

## Asymmetric Hydroboration-Oxidation of Alkenes by means of Deuterium or Tritium Labelled Asymmetric Monoalkylboranes

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### SUMMARY

(2-(1,3-Dithianyl))myrtanylborane (MDBH<sub>2</sub>), a stable asymmetric monoalkylborane, was converted into deuterated or tritiated analogues used to prepare enantiomeric labelled alcohols from 1-phenylcyclopentene with a high isotopic enrichment (90-95% for deuterium; 86-89% for tritium) and a high asymmetric induction (80% ee for deuterium; 75% ee for tritium).

**Key Words:** Tritiated Monoalkylborane, Deuterated Monoalkylborane, Asymmetric Synthesis, (2-(1,3-dithianyl))myrtanylborane (MDBH<sub>2</sub>), Chiral Labelled Alcohol.

### INTRODUCTION

Numerous ligands of interest for biochemical assays are asymmetric molecules. However, it is relatively rare that chiral tritiated radioligands result from simultaneous asymmetric induction and labelling, with a high isotopic and enantiomeric enrichment. However, it is known for a long time that chiral compounds labelled with deuterium are obtainable via organoboranes (1). We report a simple and one-pot enantioselective preparation of alcohols labelled with deuterium and tritium via organoboranes. (2-(1,3-Dithianyl))myrtanylborane (MDBH<sub>2</sub>) (Figure 1), recently described (2,3), is a stable uncomplexed monoalkylborane

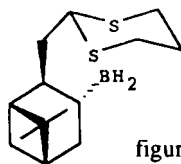


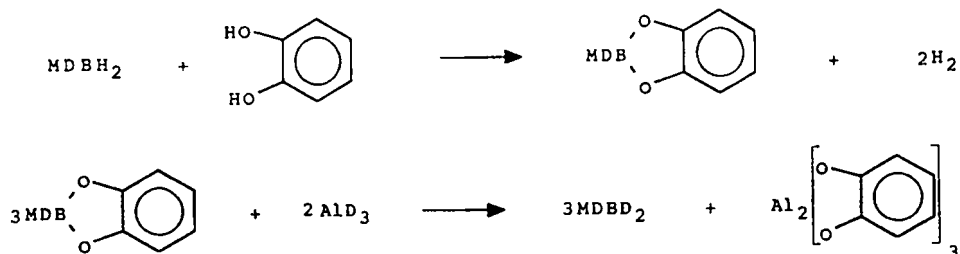
figure 1: (+)-MDBH<sub>2</sub>.

useful for hydroboration of alkenes yielding chiral alcohols with a good enantiomeric excess (ee). Furthermore, it is known in both enantiomeric forms: (+)-1R, 2S, 3R, 5R and (-)-1S, 2R, 3S, 5S. Consequently, the replacement of the two hydrogen atoms in MDBH<sub>2</sub> by deuterium or tritium may lead to interesting reagents for the preparation of chiral labelled alcohols. Taking advantage of the stability and purity of the MDBH<sub>2</sub> reagent, we were able to generate MBD<sub>2</sub> and to extend the scope of the synthesis to MDBT<sub>2</sub>. Interestingly

enough, it was not necessary to isolate the labelled reagents. 1-Phenylcyclopentene, introduced in the synthetic mixture of the labelled reagent, was easily converted into [2-<sup>2</sup>H]-*trans*-2-phenylcyclopentanol or [2-<sup>3</sup>H]-*trans*-2-phenylcyclopentanol with a very high isotopic enrichment.

### SYNTHESIS

Alkylcatecholboranes are well known to be easily reduced into corresponding boranes (4). Hence, we have prepared the catecholborane derivative of (2-(1,3-dithianyl))myrtane from MDBH<sub>2</sub> and pyrocatechol, an easier way than the hydroboration of the alkene with the catecholborane (5). It was characterized by its <sup>11</sup>B-NMR spectrum (+37 ppm from BF<sub>3</sub>/Et<sub>2</sub>O), then reduced in situ with AlD<sub>3</sub>, generated from LiAlD<sub>4</sub> and AlCl<sub>3</sub> (Scheme 1).

