

## **Reductive properties of (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethylstannane)**

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### **Abstract**

The synthesis and application of (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethylstannane) as reductive agent is reported. We focused on the reduction of  $\alpha$ -bromo esters, inspired in the work of Metzger and co-workers. These compounds can be reduced by using an organotin halide and NaCNBH<sub>3</sub> as a source of hydride. When the reaction of methyl 2-bromo-2-phenylbutanoate was performed in the conditions describe below, we observed that not only the reduction on the alpha position was achieved but also on the ester function.

**Keywords:** organotin hydrides,  $\alpha$ -bromo esters reduction

### **Introduction**

Organotin halides and hydrides have been widely used in organic synthesis.<sup>1</sup> Organotin hydrides can react at the hydrogen centre with electrophiles, nucleophiles or free radicals, all process are important, but the recent chemistry of hydrides has been dominated by the radical reactions.

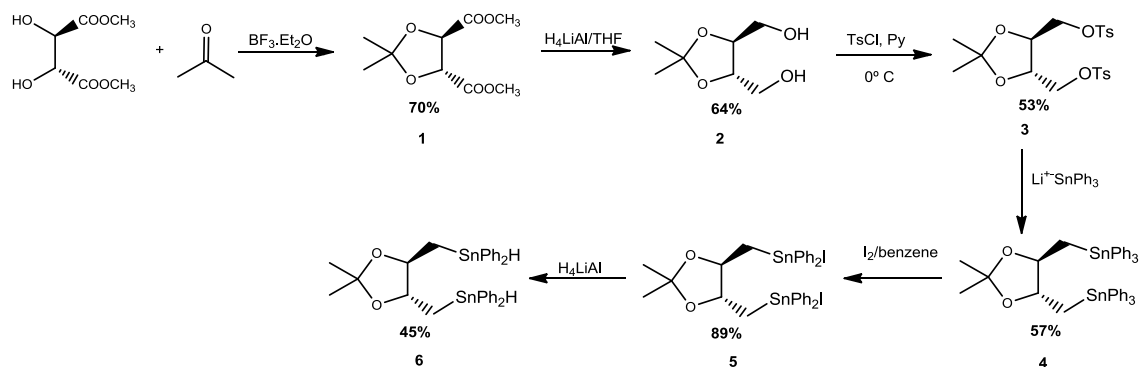
In order to use them in asymmetric synthesis, several chiral organotin compounds have been synthesized and applied in reactions such as ketone reduction,  $\alpha$ -bromo esters reduction and radical cyclization of aldehydes, among others.<sup>2</sup> There are several chiral organotin compounds known that have either a stereogenic tin atom or a tin substituent bearing a stereogenic center. While the latter have found applications in asymmetric synthesis, the forward are not useful since they tend to undergo ready racemization. In the history of chiral tin hydrides donors, several contributions were based on terpene-derived reagents, where the tin atom was bearing for example a menthyl group, and alkyl- or aryl- groups in addition to hydrogen. However, none of these compounds have shown a good performance in asymmetric reduction.<sup>3</sup>

On the other hand, C<sub>2</sub>-symmetric compounds have been found great applications in asymmetric synthesis. In 1996, Curran<sup>4</sup> and Metzger<sup>5</sup> reported the first results in the enantioselectivity hydrogen transfer using tin hydrides containing a C<sub>2</sub>-symmetric moiety. They applied the organotin hydride in the reduction of  $\alpha$ -bromo esters. It was postulated that chiral organotin hydrides are hydrogen donors, which can trap prochiral radicals without lost of chirality under free radical conditions. This reaction is an example of a stereoselectivity in which a chiral reagent distinguishes between the enantiotopic faces of a radical in diastomeric transition states, and is different from enantioselectivity reactions with chiral auxiliaries coordinated to the radical.<sup>6</sup>

### **Results and Discussions**

Owing to the succeeded of the (-)-DIOP reported by Kagan in 1968<sup>7</sup> in asymmetric hydrogenation and others important applications of dioxolane derivatives,<sup>8</sup> we decided to synthesized a new organotin hydride with the dioxolane structure.

