Standard Lithiation–Borylation

A user's guide-

Table of Contents

Experimental Setup and Handling of Reagents

Preparation of Dry Solvents

In the Aggarwal lab, the three most commonly used solvents for lithiation–borylation reactions are: Et_2O, cyclopentyl methyl ether (CPME), and *tert*-butyl methyl ether (TBME). They all are dried using the following procedure. Toluene and $CHCl_3$ can be dried as well.

1. Take a Young's tube or Strauss flask and add 3Å molecular sieves of an amount corresponding to ¼ of the total volume. Note: you can reuse the molecular sieves as long as you have removed all solvent on high vacuum prior to the introduction of fresh solvent.

2. Heat the open vessel in the microwave for 30 s; wipe away any moisture that has condensed at the neck of the flask; shake the flask to disperse hotspots.

DO NOT put molecular sieves in the microwave if you believe they still contain solvent because this will cause a fire.

The vessel must be open when in the microwave; heating a closed system will cause an **EXPLOSION**.

3. Repeat step 2 until no more water comes out of the sieves as indicated by the amount of moisture condensing at the neck; then place the flask under high vacuum to cool.

4. Once the flask and sieves have cooled (this can take up to an hour) evacuate and backfill the flask three times with N_2. At this point you can use the flask to collect dry solvents from a Grubbs system or fill it with a solvent of your choice directly from the bottle (step 5).

5. Remove the Young's tap from the flask and insert a small funnel into the opening. Bend a needle and insert it next to the funnel to allow gas to escape during addition of solvent.

6. Fill the flask with solvent, remove the funnel and needle, and seal the flask with a Suba Seal septum.

7. Degas your solvent (to remove air introduced while filling the vessel) by vigorously bubbling N_2 through the solution. The traces of O_2 or CO_2 in the solvent interfere with lithiation-borylation by consuming the organolithium reagents, thus reducing the yield. Degassing is not necessary if you get solvents from the Grubbs columns.

8. Close the vessel with a Young's tap under N_2 and leave the solvent over the molecular sieves for 24 hr to dry.

3Å Molecular sieves are excellent for drying a wide range of solvents (D. B. G. Williams, M. Lawton, *JOC*, **2010**, *75*, 8351).

Using Acros Seal Bottles

Parafilm

When wrapping the bottle, ensure that the parafilm covers both the red lid and the joint of the seal to the bottle (see right) – this prevents moisture ingress. Don't just wrap the red cap (left).

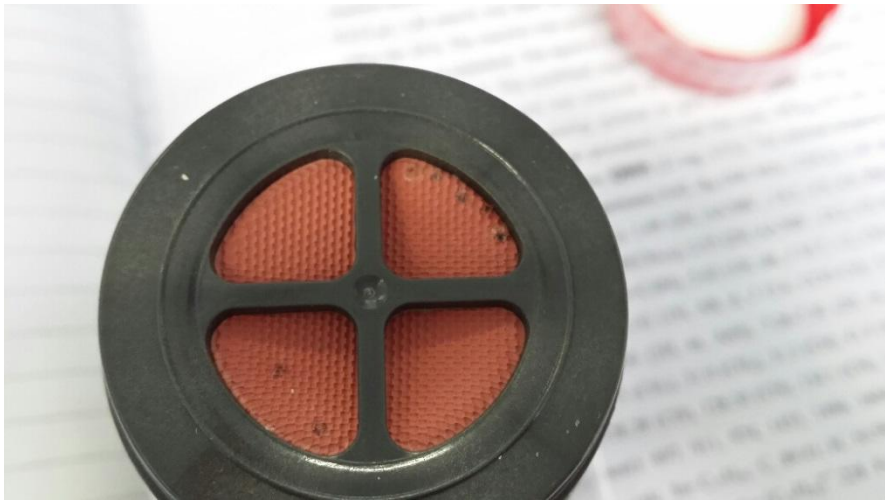
Puncturing

As you can see on the left, the seal has been punctured a few times towards the centre; the seal is not yet compromised. However, the example on the right shows how repeated puncturing in similar places towards the centre of the seal seriously compromises its integrity. The *s*BuLi in the right bottle has gone off, even though is still ~80% full.

How can this be avoided?

- Only puncture the Acros seal around the edge of the seal against the plastic rim. This is the strongest part of the seal.
- Do not puncture the same hole more than once, or too close to an existing one.
- Only use the long green needles (Gauge 21) to dispense reagents from these bottles; the yellow needles are too wide.
- Only puncture once for each portion of reagent. Use your reaction flask or a separate nitrogen-flushed vessel to flush the syringe with inert gas.
- Ensure the reagent bottle is stored upright.
- Make sure the reagent has warmed to room temperature before removing parafilm (20-30 min depending on the bottle size).
- Use a nitrogen-filled balloon or manifold to keep the bottle under nitrogen. It is also advisable to use a Luer lock syringe to prevent separation of the syringe and the needle.

Below is an example of good (top-right quadrant) and bad (bottom-left quadrant) ways to puncture an Acros seal.



General Setup of a Lithiation–Borylation Reaction

1. Take a clean Schlenk flask/tube with a stirrer bar and heat it on a Bunsen burner until the flame becomes slightly orange. Avoiding heating the side-arm tap too much as it may crack. Insert a Suba-Seal septum and allow the flask to cool under vacuum.

- The stirrer must stir freely at the bottom of the Schlenk flask and not be wider than the diameter of the vessel

- Parafilming the Suba-Seal septum is not necessary – if you think it leaks, better throw it away and take a new one.

2. Once the flask has cooled evacuate and backfill the flask with N_2 three times.

- Even though N_2 supplies are typically dry, it is recommended to have a drying trap filled with Drierite and some self-indicating silica for fine drying.

3. For carbamates or benzoates, which are oils, fill the dead volume of a syringe with your reagent and tare the syringe on the balance. After the balance has settled draw up more reagent and remove any bubbles in the syringe until you have the desired weight. Inject the syringe into the reaction flask, but do not pump the syringe, then return the dead volume to your flask of starting material.

- See the section on lithiation-borylation equivalents to determine your stoichiometries, but normally a good starting point is 1.3 equivs of benzoate, diamine, and sBuLi and 1.0 equivs of boronic ester (if boronic ester is the precious component), or 1.3 equivs of boronic ester, sparteine, and sBuLi and 1.0 equivs of benzoate (if benzoate is the precious component).

4. For solid benzoates or carbamates, weigh out the desired amount and put the solid into the Schlenk flask; then evacuate the Schlenk and refill with N_2. Repeat this twice more.

5. For any benzoates or carbamates that are thick oils or are otherwise inconvenient to weight out or take up by syringe, skip to step 6, then add your benzoate/carbamate as a solution in your reaction solvent.

- for steps 3 and 4, minimize the amount of time your Schlenk flask is exposed to the outside atmosphere

6. At this point add your diamine (TMEDA, (+)- or (−)-sparteine), by syringe using the known densities of these compounds to measure out the correct volumes under N_2. *d* = 0.775 (TMEDA), 1.02 (sparteine)

Handling of (+)- or (−)-sparteine

- If the sparteine has discoloured to yellow (or sometimes red), redistill it before use over calcium hydride – it should be colourless. (see final section for more details)

- Sparteine should be stored in a Schlenk flask with a glass stopper in the freezer. Flasks with Teflon taps should not be used as the joint can lose its seal at low temperatures.

- Sparteine often solidifies in freezer. It should be room temperature before use. You can accelerate the melting by partially immersing the sealed sparteine contained into a beaker with warm water.

- Evacuate and backfill the head space of the tap with dry N_2/Ar three times, then open the tap.

- Remove the glass stopper and replace it with a septum. Place the whole flask under vacuum, then refill with N_2.

- Evacuate a syringe three times in a separate vessel with N_2, then move the syringe to the sparteine vessel and draw up the desired amount. Pull a small N_2 bubble between the sparteine and the needle and transfer the syringe to the reaction vessel, pushing out the bubble first. Pull up a head of N_2 for the remaining dead volume and pump the syringe back into the sparteine vessel.

- Remove the Suba-Seal septum and replace it with a clean glass stopper. Put the sparteine flask under vacuum and refill with N_2. Repeat this twice more. Close the glass tap and parafilm both the end of the tap and the glass stopper joint, then place the flask back in the freezer.

6. Evacuate and backfill a syringe in a separate nitrogen-flushed flask. Evacuate and backfill your Strauss flask containing your reaction solvent and replace the Young's tap with a Suba-Seal septum. Draw up your solvent, pull up a cushion of N_2 and transfer the solvent to the reaction flask, washing the sides of the vessel to dislodge reagents that have adhered to the sides.

7. Ensure your carbamate/benzoate and diamine are completely dissolved. Place the reaction flask in a cooling bath and ensure that the stirrer moves freely without splashing the reaction mixture all over the inside of the Schlenk flask.

8. Fill the bath with dry ice and then acetone and allow the flask to cool for 5-10 mins. The bath should be *full to the brim* of dry ice; a bit at the bottom will not suffice.

9. Attach a nitrogen-filled balloon to a bottle of recently titrated *s*BuLi. Fill a syringe with nitrogen in a separate N_2-filled flask, then insert it into the BuLi bottle. Draw up the required amount of *s*BuLi. Rotate the syringe upside-down (with the needle still inside the BuLi bottle, bending the needle if required), pull up a protective cushion of N_2, then carefully move the syringe to your reaction vessel.

- *Do not evacuate the syringe in the sBuLi bottle as this shortens the seal lifetime.*

- *Always pierce the Acros seal around the edge of the seal and not in the middle.*

10. Add the *s*BuLi dropwise (~1 drop every 1-2 seconds) *until the addition is complete*

- *Push out the head of N_2 (with the syringe upside down) before adding sBuLi itself, so that you do not accidentally add the dead volume.*

- *Make sure that sBuLi drops directly into the reaction solution: if it hits the wall of the vessel, it will freeze*

----------Wait the required lithiation time----------

(2 - 5 h for primary carbamates/benzoates, 0.25 - 1 h for secondary benzylic/allylic/propargylic carbamates, 2-8 h for dialkyl benzoates)(see *J. Am. Chem. Soc.*, 2018, **140**, 14677–14686. for a list of measured lithiation half lives)

11. If the boronic ester is an oil, weigh it out as per step 3, and add the boronic ester neat in a dropwise manner.

- *Do not add the dead volume of the needle, return this to your flask of reagent.*

- *If the ice bath is bubbling vigorously, you are adding the boronic ester too quickly – lots of heat is generated.*

12. If the boronic ester is a solid, weigh it out as per step 4 into a flame-dried vial under N_2, and dissolve in the reaction solvent to 1M concentration. Then add this solution dropwise to the reaction mixture.