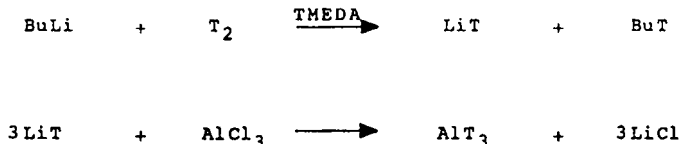


The resulting MDBD<sub>2</sub> was simply characterized via its <sup>11</sup>B-NMR spectrum (-9 ppm). As we were unable to separate the labelled reagent from the aluminium catechol complex, 1-phenylcyclopentene was added in the synthetic mixture in an equimolar ratio to the MDBH<sub>2</sub> introduced at the first step. All reactions were carried out in anhydrous THF under dry nitrogen. After oxidation by peroxide anion and purification by means of a preparative HPLC, [2-<sup>2</sup>H]-*trans*-2-phenylcyclopentanol was recovered in a good yield: 75-80% at mean. The deuterated alcohol was characterized from its <sup>13</sup>C-NMR and mass spectra (electronic impact). The isotopic enrichment computed from mass spectra (chemical ionization in ammonia) was found to be 90-95% at mean. Finally, the enantiomeric excess was determined by means of an analytical HPLC equipped with a chiral column (Chiralcel OD, UV detection, 260 nm). Alcohols yielded after two parallel experiments done with each of the MDBH<sub>2</sub> enantiomers (same enantiomeric and chemical purity) were compared with the alcohol obtained via the unlabelled reagent (-)-MDBH<sub>2</sub> known to give the (-)-alcohol (2). HPLC peaks being perfectly reliable, the computed enantiomeric excess was found to be 80% at mean for the deuterated alcohol (85% for the unlabelled one). These results correlate nicely with the α<sub>D</sub> (Table I) measured for the different alcohols obtained.

**TABLE I:** Comparison between HPLC results and α<sub>D</sub> measurements.

Reagent	Alcohol (HPLC) (% ee)	α <sub>D</sub> (c=5, ethanol)
(-)-MDBH <sub>2</sub>	85	- 61.6°
(-)-MDBD <sub>2</sub>	80	- 61.3°
(+)-MDBD <sub>2</sub>	80	+ 63.3°
litterature (6)	-	71.1°

The same one-pot process was adopted to yield tritiated asymmetric alcohols. AlT<sub>3</sub> was prepared from LiT and AlCl<sub>3</sub>, LiT resulting from the reaction between butyllithium and tritium gas in the presence of tetramethylethylene diamine (TMEDA) (7) (Scheme 2). The process was modified to avoid the complexation between TMEDA and MDBT<sub>2</sub> which



reduces the reactivity. Thus, TMEDA was evaporated under reduced pressure before the addition of AlCl<sub>3</sub>. After a purification in HPLC, [2-<sup>3</sup>H]-*trans*-2-phenylcyclopentanol, was obtained in a 15-17% radio yield. It was characterized by <sup>3</sup>H-NMR (2.81 ppm) and mass spectroscopy. Isotopic enrichment was 86-89% at mean -i.e.- a specific activity of 25.1-25.8 Ci/mmol (theoretical: 29 Ci/mmol). The enantiomeric excess determined by means of HPLC as above but with a radioactive detection was 75%.

#### DISCUSSION

Such an easy and simple one-pot synthesis of chiral labelled alcohols may be very useful for the generation of chiral tracers for biological assays requiring a high enantiomeric excess and a high isotopic enrichment. Apparently we may be observing an isotopic effect during the asymmetric induction: the ee varies from 85% with the protonated reagent to 75% with the tritiated one. It is too early for such an interpretation considering this was observed in one alkene model only. Moreover, processes are not strictly identical in the different cases particularly for tritium. Work is now in progress to generalize the scope to different kinds of unsaturated structures.