The synthesis of (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethylstannane) (**6**) was achieved in six steps starting from dimethyl-(L)-tartrate (**Scheme 1**).



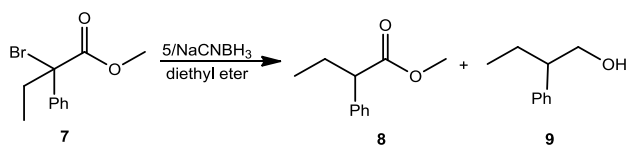
**Scheme 1**

The first attempt was to use it in the reduction of prochiral ketones. However, we faced with several disadvantages because stoichiometric amounts of the tin hydrides were needed to reduced ketones, and despite of this, the tin hydride was unable to reduce them completely (**Scheme 2**). Only 30% of the initial ketone (acetophenone and 1-indanone) was reduced. The low yield in this reaction conditions could be attributed to the formation of a cyclic diastannane.



**Scheme 2**

The work of Metzger and co-workers<sup>9</sup> inspired us to apply organotin hydride **6** in the reduction of  $\alpha$ -bromo esters. These authors have performed the reduction by using catalytic amounts of a chiral hydride or halide, and sodium cyanoborohydride as a source of hydride. In this condition, the tin hydride is generated or regenerated *in situ* because of the excess of NaCNBH<sub>3</sub>. Since the last step in the synthesis of **6** provide it in low yield, we tried the reduction of methyl 2-bromo-2-phenylbutanoate with catalytic amounts of the halide **5** and an excess of NaCNBH<sub>3</sub>. The reactions were performed with 1, 5 and 10 mol% of the organotin halide. The reaction was completed when 10 mol % was used but not only the reduction on the alpha position was achieved but also on the ester function (**Scheme 3**). The results are summarized in Table 1.



**Scheme 3**

**Table 1.** Percentage of products obtained with different amounts of **5**.

Entry	% of <b>5</b> (mol%)	T [C°]	t [h]	Products (%)
1	0	25	72	-----
2	1	25	72	<b>8</b> (8%) : <b>9</b> (67%)
3	5	25	24	<b>8</b> (19%) : <b>9</b> (30%)
4	10	25	24	<b>8</b> (21%) : <b>9</b> (78%)
5	10	0	18	<b>8</b> (29%) : <b>9</b> (71%)

In order to determine the reaction time required under the best reaction conditions which allowed the reaction to complete, we repeat the experiment of entry 4, Table 1, and took aliquots in different times, determining the percentage of each product in each sample. Results are summarized in **Table 2**.

**Table 2.** Products along the time under entry 4, Table 1 conditions

Entry	time (h)	Products (%)
1	1	-----
2	2	traces of <b>8</b> and <b>9</b>
3	4,5	<b>8</b> (17%) : <b>9</b> (7%)
4	9	<b>8</b> (25%) : <b>9</b> (75%)
5	24	<b>8</b> (21%) : <b>9</b> (78%)

The formation of the products started after 2 hours of reaction. At the beginning, product **8** was formed in higher proportion than **9**, but few hours later **9** is the predominant product.

In order to determine the possibility of obtaining the product **8** in greater proportion than **9**, we added AIBN as radical initiators to the reaction mixture. Results are summarized in **Table 3**.

**Table 3.** Reduction of methyl 2-bromo-2-phenylbutanoate (**7**) with **5** /NaCNBH<sub>3</sub> /AIBN

Entry	% of <b>5</b> (mol%)	T [C°]	t [h]	Products (%)
1	1	25	72	<b>8</b> (21%) : <b>9</b> (79%)
2	10	25	48	<b>8</b> (45%) : <b>9</b> (55%)

As can be seen, in the reaction conditions of entry 2, the yield of **8** is higher but **9** is still the most important product of the reaction. It is also noted that the addition of AIBN can achieve full substrate **7** conversion even when low concentration of hydride **5** are used

## Conclusions

The formation of product **9** is an unexpected result since we did not find in literature any mention of the reduction of ester function with organotin hydride that were used to reduced  $\alpha$ -bromo esters. In the work of Metzger and co-workers, which inspired our work, it is reported only the formation of the reductive product in the alpha position, even when the reaction time is more than 48 h.