- *If the ice bath is bubbling vigorously, you are adding the boronic ester too quickly – lots of heat is generated.*

13. Give enough time for the formation of the boronate complex (typically < 1 h, however more hindered substrates may require up to 3 h), then follow the procedure appropriate for your particular carbamate/boronic ester combination to effect 1,2-migration.

14. After the reaction is complete, if using sparteine, the reaction is quenched with HCl (2 M) for sparteine recovery. The organic layer is washed with more HCl and the combined acid washes set aside.

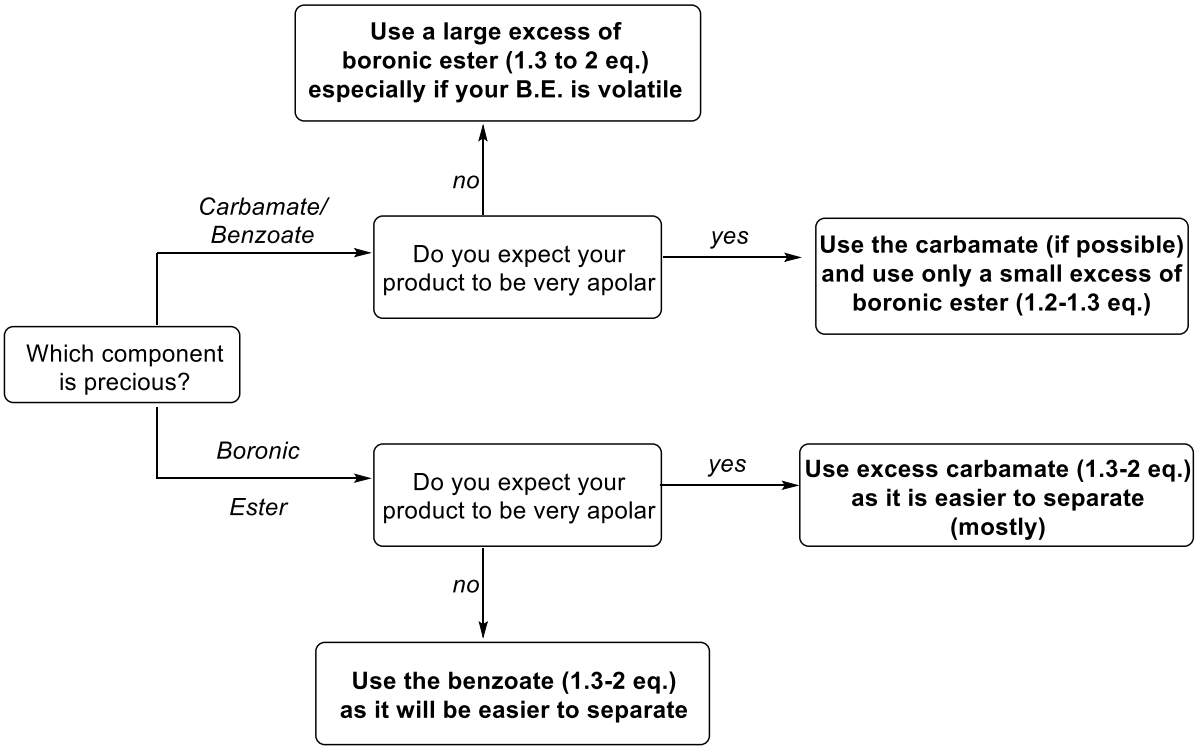
(see the section *Recovery of Sparteine* for more information)

Lithiation–Borylation Equivalents Flowchart

Deciding on the appropriate relative number of equivalents of substrates and reagents for your lithiation–borylation reaction can sometimes be difficult:

You should first identify your more precious reagent, the boronic ester or the lithiated carbamate/benzoate; this consideration is most important for total synthesis as it will determine your longest linear sequence.

If you are preparing starting materials for methodology, your boronic ester will be your most precious compound. You will want to ensure it is all consumed so you don't have to separate homologated boronic ester from starting boronic ester, a process that can be difficult. The next decision is whether to use a benzoate and carbamate as your carbenoid precursor. If you expect that your product boronic ester will be very apolar then you should use a carbamate as it will be more polar then your product. However, if your boronic ester is going to be polar then use the benzoate as it will typically be more apolar than your product. This analysis assumes that the 1,2-migration step in your lithiation-borylation reaction is facile. When 1,2-migration is challenging (phenyl, vinyl, Me, EWGs α to the boronic ester are all poor migrating groups), the use of the benzoate gives superior results. When using excess boronic ester, it is also generally a good idea to use the same stoichiometry of sBuLi and diamine as well, as this excess will react with the excess boronic ester making it easier to separate (e.g. use 1.3 eq. of boronic ester, sBuLi, and diamine with 1.0 eq. of benzoate/carbamate).

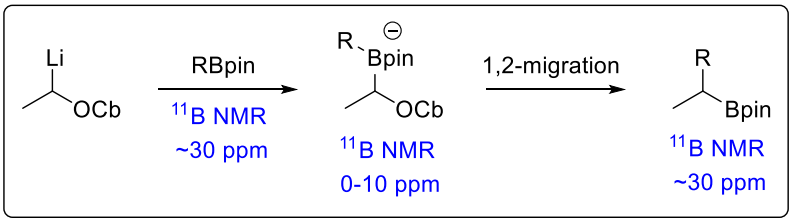


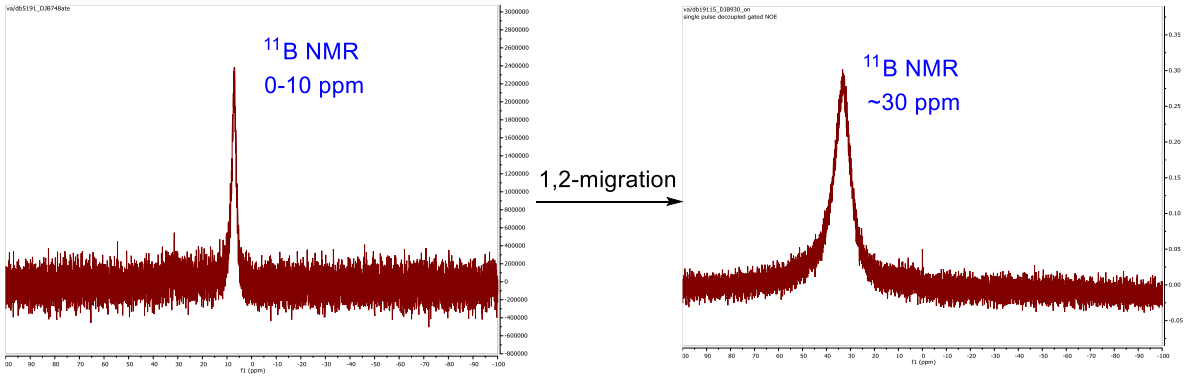
Reaction Monitoring

^{11}B NMR Spectroscopy

Lithiation–borylation reactions can be monitored by ^{11}B NMR spectroscopy. Your starting material boronic ester has a chemical shift of ~30 ppm; when you form a boronate complex, the chemical shift changes to around 0 to 10 ppm. After 1,2-migration, the product boronic ester has a chemical shift of ~30 ppm, thus allowing you to monitor the consumption of your boronate complex by ^{11}B NMR spectroscopy. On its own, ^{11}B NMR data do not tell you if your intermediate boronate complex has reverted to starting materials or has undergone 1,2-migration to products (in both cases, a boronic ester is formed); however, it does inform you as to whether your boronate complex has been consumed, and in the case where it has, your reaction is complete (for better or for worse).

GCMS and TLC analysis of your crude reaction mixture can be used in tandem with your ^{11}B NMR analysis to determine if starting material or product has formed.