#### EXPERIMENTAL SECTION

##### Materials

All chemicals were from commercial sources (Aldrich) except for tritium gas, LiAlD<sub>4</sub> (Service des Molécules Marquées, Saclay, France) and MDBH<sub>2</sub> (Expansia, Aramon, France). Tetrahydrofuran, TMEDA and 1-phenylcyclopentene (prepared in the laboratory) were purified by standard procedures and kept under nitrogen before use. All reactions were carried out under nitrogen in glassware dried at 150°C and cooled under nitrogen. NMR spectra were recorded on a Bruker AC 300 at 320.130 MHz for <sup>3</sup>H, on a Bruker WP 80 at 20.147 MHz and 25.699 MHz for <sup>13</sup>C and <sup>11</sup>B respectively. All the measurements were done in the FT mode with reference to tritiated water (external), TMS (internal) and boron trifluoride etherate (external). Mass spectra were recorded on a Quadrupole Finnigan Mat 4600. The purification of deuterated and protonated alcohols was done on a preparative HPLC (Modulprep Jobin Yvon) equipped with a refractometric detection. The column was made of 100 g of silicagel (15-35 μm). The purification of the tritiated alcohols was done on a preparative HPLC equipped with a radioactive detection. The column was made of 25 g of silicagel (15-25 μm). The chiral analytic HPLC column was a chiralcel OD from Daicel Chemical Industries, length 250 mm, diameter 4.6 mm. The final radioactivity of the tritiated samples was counted in a Shlumberger ECT34 apparatus. The optical rotations were measured by using a Perkin-Elmer spectropolarimeter.

Catecholborane of (2-(1,3-dithianyl))myrtane

MDBH<sub>2</sub> (1.86 g, 6.94 mmol) dissolved in 4 ml of tetrahydrofuran (THF) was slowly added to a stirred solution of pyrocatechol (763 mg, 6.94 mmol) in 6 ml of THF heated at 50°C. A rapid hydrogen evolution was observed. The stirring and heating were maintained until the gas evolution was stopped. The solution as prepared was used in the next step.

MDBD<sub>2</sub>

AlCl<sub>3</sub> (154 mg, 1.15 mmol) dissolved in 7.6 ml of a 0.458 M solution of LiAlD<sub>4</sub> was added at 0°C to the stirred solution obtained in the preceding step. After 15 min of stirring the solution as prepared was used in the next step.

[2-<sup>2</sup>H]-trans-2-Phenylcyclopentanol

1-Phenylcyclopentene (1 g, 6.94 mmol) was added at 0°C to the stirred solution obtained in the preceding step. Then the solution was kept at 5°C for 7 days and looked like a jelly after some days. NaOH (277 mg) in 2.15 ml of H<sub>2</sub>O<sub>2</sub> 9.7N (20.8 mmol) was slowly added at -30°C, and the temperature was allowed to rise to 20°C. After 1 hour at this temperature the solution was poured into water and extracted with ether. The organic layer washed with water to neutral was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude product was purified by means of a preparative HPLC in a mixture of hexane and ethyl ether (82/18) to give a 75-80% yield in pure alcohol.

[2-<sup>3</sup>H]-trans-2-Phenylcyclopentanol

In this one-pot procedure all reactions were carried out at 20°C. A 1.6 M solution of n-butyllithium (0.86 mmol) in hexane containing tetramethyl ethylene diamine (TMEDA) (0.92 mmol) was stirred under a tritium gas atmosphere until no more gas absorption occurred. The solvent and TMEDA were removed under reduced pressure to yield LiT. AlCl<sub>3</sub> (38.3 mg, 0.287 mmol) dissolved in 0.57 ml of THF was added to LiT. After 15 min of stirring LiCl precipitated. Then, catecholborane (obtained as in the first step of the MDBD<sub>2</sub> synthesis) (115 mg, 0.431 mmol) dissolved in 1.15 ml of THF was added. Just after this addition, 1-phenylcyclopentene (62 mg, 0.431 mmol) was also added. After 7 days the medium was oxidized by a solution of NaOH (17.2 mg, 0.431 mmol) in 0.133 ml of H<sub>2</sub>O<sub>2</sub> 9.7 N (1.29 mmol). The crude tritiated product was purified by means of a preparative HPLC in a mixture of hexane and ethyl ether (75/25) to give a 15-17% radioactive yield of labelled alcohol.

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