As we performed a witness reaction only with NaCNBH<sub>3</sub> (Entry 1, Table 1), we can be sure that this chemical is not the responsible for the ester function reduction. We postulated then that (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethylstannane) (**6**) has a high reductive power compare to the usual organotin hydrides. In order to confirmed that and to determine the extent of asymmetric induction that it can exert, further studies will be done.

## Acknowledgments

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## Experimental section

### General methods

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All reactions were carried out under an inert atmosphere.

Compounds **1**, **2** and **3** were synthesized according to literature procedures.<sup>10</sup> The synthesis of methyl 2-bromo-2-phenylbutanoate (**7**) have already been reported.<sup>11</sup> All solvents were dried following typical procedures.<sup>12</sup>

### Synthesis of (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-bis(triphenylstannane) (**4**)

In a two necked round-bottom flask, 1, 49 g (4,2 mmol) of triphenyltin lithium<sup>13</sup>, were placed. A solution of 500 mg of **3** (1,06 mmol) in 7 ml of THF was slowly added. After addition, the reaction was stirred at room temperature for 10 minutes. Then 5 ml of a saturated solution of NH<sub>4</sub>Cl was added. The layers were separated and the aqueous were extracted with ethyl acetate. The combined organic layers were dried over MgSO<sub>4</sub> and the solvent was removed under vacuum.

The product was recrystallized in ethanol and afforded 501 mg (0,6 mmol, 57%) of (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-bis(triphenylstannane) (**4**) as a white solid. m.p: 102 -104 °C.  $[\alpha]_D^{22} = -27,5$  (C 0,12 CHCl<sub>3</sub>).

### (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenyltiniodide) (**5**)

In a two necked round-bottom flask, 740 mg (0,89 mmol, 1 eq) of **4** and 10 ml of benzene were placed. A solution of I<sub>2</sub>, 453 mg (1,78 mmol, 2 eq.) in 20 ml of benzene was slowly added. Once the addition was complete, the solution was stirred at room temperature for 1 h. Then the solvent was removed under vacuum. The crude product was washed two times with hexane. The product **5** was obtained as a pale yellow solid (740mg, 89%). m.p = 109-111°C.  $[\alpha]_D^{22} = -18,75$  (C 0,4 acetone)

### (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethylstannane) (**6**)

In a two necked round-bottom flask 87 mg (2,3 mmols) of H<sub>4</sub>LiAl and 3,5 ml of diethyl ether were placed. The solution was cooled down to 0° C. Then a solution of **5** 1,07g (1,15 mmol) in 11 ml of diethyl ether was added drop by drop. After 30 minutes a few drops of a saturated solution of NH<sub>4</sub>Cl were added. The layers were allowed to separate and the organic was transferred to another flask and CaCl<sub>2</sub> was added. The solution was transferred again to another flask and the solvent was evaporated. All the procedures were carried out under inert atmosphere. The product was purified by column chromatography and afforded 350 mg (0,5 mmol, 45%) of the desired tin hydride.

### Typical procedure for the reduction of **7**

All the reactions were carried out following the same procedure. One experiment is described in detail in order to illustrate the methods used.

In a two necked round-bottom flask 73 mg (1,1 mmol, 3 eq.) of NaCNBH<sub>3</sub>, 36 mg (10mol%) of **5** and 2 ml of dry diethyl ether were placed. Then 100 mg (0,39 mmol, 1eq) of methyl 2-bromo-2-phenylbutanoate (**7**) were added by means a syringe. The reaction was stirred at room temperature for 24 h. After this, 1 ml of a saturated solution of NH<sub>4</sub>Cl was added. The layers were separated and the organic layer was dried over MgSO<sub>4</sub>. The solvent was evaporated under vacuum.

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