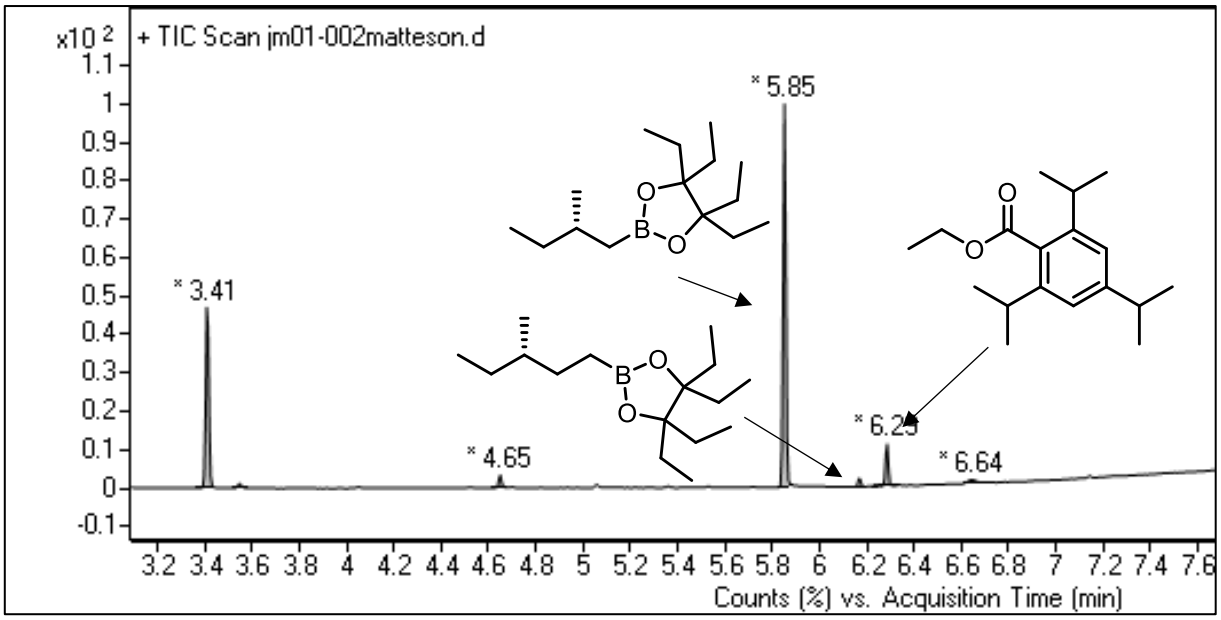


A useful resource for other chemical shifts can be found here

http://www.chemistry.sdsu.edu/research/BNMR/

GC-MS

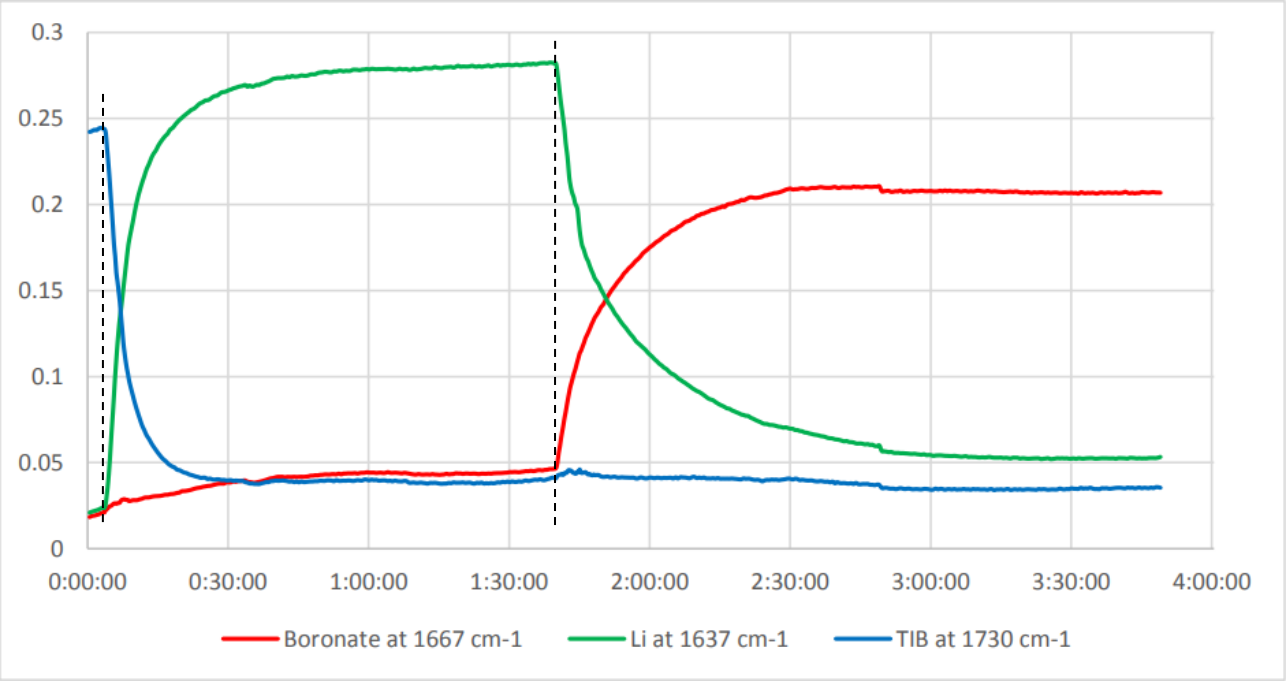
GC-MS monitoring is a very useful tool for homologation reactions, as it allows identification of any remaining starting material, product, and any potential over-homologation products. Addition of an internal standard also allows for quantification of the various products directly from the crude reaction mixture. This method works even if there is little to no separation by TLC, rendering GCMS invaluable for homologations when only a few atoms are being added.



In-Situ monitoring with ReactIR

ReactIR is a technique which allows for in situ IR monitoring of reaction mixtures to track react ants, intermediates and products. This gives insight into the rates of formation of certain intermediates. This is particularly useful for lithiation-borylation reactions, as it enables the rates of lithiation and the rates of borylation to be established for different substrates under different conditions. This provides valuable insight into the time required for each step to occur, particularly the lithiation step, and this tends to vary much more drastically between substrates.

Using in situ ReactIR, the strong ν(C=O) band present in the carbamate or benzoate ester can be monitored throughout the reaction. The initial carbenoid precursor shows a strong band at ~1697 cm^{-1} for the carbamate and ~1730 cm^{-1} for the benzoate. Upon lithiation, the lithium ion complexes with the carbonyl, leading to slight weakening of the carbonyl bond and resulting in a shift of the ν(C=O) band to ~1616 cm^{-1} (carbamate) ~1633 cm^{-1} (benzoate). After allowing sufficient time for full lithiation, the boronic ester is added, resulting in formation of the boronate complex and a shift of the ν(C=O) band to ~1642 cm^{-1} (carbamate) or ~1667 cm^{-1} (benzoate). Plotting the absorbance of each respective IR stretch over time produces a graph (shown below) from which an approximate half-life ($t_{1/2}$) for the lithiation step and borylation step can be obtained.



The $t_{1/2}$ for the lithiation step in this reaction was 4 minutes, and the $t_{1/2}$ for borylation was 12 minutes. More information included tables of $t_{1/2}$ Li and $t_{1/2}$ B values for different substrates and conditions can be found here: *J. Am. Chem. Soc.*, 2018, **140**, 14677–14686.

TLC

Homologation reactions can usually be followed by TLC, however it may be less useful when only adding small units (e.g. a single methylene unit) as the retention factors between the starting material and product(s) tend to be very similar.

Useful TLC stains include anisaldehyde (primary and secondary boronic esters usually show up as different colours, making differentiation easier for close spots), phosphomolybdic acid (PMA), and cerium ammonium molybdate (CAM).

Purification of Homologation Reactions

In general, homologation reactions can be purified by column chromatography. When using benzoates, one of the byproducts of the reaction is LiOTIB. The protonated form (TIBOH) can streak on silica, which can lead to co-elution with your desired product. It is sometimes beneficial to try and remove the majority of the TIBOH before column chromatography with a basic wash, or by eluting the crude material through a silica plug with Et_2O with a triethylamine additive. However, depending on the separation, this is often not necessary. For homologations with α-stannyl benzoates, the standard workup is filtration through a pad of silica to remove LiOTIB, as all the other by-products are tolerated in further homologations.

Purification of very non-polar boronic esters from homologations with hindered benzoates can be tricky. We have found that generally ethyl acetate:hexane systems are not effective for good separation, and instead the following were more useful:

- *Diethyl ether:hexane* – Similar to ethyl acetate:hexane, but using a slightly less strong solvent. Products are not pulled through the column as quickly, and it is easier to create a gradient.

- *Toluene:hexane* – Toluene is a much weaker solvent so more can be added to the eluent so is easier to gradient. Toluene systems are particularly effective for separating excess benzoate ester, presumably due to breaking up pi-interactions between the benzoate ester and the product. Small amounts can also be added to other eluents for similar results (see SI of *Nature*, 2014, **513**, 183–188.).

- *Acetone:hexane* – This system has proved useful for separating mono- and overhomologation products of very non-polar boronic esters (see SI of *Nat. Chem.*, 2023, **15**, 248–256.).

Preparatory HPLC is also a very useful tool for tricky separations. Moreover, if oxidation of the boronic ester to the alcohol is possible, this often makes separation considerable easier. Oftentimes, homologation reaction crude mixtures can simply be channelled through to the next step without intermediate purification, and purification at a later stage may prove easier.

Troubleshooting Lithiation-Borylation Reactions

Lithiation-borylation reactions have 3 principle steps, and poor yield of product may be a result of problems in any of the three steps. Below is shown some common issues and solutions.

Lithiation Step:

- The lithiation step may be slower than you think for a particular substrate. Leave the lithiation for a longer time, or attempt to measure the lithiation half-life with ReactIR or with a deuterium quenching experiment (see *J. Am. Chem. Soc., **2013**, 135, 16054*).
- There may be some unwanted water in the reaction which is quenching the *s*-BuLi or carbenoid. Make sure the reaction is free of air, and the solvent is free of water and oxygen. If you believe your carbenoid precursor may contain water, azeotrope 3 times with toluene, and dry under high vacuum.
- Check the integrity of the Acros seal on the bottle, and consider titrating the BuLi (or turbo Grignard for α-sulfinyl benzoate homologations). See *J. Organomet. Chem.*, 1997, **542**, 281–283.

Borylation Step:

- Sometimes hindered carbenoids and boronic esters may be particularly slow to form the ate complex. Loading the boronic ester as a 1 M solution in THF instead of Et_2O greatly accelerates this process as the THF outcompetes the bulky sparteine ligand for lithium ligation, allowing for faster ate complex formation.
- The use of α-Sulfinyl or α-Stannyl benzoates instead of a traditional lithiation-borylation can prove beneficial as the lithium is only solvated by the solvent, rather than the bulky sparteine ligand, which greatly accelerates borylation.

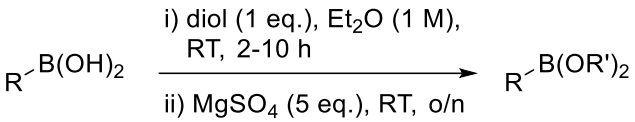
Migration Step:

- If you are leaving the migration at room temperature and ^{11}B NMR indicates that ate complex still remains, reflux the solution instead.
- If you are using a carbamate, switch to using a TIB ester, as TIB esters undergo 1,2-migration much faster.

- Stubborn migrations can also be effected by switching to a more non-polar solvent. After warming to room temperature after the borylation step, remove the solvent *in vacuo* and replace with chloroform or toluene and heat to reflux.

Boronic Ester Handling and Purification

Preparation of Simple Boronic Ester Starting Materials from the Corresponding Boronic Acids



Boronic acid (1.0 mmol) and diol (1.0 mmol) were stirred in anhydrous Et_2O (1.0 ml) at ambient temperature under a nitrogen atmosphere for 2–10 h. Flame-dried $MgSO_4$ (5 mmol) was added to the reaction mixture and stirring continued for 12 h. The reaction mixture was filtered and the solvent removed in vacuo. The crude material was purified by distillation or flash column chromatography.

Volatile Boronic Esters

If your product boronic ester is of low molecular weight, take care when evaporating your solvent as the boronic ester can azeotrope with the Et_2O. The best way to avoid this is to evaporate the Et_2O without using the vacuum on your rotary evaporator and setting the bath to 40–50 °C – this works best with an efficient dry-ice condenser.

Pinacol Boronic Esters

Pinacol boronic esters are, for the most part, bench stable and will only slowly decompose through oxidation/protodeboronation over periods of time >1 year. They can be purified by column chromatography or Kugelrohr distillation. The latter is especially useful when your starting material boronic ester is substantially more volatile than your product boronic ester. Do not be afraid to heat your boronic esters in the Kugelrohr apparatus; many are stable to such treatment (See the Supporting Information of the following paper: *Angew. Chem. Int. Ed.*, **2010**, *49*, 5142). Pinacol has been shown to form an azeotrope with water and methanolIf pinacol is the only impurity in your boronic ester, addition of MeOH:H_2O (1:1) followed by evacuation several times can remove it. (see *Tetrahedron*, 2009, **65**, 9956–9960.)

