

An improved procedure for the separation of (+) or (–)-isopinocampheol, the major side product of the oxidation workup procedure of Brown's asymmetric crotylboration

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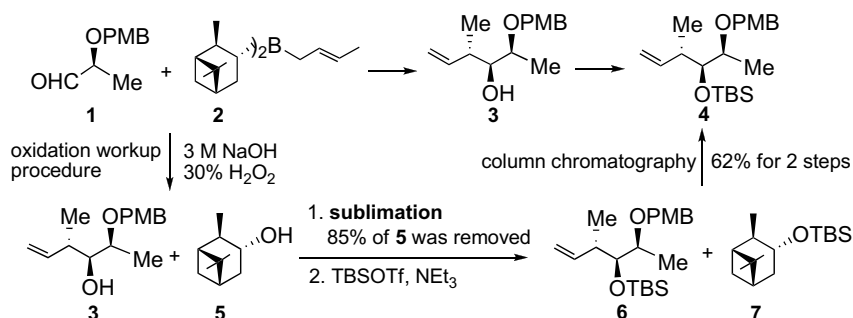
Abstract—Separation of (+) or (–)-isopinocampheol, the major side product of the oxidation workup procedure of Brown's asymmetric reactions such as crotylboration from the desired product is quite tedious and often requires repeated column chromatography. It is discovered that a sublimation process can be used to easily separate this major side product.
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Over the last two decades, asymmetric allyl- and crotylborane reagents have received a great deal of attention for their ability to create carbon–carbon bonds in a highly stereodefined fashion.¹ The asymmetric allylboration and crotylboration developed by Brown are two of the most popular reactions in organic chemistry² and numerous natural products were synthesized in recent years using these reactions.³

During the application of Brown's asymmetric allyl- or crotylboration reaction, the chiral auxiliary is typically destroyed by hydrogen peroxide oxidation and a large quantity of terpenol byproduct is produced. Although

the byproduct sometimes can be separated by column chromatography, difficulty in the isolation and purification is often observed when the desired product and the terpenol byproduct have similar R_f values.⁴

In connection with a total synthesis project in our laboratories, Brown's asymmetric crotylboration was employed to convert aldehyde **1** to homoallyl alcohol **3**, which would be protected by a TBS group (Scheme 1).⁵ Although the reaction provided the desired product **3** with excellent diastereoselectivity, it was very tedious to isolate and purify compound **3** in the presence of boron-containing side products. We first tried the



Scheme 1.

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ethanolamine workup procedure,^{2d} but we found that it was impossible to completely filter off the ethanolamine adduct, and repeated column chromatography was needed, which resulted in lower yield of compound **3**. We then employed the oxidation procedure^{2a} by quenching the reaction with 3 M NaOH solution followed by the addition of 30% H₂O₂. However, we found that it was very hard to separate compound **3** from the major side product of this procedure, (–)-isopinocampheol **5** by silica gel column chromatography because they had very close *R_f* values on the TLC in various solvent systems. This prompted us to search for a better method to separate compound **3** from compound **5**.

During the evaporation of the solvent of the crude reaction mixture after the oxidation workup, some white crystals of compound **5** were found inside the anti-splash adapter on the rotary evaporator. This observation suggested that isopinocampheol could undergo sublimation on heating. Therefore, we decided to investigate the possibility to separate the major side product **5** by the means of sublimation.

We found that the sublimation was quite slow when the crude mixture was heated at 65 °C. The sublimation was still slow with the combination of heating and reduced pressure via a vacuum pump. However, the sublimation was much faster when the crude mixture was heated at 65 °C under reduced pressure via a water aspirator. A dry-ice condenser was placed on top of a round-bottom flask as the cooling trap (Fig. 1). To fully utilize the sur-

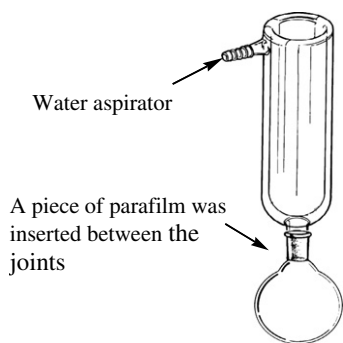
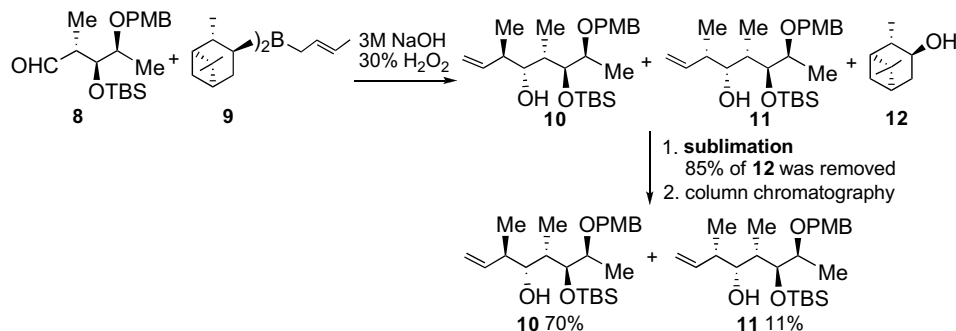


Figure 1. Sublimation apparatus in our procedure.



Scheme 2.

face of the dry-ice condenser, no dry-ice or ice was added to the condenser, and air-cooling was used. It was interesting to note that placing a piece of parafilm between the joints of the condenser and the round-bottom-flask significantly speeded up the sublimation process. With this setup, the side product **5** underwent quick sublimation and crystallized on the surface of the condenser as beautiful white needles. This procedure worked very well with large scale, and more than 85% of the side product **5** was removed. The remaining mixture (containing about 15% of compound **5**) reacted with TBS triplate, and compound **4** was easily separated from compound **7** by flash column chromatography (only once).

After successfully separating (–)-isopinocampheol **5** via sublimation, the same procedure was applied to separate (+)-isopinocampheol **12** from another Brown's asymmetric crotylboration as shown (Scheme 2).⁵ It also worked very well, and 70% yield of the desired product **10** was isolated.

In summary, we discovered that sublimation is a very efficient method for the separation of (+) or (–)-isopinocampheol, the major side product of the oxidation workup procedure of Brown's asymmetric crotylborations. In addition, it should be pointed out that this method is not just limited to Brown's asymmetric crotylborations. Side product (+) or (–)-isopinocampheol that is generated in Brown's other asymmetric reactions⁶ can also be separated employing this procedure.

The following is our detailed experimental procedure: After the completion of the reaction, the reaction mixture was treated with 3 M NaOH solution and 30% H₂O₂. Then the mixture was heated at reflux to ensure the complete cleavage of borane. Once the oxidation was complete, the mixture was extracted with CH₂Cl₂, washed with brine, dried over anhydrous Na₂SO₄, and concentrated by rotary evaporation.

The crude mixture was placed in a 250 mL round-bottom flask with a 24/40 joint. A dry-ice condenser with 24/40 joint was placed on top of the flask as shown in Figure 1. A magnetic stirring bar was placed inside the flask to stir the crude mixture. It is important to place a small piece of parafilm between the joints to ensure efficient sublimation. The condenser was connected to

a water aspirator and the round-bottom flask was heated in an oil bath at 65 °C.

After the white crystal accumulated, the condenser was removed and washed with acetone to clean out compound **5**. Then the condenser was placed on the flask again and the process was repeated until the sublimation stopped. About 85% of (+) or (–)-isopinocampheol can be removed from the mixture by employing this procedure.

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