantiopure germanium hydride from (R)-**9a** was also prepared from (R)-**5a**,¹⁶ and its hydrogermylation reactions with methyl methacrylate are presented below.

To evaluate the effects of bulky substituents at C3 and C3', germanium hydride **9b** was prepared from both racemic and (R)-dithiol **5b** bearing two trimethylsilyl



Equation 3

groups.^{17,18} Conversion to the dithiogermanium chloride **8b** was straightforward, but reduction to **9b** again required great care to prevent over-reduction to return **5b**. However, both racemic and enantiopure hydrides **9b** could be purified by recrystallization (>95% pure, 65–80% yield).

In a preliminary assessment of the structural effects on stereochemistry, we conducted hydrometallations of methyl methacrylate with the previously reported (*S*)-trialkyltin hydride **1a**³ and both of the new dithiogermanium hydrides **9a,b** (both racemic and enantiopure) under standard conditions. The results of some representative experiments are shown in Figure 2 and the Table. Hydrostannation with (*S*)-**1a** provided **10a/11a** in a ratio of 1.3/1. The diastereomeric products were not separable, and the relative configurations were not assigned. Hydrogermylation with (rac)-**9a** provided (rac)-**12a/13a** in a 1.7/1 ratio, while the use of (R)-**9a** gave enantiopure **12a/13a** in a 3/1 ratio. These products were separated by chromatography, and the crystal structure of the minor isomer was solved to assign the relative configuration.

In contrast to these relatively low selectivities, hydrogermylation with **9b** was quite selective. Racemic **9b** provided racemic **12b/13b** in an 11/1 ratio at room temperature and a 14/1 ratio at –20 °C, while the use of (R)-**9b** gave enantiopure **12b/13b** in improved ratios: 15/1 at 25 °C and 25/1 at –20 °C. The major isomer **12b** could be isolated in

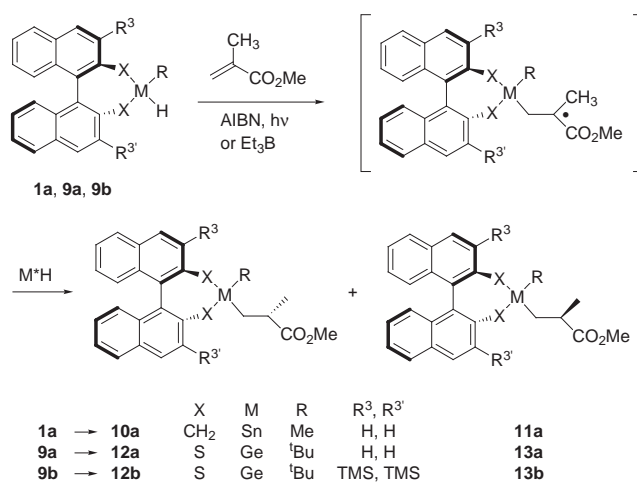


Figure 2

Table Hydrometallation of Methyl Methacrylate with Tin Hydride **1a** and Germanium Hydrides **9a,b**.

Entry	Hydride	Temp	Products	Yield ^a	Ratio
1	(S)- 1a	25°C	(S)- 10a/11a	60%	1.3/1 ^{b,c}
2	(rac)- 9a	25°C	(rac)- 12a/13a	57%	1.8/1 ^b
3	(rac)- 9a	−78°C	(rac)- 12a/13a	77%	1.7/1 ^b
4	(R)- 9a	−78°C	(R)- 12a/13a	61%	3/1 ^b
5	(rac)- 9b	25°C	(rac)- 12b/13b	61%	11/1 ^d
6	(rac)- 9b	−20°C	(rac)- 12b/13b	63%	14/1 ^d
7	(R)- 9b	25°C	(R)- 12b/13b	56% ^e	15/1 ^d
8	(R)- 9b	−20°C	(R)- 12b/13b	55% ^e	25/1 ^d

a) Isolated yield of mixture unless otherwise indicated; b) by NMR analysis; c) configurations of **10a/11a** not known; d) by HPLC analysis; e) isolated yield of pure **12b**.

pure form by chromatographic purification, and the crystal structure of the alcohol (not shown) obtained by DIBAL reduction was solved to assign the relative configuration.

The change from dialkyltin hydride **1a** to dithiogerma- nium hydride **9a** has relatively little effect on the stereoselectivity, but the addition of the two trimethylsilyl groups, **9b**, has a strong beneficial effect. This supports the notion that bulky substituents in the vicinity of the Ge–H bond can enhance selectivity. Two germaniums are involved in the asymmetric hydrogen transfer step in a kind of double asymmetric induction. Comparison of the results with racemic and enantiopure hydrides suggests that the germanium atom bonded to the radical plays the major role while the germanium atom that donates the hydrogen enhances the selectivity somewhat if both germaniums are of the same configuration (matched pair).

These results encourage further work on the design and synthesis of tin, germanium or silicon hydrides where the M–H bond begins to reside in a cleft defined by the substituents. Detailed studies on the structure (x-ray, NMR) and reactivity (rate constants, *ees*) of the two new germanium hydrides will be reported in a forthcoming full paper.

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- (18) Representative Procedures: **4-tert-Butyl-4-chloro-2,6-bis-trimethylsilyl-3,5-dithia-4-germa-cyclohepta[2,1-a;3,4-a']dinaphthalene (8b)**. Triethylamine (1 mL, 7.2 mmol) was added dropwise to a stirred solution of 3,3'-bis(trimethylsilyl)-1,1'-binaphtho-2,2'-dithiol (**5b**) (845 mg, 1.8 mmol) and *t*-BuGeCl₃ (480 mg, 2.0 mmol) in THF (40 mL) at 0 °C. After addition was complete, the ice bath was removed and the reaction mixture allowed to warm to room temperature. After stirring for 2 h, the mixture was diluted with diethyl ether and filtered. The filtrate was concentrated under reduced pressure and the residue recrystallized from hexanes to afford 1.11 g (97%) of **8b** as white crystals.

4-tert-Butyl-2,6-bis-trimethylsilyl-3,5-dithia-4-germa-cyclohepta[2,1-a;3,4-a']dinaphthalene (9b). Lithium borohydride (2.0 M solution in THF, 6.2 mL, 12.4 mmol) was added to a stirred solution of **8b** (388 mg, 0.62 mmol) in THF (20 mL) at 0 °C. The reaction mixture was kept at −8 °C without stirring for 5 days, then it was diluted with diethyl ether and poured into 100 mL of cold NH₄Cl aqueous solution

with stirring. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 30 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. After recrystallization from hexanes, 285 mg of **9b** (78%) were obtained as white crystals.

General procedure for hydrogermylation of methyl methacrylate with 9b. In a sealed tube purged with argon were placed methyl methacrylate (2.0 equiv, 21 μL , 0.20 mmol), the germanium hydride **9b** (60 mg, 0.10 mmol) and toluene (benzene for reactions at r.t., 1 mL). Triethylborane (1.0 M soln in hexanes, 25 μL , 0.025 mmol) was then added and the resulting mixture was stirred at the appropriate temperature

until TLC analysis showed complete conversion of the germanium hydride. Triethylborane (1.0 M soln in hexanes, 25 μL , 0.025 mmol) was added periodically if needed. After completion, the crude mixture was filtered through a silica gel plug and analyzed by HPLC. After removal of the solvent, the crude mixture was subjected to column chromatography (ethyl acetate/hexanes 2:98) or preparative HPLC (ethyl acetate/hexanes 1:99) to give 55–77% yield of the adducts **12b** and **13b**.

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