Some substrates require extra care in their handling such as allylic or propargylic boronic esters as they can decompose upon chromatographic purification; in some cases, switching the constituent polar eluent from diethyl ether to ethyl acetate (or indeed vice versa) can lead to superior yields of product.

Separating Mixtures of Secondary and Tertiary Pinacol Boronic Esters

In a few isolated cases where tertiary pinacol boronic esters are contaminated with small amounts of starting secondary pinacol boronic ester, the latter could be removed by the following treatment: the mixture was dissolved in diethyl ether; the organic phase was washed several times with 0.5 M aq. NaOH solution; the solvent was removed in vacuo to give the pure tertiary pinacol boronic ester.

Note: This was done with specific hindered tertiary boronic esters and it is not known how general this procedure is.

Neopentyl Glycol Boronic Esters

These boronic esters must be stored under N_2 if they are to be kept for long periods of time, otherwise oxidation/protodeboronation will occur. For instance, a good way to store simple boronic esters, such as *i*PrBneo, is in a Young's tube.

Neopentyl glycol boronic esters can be purified by chromatography, but the amount of time the material is in contact with the silica gel needs to be minimal. By TLC, the spots will usually appear as streaks for unhindered neopentyl glycol boronic esters and well-defined spots for hindered neopentyl glycol boronic esters. Usually, simple primary neopentyl glycol esters will decompose on silica gel faster than more hindered secondary/tertiary neopentyl glycol boronic esters, thus allowing hindered boronic ester products to be separated from less hindered starting boronic esters through the latter's more rapid decomposition on silica gel.

Transesterification from tertiary neopentyl glycol to pinacol boronic esters

After a lithiation–borylation reaction (2.00 mmol scale), the volatiles were removed from the reaction mixture *in vacuo* and the residue dissolved in THF (6 ml). To the stirred solution was added pinacol (709 mg, 6.00 mmol) and 0.2 M aq. NaOH (2 ml). The reaction mixture was stirred for 5 h at 60 °C or until such point as the tertiary neopentyl boronic ester is converted into the corresponding pinacol boronic ester (as determined by GCMS or otherwise). The reaction mixture was cooled to ambient temperature and Et_2O (10 ml) and water (5 ml) was added. The phases were separated and the aqueous phase extracted with Et_2O (3 × 20 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo. The crude material was purified by flash column chromatography.

Ethylene Glycol Boronic Esters

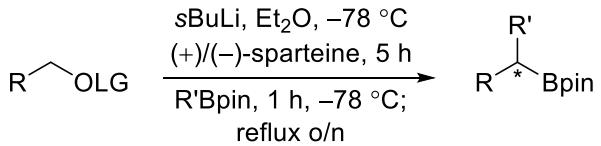
These boronic esters are exceptionally air and moisture sensitive and should always be stored under N_2. They should be distilled or used without purification as they cannot be purified by column chromatography. These boronic esters are very hygroscopic so solid ethylene glycol boronic esters should be stored as solutions over $CaCl_2$ or 3Å MS, and oils should be stored neat over $CaCl_2$.

Transesterification from ethylene glycol to pinacol boronic esters after a lithiation–borylation reaction

After a lithiation–borylation reaction, the volatiles were removed *in vacuo* (~0.3 mbar) and the residue was redissolved in anhydrous Et_2O. Pinacol (1.0–1.5 eq.) was added and the mixture was stirred at room temperature for 16 hours before being diluted with H_2O. The phases were separated and the aqueous phase extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo. The crude material was purified by flash column chromatography.

General Procedures for Homologations

Lithiation–Borylation of Primary Carbamates/Benzoates



Appropriate citations for this methodology

ACIE, **2007**, *46*, 7491; *Chem. Commun.*, **2011**, *47*, 12592; *Org. Synth.*, **2011**, *88*, 247; *Acc. Chem. Res.*, **2014**, *47*, 3174.

Carbenoid as Limiting Reagent

To a solution of carbamate/benzoate (1.0 mmol) and (−)-sparteine (1.3 mmol) in dry Et_2O (5 mL) at –78 °C was added *s*BuLi (1.3 M in cyclohexane, 1.3 mmol) dropwise. This mixture was stirred at –78 °C for the appropriate lithiation time (most substrates will completely lithiate within 5 hours). A solution of boronic ester (1 M in Et_2O, 1.3 mmol) was added dropwise and the reaction mixture was stirred for a further hour at –78 °C. The reaction mixture was then heated at reflux until the boronate complex was consumed. The reaction mixture was diluted with Et_2O (20 mL) and quenched through addition of 2M aq. HCl (20 mL). After stirring for 10 min, the phases were separated, and the aqueous phase was re-extracted with diethyl ether (2 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The aqueous phase was retained for recovery of sparteine [see - *Org. Synth.* **1997**, *74*, 23, *Nature*, **2014**, *513*, 183]. The crude product was purified by column chromatography to afford the secondary boronic ester.

To isolate the secondary alcohol:

The reaction mixture was diluted with THF (5 mL) and then cooled to 0 °C. A premixed solution of NaOH (2 M)/H_2O_2 (30%) (2:1 v/v, 4.0 mL) was added dropwise. The biphasic mixture was stirred for 1h at rt and quenched with 2 M NaOH (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography.

Formation of $MgBr_2$•Et_2O

In some cases, addition of this Lewis acid is necessary to promote 1,2-migration with primary carbamates.

1,2-Dibromoethane (1.3 mmol, 1.3 eq.) was added to Mg turnings (2 eq., 2.0 mmol) suspended in Et_2O (5 mL). The reaction mixture was gently heated to initiate the reaction and stirred until reflux has stopped. The biphasic mixture was added to the lithiation-borylation reaction mixture, stirred at –78 °C for 20 min, then warmed to r.t. and heated at reflux for ≥ 12h.

Boronic Ester as Limiting Reagent

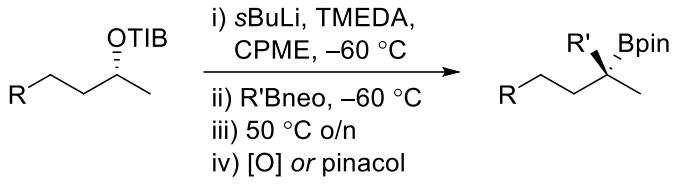
To a solution of carbamate/benzoate (1.5 mmol) and (−)-sparteine (304 mg, 1.5 mmol) in dry Et_2O (7.5 mL) at –78 °C was added *s*BuLi (1.3 M in cyclohexane, 1.4 mmol) dropwise. This mixture was stirred at –78 °C for the appropriate lithiation time. A solution of boronic ester (1 M in Et_2O, 1.0 mmol) was added dropwise and the reaction mixture was stirred for a further hour at –78 °C. The reaction mixture was then heated at reflux until the boronate complex was consumed. The reaction mixture was diluted with Et_2O (20 mL) and quenched through addition of 2M aq. HCl (20 mL). After stirring for 10 min, the phases were separated, and the aqueous phase was re-extracted with diethyl ether (2 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The aqueous phase was retained for recovery of sparteine. The crude product was purified by column chromatography to afford the secondary boronic ester.

Notes:

- The lithiated carbamate should appear pale yellow and the benzoate should appear pale yellow, brown or purple depending on how it has been prepared.

- As benzoates and sparteine are quite viscous it is important to ensure they are fully dissolved before introduction of the organolithium.

Lithiation-Borylation of Dialkyl Benzoates



Appropriate citations for this chemistry

JACS, **2013**, *135*, 16054; *Acc. Chem. Res.*, **2014**, *47*, 3174.

To a vigorously stirred solution of benzoate (0.50 mmol) and TMEDA (0.46 ml, 3.00 mmol) in anhydrous CPME (3 ml) at −60 °C (internal temperature) under a nitrogen atmosphere, was added *s*BuLi (1.3 M in hexane, 0.62 ml, 0.80 mmol) dropwise over 10 min. After 2 h, a solution of the neopentylglycol boronic ester (1.0 mmol) in CPME (0.5 ml) was added dropwise over 10 min. The reaction mixture was stirred at −60 °C for 1 h and then the cooling bath was removed and the reaction mixture was stirred at the 50 °C (migration temperature) overnight (~16 h).

For isolation of the tertiary pinacol boronic ester -

The volatiles were removed from the reaction mixture in vacuo and the residue dissolved in THF (6 ml). To the stirred solution was added pinacol (709 mg, 6.00 mmol) and 0.2 M aq. NaOH (2 ml). The reaction mixture was stirred for 5 h at 60 °C at which point GCMS showed 95% conversion of the tertiary neopentylglycol boronic ester to the corresponding pinacol boronic ester. The reaction mixture was cooled to ambient temperature and Et_2O (10 ml) and water (5 ml) was added. The phases were separated and the aqueous phase extracted with Et_2O (3 × 20 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo. The crude material was purified by flash column chromatography eluting 1–1.8% Et_2O/pentane to give tertiary boronic ester.

For isolation of the tertiary alcohol -

The reaction mixture was cooled to 0 °C (water/ice bath) and degassed THF (2 ml) containing BHT (~2 mg) was added. An ice-cold degassed mixture of 3 M NaOH (3.6 ml) containing EDTA (1 g/L) and 30% aqueous H_2O_2 (1.8 ml) was added all at once. The reaction mixture was vigorously stirred and allowed to reach ambient temperature overnight. The reaction mixture was diluted with water (5 ml) and extracted with Et_2O (4 × 20 ml). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the crude material purified by flash chromatography.

Notes:

- It is important the reaction mixture does not splash all over the flask during the lithiation step, otherwise the lithiation is not as successful

- −60 °C should be maintained using a pre-equilibrated cryostat bath using acetone as the coolant. A mechanical stirrer should be used to ensure the cooling bath is homogeneous, DO NOT use a stirrer bar to stir the bath as this will cause the reaction flask to stir erratically.

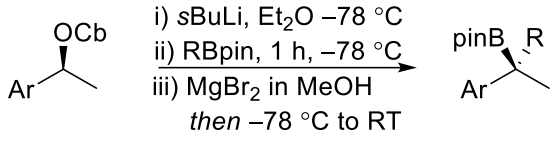
- Attempting to put two reaction vessels into the −60 °C cooling bath at once will lead to less reproducible results due to poor stirring.

- Exact lithiation times are substrate specific see - J. Am. Chem. Soc., 2018, **140**, 14677–14686.

- The lithiated benzoate should appear purple or brown.

- The tertiary pinacol boronic ester products and the starting material secondary benzoates will be very similar in polarity, unless the boronic ester used contains polar groups.

Lithiation-Borylation of Secondary Benzylic Carbamates



Appropriate citation for this chemistry

Nature, **2008**, *456*, 778; *ACIE*, **2012**, *49*, 5142; *Chem. Sci.*, *2015*, **6**, 3718.

A solution of secondary benzylic carbamate (1.00 mmol, 1.0 equiv) in anhydrous diethyl ether or TBME (3.0 mL) was cooled to −78 °C. *s*BuLi (1.00 mL, 1.30 mmol, 1.3 equiv) was added dropwise and the reaction mixture was stirred at this temperature for 0.15–1 h. A solution of the boronic ester (1.50 mmol, 1.5 equiv) in anhydrous diethyl ether (1.5 mL) was added dropwise and the mixture was stirred for 1–3 h at −78 °C [boronate complex formation]. A 1.0 M solution of $MgBr_2$ in anhydrous MeOH (1.30 mL, 1.30 mmol, 1.3 equiv) was added slowly at −78 °C. After 5 min, the cooling bath was removed and stirring was continued at room temperature until disappearance of the boronate complex (5–8 ppm) monitored by ^{11}B NMR spectroscopy. The reaction mixture was then cooled to 0 °C and 1.0 M aq. KH_2PO_4 (2.0 mL) was added slowly. After stirring for 10 min, the phases were separated, and the aqueous phase was re-extracted with diethyl ether (4 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography to afford the tertiary boronic ester.

For isolation of the tertiary alcohol -

The reaction was cooled to 0 °C (water/ice bath) and degassed THF (2 ml) containing BHT (~2 mg) was added. An ice-cold degassed mixture of 3 M NaOH (3.6 ml) containing EDTA (1 g/l) and 30% aqueous H_2O_2 (1.8 ml) was added all at once. The reaction mixture was vigorously stirred and allowed to reach ambient temperature overnight. The reaction was diluted with water (5 ml) and extracted with Et_2O (4 × 20 ml). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the crude material purified by flash chromatography.

Notes:

- *For carbamates with electron-donating groups, TMEDA (1.3 eq) should be added before performing your lithiation.*
- *The lithiated carbamate should appear anywhere from yellow to deep orange in colour.*
- *THF should not be used for these lithiations as it will cause your lithiated carbamate to become configurationally unstable.*
- *$MgBr_2$ in MeOH was prepared by drying $MgBr_2$ at 100 °C overnight under high vacuum, followed by addition of anhydrous MeOH. A large batch can be prepared and stored over a long period of time; however, take care as during the initial stages of dissolution, the MeOH will start to boil. Any soilds formed (MgO) should be left to settle before using the reagent.*

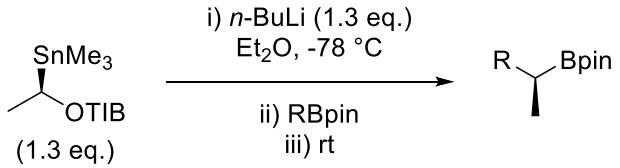
For Pyridyl Boronic Ester Substrates

Carbamate (0.40 mmol) was dissolved in anhydrous Et_2O (1 ml), cooled to –78 °C and sBuLi (0.37 ml of a 1.3 M hexane:cyclohexane solution, 0.48 mmol) was added dropwise over 5 min. After stirring for 20 min, the respective pyridyl boronic ester (0.60 ml of a 1.0 M Et_2O solution, or 1.20 ml of a 0.5 M PhMe solution 0.60 mmol) was added dropwise over 5 min. The reaction mixture was stirred for an additional 1 h, then $MgBr_2$ (0.60 ml of a 1.0 M MeOH solution) was added dropwise over 2-3 min. After 15 min the cooling bath was removed and stirring was continued at rt for 16 h. The reaction mixture was diluted with anhydrous THF (2 ml), chilled to ~0 °C, and 0.30 ml of a degassed mixture of 3.0 M aq. NaOH (containing EDTA, 1.0 g/l) and 30% aq. H_2O_2, 1:1 (vol) was added. The cooling bath was removed and the reaction mixture was stirred at rt for 30 min. The reaction was diluted with water (5 ml) and Et_2O (5 ml) and extracted with Et_2O (3 × 5 ml). The combined organic phases were washed with water (5 ml), brine (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography to give pure tertiary alcohol.

For Homologation of Tertiary Boronic Esters - *J. Am. Chem. Soc.*, **2014**, *136*, 17370

Tertiary boronic ester (0.3 mmol) was dissolved in anhydrous Et_2O (1 ml) and cooled to 0 °C. MeMgBr (0.6 ml of a 1 M Et_2O solution, 0.60 mmol) was added and the reaction allowed to stir at rt for 5 min. Secondary benzylic carbamate (0.2 mmol) was dissolved in anhydrous Et_2O (1 ml), cooled to –78 °C and sBuLi (160 µl of a 1.30 M hexane:cyclohexane solution, 0.21 mmol) added dropwise over 2 min. After stirring for 20 min, both the lithiated carbamate and borane were cooled to – 96 °C (MeOH/N_2(l) bath) and the borane transferred into to the lithiated carbamate via cannula. The reaction mixture was stirred at this temperature for 5 min, then rt for 1 h. The reaction mixture was chilled at 0 °C, and 0.30 ml of a degassed mixture of 3.0 M aq. NaOH (containing EDTA, 1.0 g/l) and 30% aq. H_2O_2, 1:1 (vol) was added. The cooling bath was removed and the reaction mixture was stirred at rt for 30 min. The reaction was diluted with water (5 ml) and Et_2O (5 ml) and extracted with Et_2O (3 × 5 ml). The combined organic phases were washed with water (5 ml), brine (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/petroleum ether 40-60, 1:9) to give pure tertiary alcohol.

Homologations with α-Stannyl Benzoates



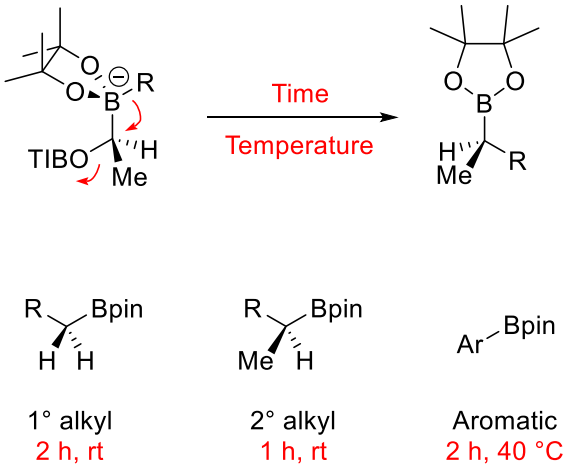
Appropriate citation for this chemistry: *J. Am. Chem. Soc.*, 2015, **137**, 4398–4403; *Asian J. Org. Chem.*, 2021, **10**, 2338–2341.

A solution of α-stannyl benzoate (1.3 eq.) in a Schlenk flask was dissolved in anhydrous Et_2O (0.2 M) under an atmosphere of nitrogen. The reaction mixture was cooled to –78 °C and *n*BuLi (1.5–1.6 M in hexanes, 1.3 eq.) was added dropwise to the reaction mixture at –78 °C. The reaction mixture was stirred for 1 h at –78 °C. Boronic ester (0.5 M in anhydrous Et_2O, 1.0 eq) was then added dropwise to the reaction mixture at –78 °C. The reaction mixture was stirred at –78 °C for 30-60 mins. The reaction mixture was removed from the cooling bath and stirred at the desired temperature for the desired time (see below for time and temperature

guide for 1,2-migration). The reaction mixture was filtered through silica (~10 mm depth of wetted (Et_2O, 1% NEt_3 additive) silica, using a filter frit connected directly to an oven dried receiving vessel) to give a colourless to pale yellow translucent solution. The silica was washed with Et_2O, the filter frit was removed and solvent was removed under reduced pressure to give the crude boronic ester. The crude boronic ester could then be re-dissolved in anhydrous Et_2O and used in further homologations or purified by flash column chromatography.

Notes:

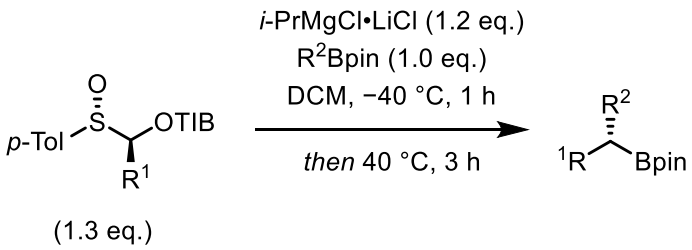
- Depending on the volume, a syringe pump can be used for the dropwise additions, set to 0.2-0.3 ml/min.
- When cooling the solution of stannane to –78 °C , the solution becomes cloudy as some stannane precipitates out of solution.
- When the tin–lithium exchange is complete the reaction mixture will be a translucent pale yellow solution with no stannane precipitate remaining
- Upon warming to room temperature, the pale yellow solution becomes colourless at the excess lithiated carbenoid decomposes.
- As the solution is stirred at room temperature, it will become cloudy as insoluble LiOTIB salts form.



Homologations with α-Sulfinyl Benzoates

Appropriate citation for this chemistry: *J. Am. Chem. Soc.*, 2017, **139**, 11877–11886; *Nat. Chem*. 2023, **15**, 248–256; *Nat. Synth.*, 2025, 1–10.

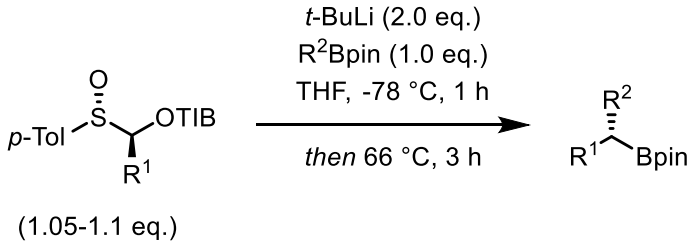
<u>In-situ conditions with *i*-PrMgCl•LiCl</u>



i-PrMgCl•LiCl (1.3 M in THF, 1.2 equiv) was added dropwise to a mixture of sulfoxide (1.1 equiv) and pinacol boronic ester (1.0 equiv) in anhydrous DCM (0.2 M with respect to the boronic ester) at −40 °C. After the addition was complete, the reaction was slowly allowed to warm to room temperature over the course of 1 hour. After room temperature was reached, the reaction mixture was heated to 40 °C for 3 h, cooled to room temperature, diluted with Et_2O and sat. NH_4Cl was added. The phases were separated and the aqueous phase was extracted with Et_2O (x3). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude mixture was purified by chromatography on silica gel to afford the desired homologated boronic ester.

- The −40 °C cooling bath can be replaced with an ice bath to aid with slow warming.
- These conditions work best for primary boronic esters, for boronic esters with more sensitive groups, and when selectivity of a primary over a secondary boronic ester is needed.
- Filtration through a plug of Et_3N-deactivated silica can help with removal of excess TIBOH if this co-elutes with the product.

<u>In-situ conditions with *t*-BuLi:</u>

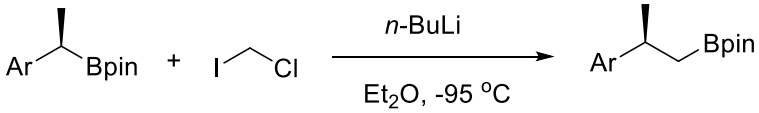


tBuLi (1.7 M in pentane, 2.0 equiv) was added dropwise to a mixture of sulfoxide (1.05–1.10 equiv) and pinacol boronic ester (1.0 equiv) in anhydrous THF (0.1 M with respect to the boronic ester) at – 78 °C and the resulting solution was stirred at this temperature for 1 h. After warming to room temperature, the reaction mixture was heated at 66 °C for 3 h, cooled to room temperature, diluted with Et_2O and sat. NH_4Cl was added. The phases were separated and the aqueous phase was extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Purification of the crude reaction mixture by chromatography on silica gel afforded the desired homologated boronic ester.

- These conditions work best for more hindered boronic esters
- PMDTA (equimolar with tBuLi), a sterically bulky tridentate ligand, can be included in order to promote selectivity for homologation of a primary boronic ester in the presence of secondary boronic esters.

-

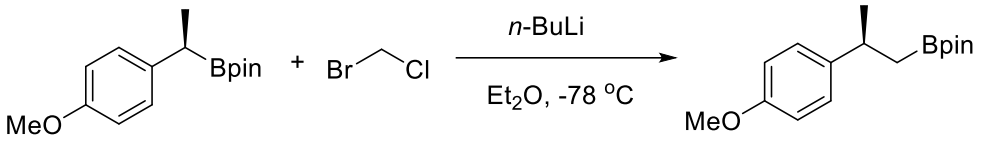
General Procedure: Matteson Homologation



Appropriate citations

*Asian J. Org. Chem., 2021, **10**, 2338–2341. JACS,* **2015**, *137*, 4398; *ACIE*, **2011**, *50*, 3760; *JACS*, **1980**, *102*, 7588; *Organometallics*, **1983**, *2*, 1529, *Organometallics*, **1992**, *11*, 1948.

In a flamed-dried flask under nitrogen a solution of boronic ester (1.0 equiv.) and chloroiodomethane (3.0 equiv.) in anhydrous Et_2O (0.2 M) was cooled to −95 °C (MeOH/liq.N_2) and stirred vigorously (deep vortex). *n*-Butyllithium (1.5–1.6 M in hexanes, 2.95 equiv.) was added slowly using a syringe pump (0.05 mL/min or slower). The reaction mixture was stirred for 30 min at −95 °C and then warmed to RT and stirred for a further 1 h. The cloudy solution was filtered through a plug of silica (~ 10 mm depth of silica, using a glass-fritted Büchner funnel connected directly to a receiving round-bottom flask) to give a colourless solution. The silica was washed with Et_2O (reagent grade), the funnel was removed and solvent was evaporated under reduced pressure to give the crude boronic ester (for the example shown above: 99%, <1% starting material by GCMS analysis).



In a flamed-dried flask under nitrogen a solution of boronic ester (1.0 equiv.) and bromochloromethane (3.0 equiv.) in anhydrous Et_2O (0.2 M) was cooled to −78 °C or −90 °C (acetone/dry ice) and stirred vigorously (deep vortex). *n*-Butyllithium (1.5-1.6 M in hexanes, 2.5 equiv.) was added slowly using a syringe pump (0.05 mL/min or slower). The reaction mixture was stirred for 30 min at −78 °C then warmed to RT and stirred for a further 1 h. The cloudy solution was filtered through a plug of silica (~ 10 mm depth of silica, using a glass-fritted Büchner funnel connected directly to a receiving round-bottom flask) to give a colourless solution. The silica was washed with Et_2O (reagent grade), the funnel was removed and solvent was evaporated under reduced pressure to give the crude boronic ester (for the example shown above: 99%, <1% starting material by GCMS analysis).

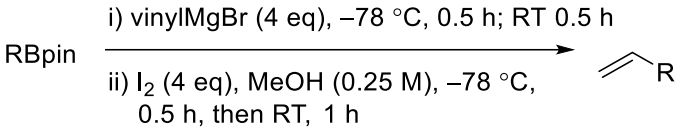
Notes:

- Overhomologation is often observed as a byproduct. In this case, consider diluting further, or diluting the *n*-BuLi before addition.

General Procedure: Zweifel Olefination

Appropriate citations
ACIE, **2011**, *50*, 3760; *ACIE*, **2009**, *48*, 6317; *JACS*, **1967**, *89*, 3652; *JOC*, **1976**, *41*, 3947.

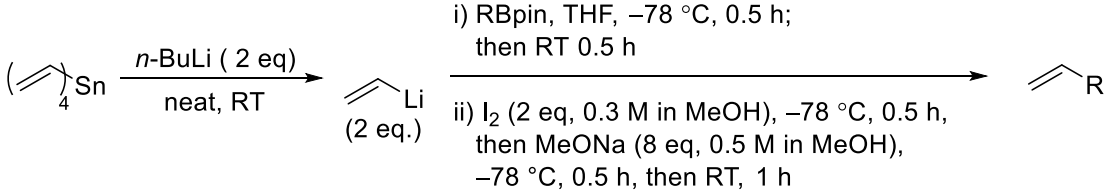
Use a vinyl Grignard for simple unhindered substrates:



To a solution of boronic ester (0.30 mmol) in anhydrous THF (3.0 mL, 0.1 M) at room temperature was added a vinylmagnesium bromide (1.0 M in THF, 1.2 mmol) dropwise. The resulting mixture was stirred at room temperature for 30 min and cooled down to –78 °C. A solution of iodine (1.2 mmol) in MeOH (4 mL) was added dropwise to the reaction mixture via cannula; 30 min later, a solution of MeONa (2.4 mmol) in MeOH

(5 mL) was added. The reaction mixture was then allowed to warm to room temperature and stirred for an additional 1 h, diluted with pentane (40 mL) and washed with a 20% aq. $Na_2S_2O_3$ solution (5 mL) and water (10 mL). The phases were separated, the aqueous layer was extracted with pentane (2 × 20 mL); the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Use vinyllithium for more hindered substrates:



To neat tetravinyltin (0.30 mmol) at room temperature was added *n*BuLi (1.6 M in hexanes, 0.60 mmol) dropwise. The resulting solution was stirred for 5 min at room temperature, and then allowed to settle for 3 h. The supernatant was removed, and the white solid was carefully washed with hexane (2×), attention being paid not to remove any of the precipitate. The solid vinyl lithium was then dissolved in THF (0.6 mL, 1 M, 0.6 mmol).

To a solution of boronic ester (0.30 mmol) in anhydrous THF (3.0 mL, 0.1 M) at −78 °C was added dropwise the vinyl lithium solution. The resulting mixture was stirred for 45 min, removed from the bath and stirred at room temperature for 30 min. The reaction mixture was then cooled down to −78 °C and a solution of iodine (0.6 mmol) in MeOH (2 mL) was added dropwise to the reaction mixture; 30 min later, a solution of MeONa (2.4 mmol) in MeOH (5 mL) was added. The reaction mixture was stirred at −78 °C for 30 min, then allowed to warm to room temperature and stirred for an additional 1 h, then diluted with pentane (40 mL) and washed with a 20% aq. $Na_2S_2O_3$ solution (5 mL) and water (10 mL). The phases were separated and the aqueous layer was extracted with pentane (2 × 20 mL); the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography to yield the desired product.

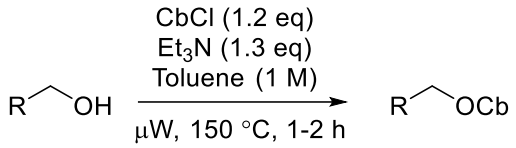
Notes:

The most important stage of the reaction is the warming of the reaction mixture to room temperature after addition of the vinyl lithium. This ensures that you achieve complete boronate complex formation.

We have reported alternate procedures involving the addition of just I_2 in MeOH to effect 1,2-metallated rearrangement and elimination. However, investigation of more complex and challenging substrates has indicated that the addition of NaOMe is beneficial and therefore should be used more generally.

General Procedures for the Preparation of Carbamates and Benzoates

Preparation of Primary Carbamates in the Microwave



N,*N*-diisopropylcarbamoyl chloride (1.2 eq.), triethylamine (1.3 eq.) and primary alcohol (1 eq.) were added to a flame-dried microwave vial and dissolved in toluene (1M in alcohol). The mixture was stirred briefly to ensure that everything was dissolved and then heated in the microwave reactor for 1–2 h at 150 °C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica to remove Et_3N•HCl and the filter cake washed with Et_2O. Further purification of the carbamate by standard column chromatography will afford analytically pure material.

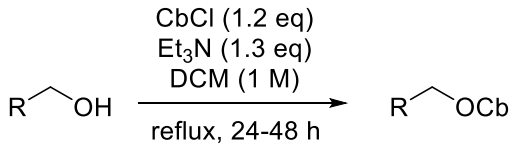
Notes:

- Most substrates will be transformed within 1 h at 150 °C. Sometimes conversion is incomplete after such time owing to the precipitated Et_3N•HCl preventing efficient mixing; in such cases, shaking the vial and heating the mixture again for 1 h at 150 °C should suffice to achieve complete conversion.

- For substrates which fail to lithiate to completion, additional distillation of the carbamate after chromatography may be required and/or azeotropic removal of trace water using dry toluene.

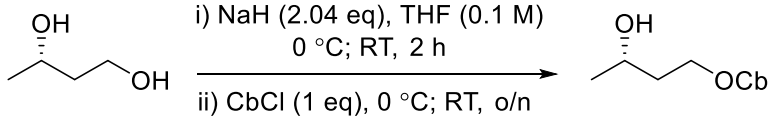
- The biggest vials that fit in our microwave can take 20 mL which equates to roughly 15 mL of toluene + other reagents, and is therefore ideally suited to small-to-medium-scale reactions.

Preparation of Primary Carbamates under Reflux – for Big-Scale Reactions



N,*N*-diisopropylcarbamoyl chloride (1.2 eq.), triethylamine (1.3 eq.) and primary alcohol (1 eq.) were added to a flame-dried round-bottomed flask and dissolved in dichloromethane (1M in alcohol). A reflux condenser was attached and the reaction mixture was heated at reflux for 24 to 48 h. After cooling to room temperature, the reaction mixture was quenched through the addition of water and the phases were separated. After extracting the aqueous phased with DCM (x 3), the combined organics were dried over $MgSO_4$, filtered and concentrated. Purification of the residue by column chromatography or in some cases kugelrohr distillation will afford analytically pure material.

Selective Carbamate Formation on Primary alcohol using NaH

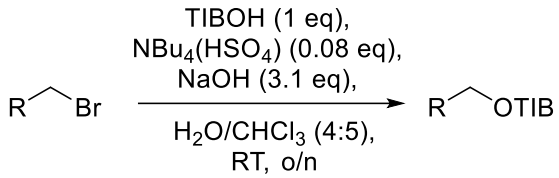


(*S*)-(+)-1,3-Butane diol (3.0 mL, 33.5 mmol, 1 eq.) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 2.74 g, 68.6 mmol) in THF (330 mL) at 0 °C. The mixture was warmed to RT and stirred for 2 h. The mixture was cooled to 0 °C and a solution of *N*,*N*-diisopropylcarbamoyl chloride (5.48 g, 33.5 mmol) in THF (33 mL) was added dropwise. The mixture was allowed to warm to RT slowly over 16 h. Water (300 mL) and Et_2O (300 mL) were added and the layers were separated; the aqueous phase was extracted with Et_2O (2 × 300 mL). The combined organic phases were washed with brine (300 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (pentane/EtOAc 3:1) gave (*S*)-3-hydroxybutyl diisopropylcarbamate as an oil (5.41 g, 74%).

Notes: - *Can also be performed on simple primary alcohols however the CbCl/Et3N is practically simpler for these substrates*

- Add the alcohol slowly otherwise it will foam out of the flask

Preparation of Primary Benzoates using Phase Transfer Conditions



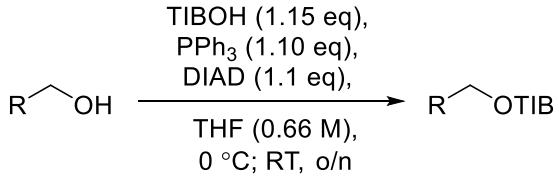
A biphasic mixture of 2,4,6-triisopropylbenzoic acid (20.2 g, 81.3 mmol, 1.0 eq), $NBu_4(HSO_4)$ (2.21 g, 6.5 mmol, 0.08 eq), NaOH (10.1 g, 252.0 mmol, 3.1 eq) and bromoethane (30.0 mL, 407 mmol, 5.0 eq) in $CHCl_3$ (400 mL) and H_2O (320 mL) in a 1 L round- bottomed flask was vigorously stirred overnight at room temperature. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine (300 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was dissolved in pentane (60 mL) and the insoluble salts filtered off. The solvent was removed from the filtrate under reduced pressure to give ethyl TIB ester (20.1 g, 90%) as a colourless oil.

Notes:

- Works for simple aliphatic alkyl halides such as ethyl bromide, n-propyl bromide, 3-butenyl bromide, 1-bromo-3-phenyl-propane, but not for more hindered substrates such as isobutyl bromide.

- Can be used without further purification.

Preparation of Primary Benzoates using the Mitsunobu Reaction



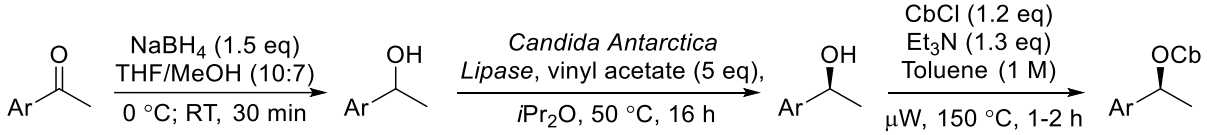
To a stirred solution of PPh_3 (11 mmol), secondary alcohol (10 mmol) and 2,4,6-triisopropylbenzoic acid (11.5 mmol) in THF (15 ml) at 0 °C (ice bath), was added DIAD (11 mmol) dropwise over 10 min. After stirring the mixture for 4 h at 0 °C (ice bath), the volatiles were removed in vacuo. The residue was dissolved in pentane (15 ml) and the resulting solution stirred in for 5 min. The white suspension was filtered and the filter cake washed with pentane (100 ml). The solvent was removed *in vacuo* and the residue purified by flash column chromatography to give pure benzoate.

Notes:

- Separation of trace PPh_3 can be difficult sometimes; however, the purification can be simplified through dissolving the triturated crude mixture in THF, adding an excess of 30% aq. H_2O_2, and stirring the resulting mixture, thus converting PPh_3 into $OPPh_3$.

- Developed TLC plates will often suggest an easy purification by column chromatography; however, the use of too polar an eluent will cause $OPPh_3$ to slowly leach through the column and contaminate product fractions.

Preparation of Secondary Benzylic Carbamates



Reduction of benzylic ketones

To a solution of ketone (10.0 mmol, 1 eq.) in MeOH (7 mL) and THF (10 mL) at 0 °C was added $NaBH_4$ (567 mg, 15.0 mmol, 1.5 eq.) portionwise over 5 minutes with vigorous stirring. The reaction mixture was then

warmed to RT and stirred for 30 min at which point TLC (20% EtOAc:petrol) indicated complete conversion of starting material. The reaction was quenched by addition of aq. NH_4Cl (5 mL) and diluted with H_2O (10 mL) and EtOAc (100 mL). The layers were separated and the organic layer was washed sequentially with H_2O (15 mL) and brine (2 × 15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give essentially pure product.

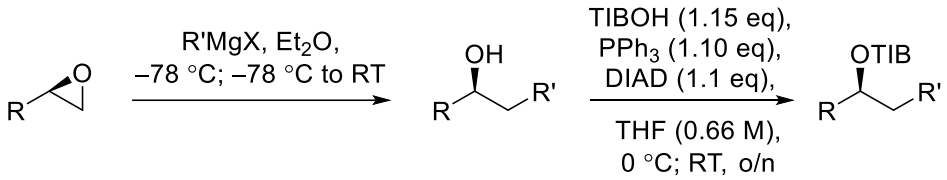
Enzymatic resolution of benzylic alcohols

To a solution of benzylic alcohol (9.8 mmol, 1 eq.) in diisopropyl ether (4 mL) was added acrylic resin bound lipase from *Candida Antarctica* (59 mg, 6 mg per mmol of alcohol) followed by vinyl acetate (4.3 mL, 49 mmol, 5 eq.). The suspension was then heated to 50 °C and stirred for 16 h, after which chiral HPLC analysis should indicate the alcohol having >99:1 *er*. The reaction mixture was filtered through a plug of SiO_2 with EtOAc as eluent, concentred *in vacuo* and purified by flash column chromatography (20% EtOAc:petrol) to give the enantioenriched (*S*)-alcohol and (*R*)-acetate products.

Carbamoylation of secondary benzylic alcohols

To a solution of benzylic alcohol (3.47 mmol, 1.00 eq.) in PhMe (3.5 mL) in a sealable microwave vial under N_2 was added *N*,*N*-diisopropylcarbamoyl chloride (681 mg, 4.16 mmol, 1.20 eq.) followed by Et_3N (0.63 mL, 4.51 mmol, 1.30 eq.). The vial was then sealed and heated under microwave irradiation at 150 °C for 2 h. The reaction mixture was then cooled to room temperature, filtered through a plug of SiO_2 with Et_2O as eluent, concentrated *in vacuo* and purified by bulb-to-bulb distillation under reduced pressure to give pure product.

Preparation of Secondary Benzoates



Synthesis of secondary alcohol from enantiopure epoxide

(*S*)-Propylene oxide (5.0 mL, 69 mmol, 1 eq., >99:1 *er*) was added dropwise to allyl magnesium bromide (1M in Et_2O, 103 mL, 103 mmol, 1.5 eq.) at −78 °C and the resulting mixture was stirred for 2 h at this temperature. The reaction mixture was then warmed to room temperature and sat. aq. NH_4Cl (100 mL) was added and the organic phase separated. The aqueous layer was washed with Et_2O (2 × 100 mL), the organic phases were combined, dried ($MgSO_4$) and concentrated in vacuo to afford (*S*)-hex-5-en-ol, >99:1 *er.*

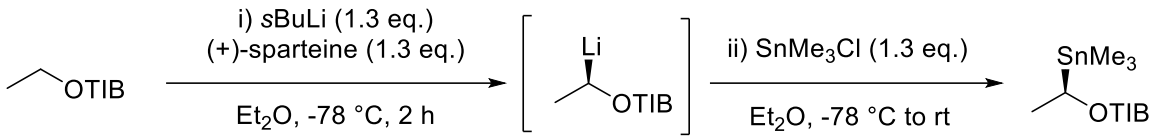
Benzoate formation through Mitsunobu reaction

To a stirred solution of PPh_3 (11 mmol), secondary alcohol (10 mmol) and 2,4,6-triisopropylbenzoic acid (11.5 mmol) in THF (15 ml) at 0 °C (ice bath), was added DIAD (11 mmol) dropwise over 10 min. After stirring for 4 h at 0 °C (ice bath), the volatiles were removed in vacuo. The residue was dissolved in pentane (15 ml) and stirred in for 5 min. The white suspension was filtered and the filter cake washed with pentane (100 ml). The solvent was remove *in vacuo* and the residue purified by flash column chromatography to give pure benzoate.

Notes:

- Sometimes separation of the excess PPh_3 from the product by chromatography can be challenging. You can distil your benzoate or take it up in THF and add 30% aq. H_2O_2 to form PPh_3O, which is easier to separate.

Preparation of α-Stannyl Benzoates



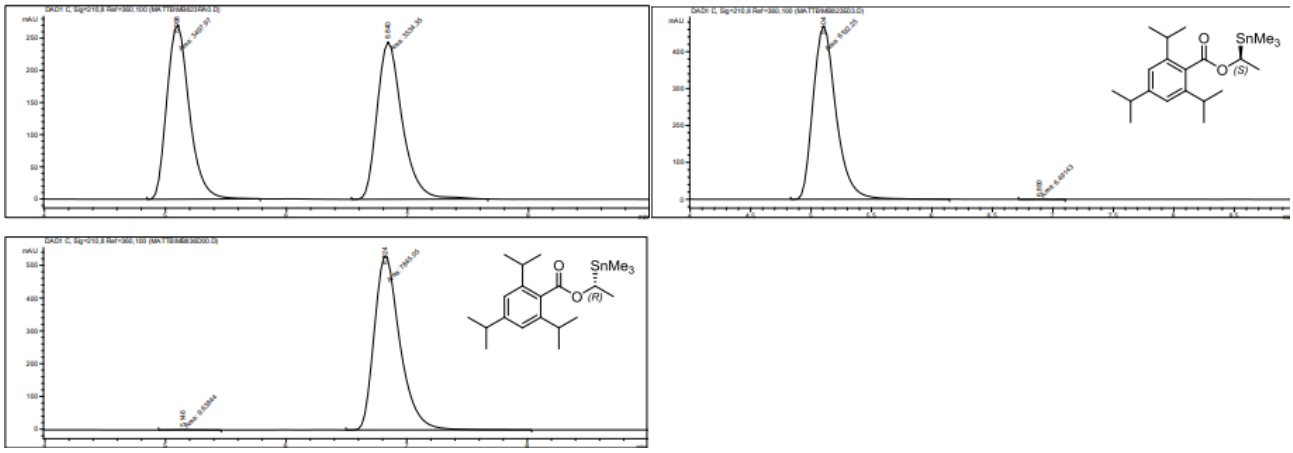
To a Schlenk flask under N_2 was added EtOTIB (10.00 g, 36.20 mmol), (+)-sparteine (10.81 ml, 47.06 mmol), and anhydrous Et_2O (181 ml). The flask was cooled to -78 °C before dropwise addition of sBuLi. The reaction mixture was stirred at this temperature for 2 h. Me_3SnCl (1.0 M in hexanes, 47.06 ml, 47.06 mmol) was added dropwise and the reaction stirred at this temperature for a further 20 min, before allowing the reaction to warm to room temperature. The reaction was stirred at room temperature for 1 h, before quenching with 2 M HCl (100 ml). The mixture was stirred for 20 min. The layers were separated, and the organic layer washed with 2 M HCl (4 x 100 ml). The combined aqueous layers were extracted with Et_2O (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the crude stannane. The crude stannane was dissolved in MeOH (2.0 mLg^{-1}), a condenser fitted, and the solution heated until no further solid remained. The mixture was allowed to cool to room temperature. Crystals of pure stannane appeared after 10 min to 5 hr after cooling. Combining recrystallised crops and further recrystallization gave the desired stannane as white needles (50 %, e.r 99.9:0.01)

Notes:

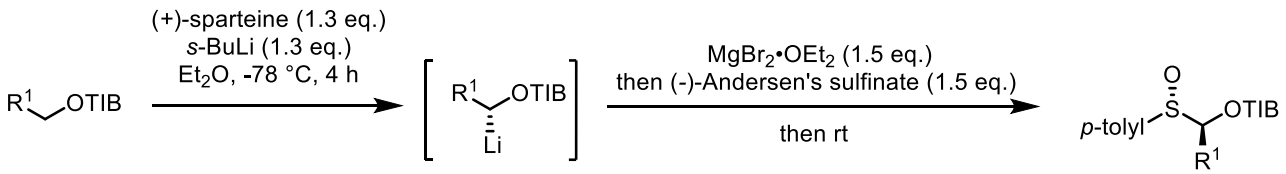
- $SnMe_3Cl$ is toxic, and care should be taken when handling. Tin contaminated waste, and washings from glassware, should be collected and disposed of in a separate waste container.

- While other α-stannyl benzoates can be prepared, the stannane derived from EtOTIB is one of the only ones we have found to be a crystalline solid, meaning it can be recrystallised to enantiopurity.

***Chiral HPLC**: (Daicel Chiralpak-IB column (25 cm) with guard, hexane, 0.9 mL/min, room temperature, 210.8 nm): tR = 5.1 min (S), 6.8 min (R), e. r. = 99.9 :0.1*



Preparation of α-Sulfinyl Benzoates



To a stirred solution of 2,4,6-triisopropylbenzoate (1.0 equiv) and sparteine (1.2–1.5 equiv) in anhydrous Et_2O (0.3 M wrt TIB ester) was added s-BuLi (1.3 M in cyclohexane/hexane, 1.2–1.5 equiv) dropwise at –78 °C. After stirring for the required lithiation time at –78 °C, a solution of freshly prepared $MgBr_2 \bullet Et_2O$ (see below) (1.5 equiv, 0.8 M in Et_2O) was added at –78 °C and the reaction mixture was stirred for 2 h at that temperature. At this point a solution of Andersen's sulfinate (1.5 equiv) in anhydrous THF (1.0 M) was added dropwise at –78 °C. The mixture was stirred for an additional hour at that temperature before being warmed to room temperature and stirred overnight. The reaction mixture was then diluted with Et_2O and HCl (2 M) was added. the phases were separated and the aqueous phase was extracted with Et_2O (x3). The combined organic layers were washed with four times with HCl (2 M). The combined acidic washes were then set aside for the recovery of sparteine. The organics were then washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure.

To assist with chromatographic purification, silylation of the menthol byproduct is often required: To a solution of the crude mixture in anhydrous DCM (0.5 M) was added Et_3N (1.5 equiv). TESCl (1.3 equiv) was added dropwise at room temperature, the resulting mixture was stirred for 20 min, diluted with Et_2O and washed with H_2O. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a crude residue, which was purified by flash column chromatography (hexane:EtOAc) to afford the desired product.

Preparation of $MgBr_2 \bullet Et_2O$

Oven-dried Mg turnings (4.0 equiv) were placed in a flask under a N_2 atmosphere and a condenser fitted. Anhydrous Et_2O (0.8 M with respect to dibromoethane) was added. The solution was cooled to 0 °C and 1,2-dibromoethane (1.5 equiv) was added dropwise. The ice bath was replaced with a water bath with room temperature water and reflux initiated spontaneously. After gas evolution ceased, the reaction mixture was stirred for an additional 30 min. A colourless layer and a grey layer should have formed. Both layers should be added to the reaction mixture.

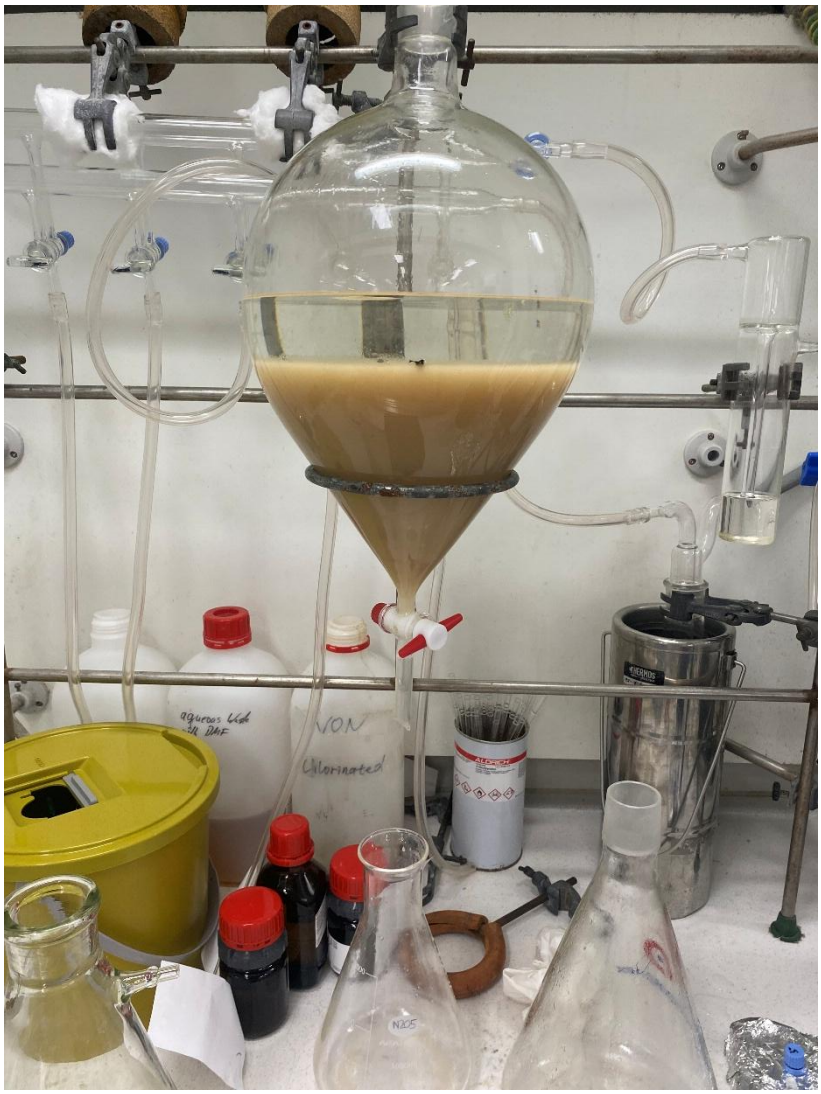
- A large, thick stirrer bar should be used to ensure strong, uninterrupted stirring throughout the reaction.
- When transferring the $MgBr_2 \bullet Et_2O$ solution, a large bore needle or cannula should be used. Both layers should be transferred but not any of the remaining solid. The needle should not be lowered too far into the cold flask of the reaction mixture as this can cause blockages.
- The Andersen's sulfinate should be perfectly white before use. If it is yellow, it should be recrystallised before use (acetone or Et_2O, cool to -20 °C to effect precipitation).
- Occassionally, especially on small scale, autoreflux does not appear to start when preparing the magnesium bromide etherate; in this case, careful intermittent use of a heat gun (lowest setting) can be used to initiate reflux.
- Oftentimes, the *syn* diastereomer is less polar, which can lead to easier separation by column chromatography.

Recovery of Sparteine

Reference**:** Org. Synth. 1997, 74, 23; Nature 2014, 513, 183

The combined aqueous layers were made basic (brought to about pH 14) by slowly adding NaOH (20 % aq or solid pellets if large volume) in an ice bath. The aqueous phase was extracted with Et_2O (x5). The combined aqueous layers were dried (K_2CO_3), filtered and concentrated under reduced pressure to give crude sparteine. A few scoops of CaH_2 were added and the sparteine was stirred under high vacuum overnight. Distillation the residual oil gives sparteine as a colourless oil. The sparteine was distilled directly into a Schlenk tube (see image below). After the distillation the Schlenk tube was stoppered and the joints wrapped in parafilm. Sparteine is stored under N_2 in the freezer.

(Distillation conditions: bulb to bulb; 10 cm Vigreux column; pressure: 2 mbar; oil bath: 150 °C, CaH_2 (100 mg/mL); (-)-sparteine bp: 137-138 °C (1.33 mbar)




Vac
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149
285
PASSED SAFETY TEST
10/25 M
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SCHOOL OF CHEMISTRY
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TEMPERATURE °C
STIRRING