Bill-Board Description and Use

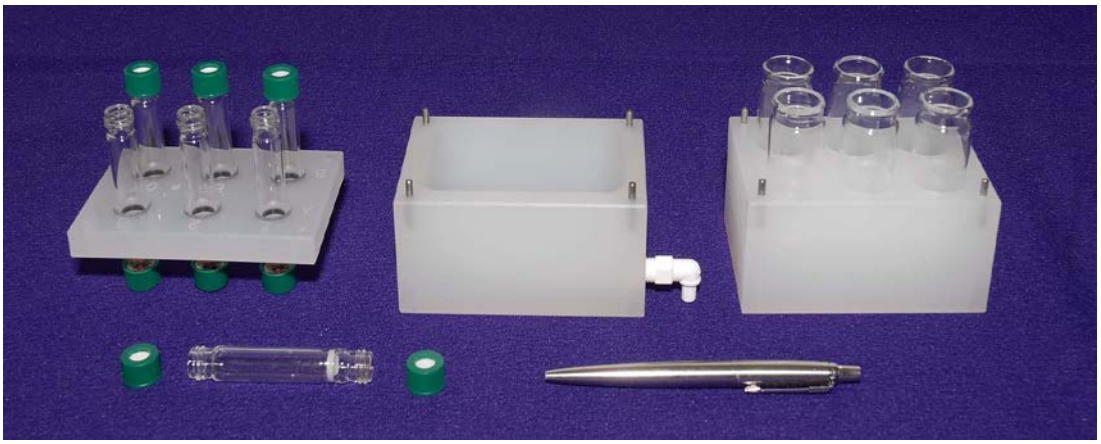
The Bill-Board 6-pack set has been designed to simplify and expedite multiple, manual solid-phase syntheses. 6 reactions can be conducted simultaneously in fritted glass reaction vessels (often called "micro filter funnels). Bill-Board equipment keeps the solid-phase reactions organized in a grid (for potential combinatorial reaction sequences) and simplifies the essential steps of solid-phase synthesis which involve repeated cycles of reactions and washings, followed by a final cleavage, product collection, and solvent evaporation step. On a typical 50 μmole scale, 50 mg of resin (loading of 1mmol/g) is used in each vessel. This leads to approximately 10-15 mg of each of the products (assuming a product MW of 300 and a yield of greater than 70%). The Bill-Board may also be used for any procedures that require multiple filtrations. It has been used for multiple simultaneous silica gel chromatography.

The complete Bill-Board 6-pack synthesis set consists of:

Essential:

1. A polypropylene "Bill-Board" with 6 holes containing O-rings to hold the fritted reaction vessels.
2. Fritted glass reaction vessels (typically 3.5 ml capacity, 7.5 cm long) which are inserted in the "Bill-Board".
3. A Bill-Board drain tray.
4. A Bill-Board collection vial rack.
5. 12 open-top polypropylene screw caps with 12 teflon-lined septa for caps.
6. 6 glass collection vials.

Some of the essential parts of the 6-pack are shown below:



Bill-Board 6-pack Bill-Board Drain Tray Collection Vial Rack

For purification:

1. Blank Bill-Board chromatography plate to hold up to six small chromatography columns.
2. 4-polypropylene dowels, 7.5 cm long, to suspend chromatography plate above vials in collection vial rack.

Points to note:

Safety Issues: When using the Bill-Board remember to use appropriate protective equipment (gloves, safety glasses, safety shields, etc) while working with hazardous reagents and solvents. When inserting or removing the glass reaction vessels use gloves appropriate for protection from potential cuts from glassware breakage. To avoid possible breakage do not force the glass vessels in or out of the plate. Once in place the vessels rarely need to be removed.

A. Assembly

1) The top of the Bill-Board is smooth and has column numbers and row letters engraved in the surface. The underside has a shallow counter-bored surface to help locate glass vials for the final collection step. When initially inserting the fritted glass reaction vessels (fritted side down) into the "Bill-Board" a *very* small amount of stopcock grease can be used to make insertion easier (we find a good place to apply the small amount of stopcock grease is to the o-rings in the plastic board.) This will also make their removal easier. Too much grease will allow the vessels to be moved under the pressure of the air-push device.

2) More of the glass (~ 4 cm) will be above the Bill-Board than below. This shorter distance (~ 2 cm) on the frit side is about right to ensure they will not "bottom out" when the Bill-Board is placed on the drain tray, and will also be at the right depth to drip into the vials when collecting product using the vial collection rack.
To make sure the fritted glass reaction vessels are at the appropriate depth when they are inserted into the Bill-Board, set the Bill-Board on the vial collection rack and push each glass vessel (fritted end down) through until it is stopped by the bottom of the vial holder (they will now extend below the Bill-Board by about 1.8 cm).

B. Operation

1) Caps should be snugly secured but not so tight the threads break. (Caps may be re-used. Simply wash in a beaker of appropriate solvent, drain by dumping the caps (or, for the caps with re-usable liners, the removed liners) into a glass funnel and dry this set in the vacuum oven. Keep two sets. One for current use and one drying. Make sure the red-Teflon-lined side of the septa is facing inside. When liners eventually degrade (TFA will accelerate this process) just pop them out and replace with a new Teflon-lined septa.

2) If required, the Bill-Board can be agitated (gently please) by all sorts of methods. We have used orbital shakers (with the Bill-Board on its side), motors with a three pronged clamp, motors used for peptide synthesizers, custom made mixers for one to 18 Bill-

Boards at a time, and other sundry mixers. We also have adapters to use rotary evaporator motors for rotation. Your imagination will find a solution if you don't already have an obvious shaking/rotating source.

3) For washings the drain tray can be elevated with a lab jack or wooden block and wash solvents allowed to drain into a beaker on the side.

4) By gravity, some reaction vessels may drain slower than others. Moderately slow ones can be assisted with a positive pressure of nitrogen or air. To do this, what we call an "air push" apparatus can made from a disposable plastic pipet inserted into a hole made in an inverted O.D. 13 mm septa. It is a simple, inexpensive way to enable an "air push". We prefer gravity draining – it provides for more resin contact time in the washing stages. Vessels that drain *much* more slowly than the rest, and whose draining cannot be accelerated via the "air push" should be replaced to speed up future steps.

5) Sometimes the final cleavage of product from resin needs to be carried out in a closed vessel. In this case, after cleavage invert the Bill-Board, uncap all the bottom caps (which are now face up), place inverted vials into the recesses surrounding each reaction vessel in the Bill-Board, place the inverted vial collection tray over all the inverted vials and smoothly turn the whole setup to the upright position. The top caps can now be removed and the product (in solution) will gently drip into the collection vials.

Cleaning caps: Dump used caps into a beaker. Cover with DMF. Swirl and pour caps/DMF through a ceramic Buchner funnel. Recycle DMF for future washes. Repeat process 2x, now with THF. Discard first THF wash but recycle second wash to be used as first wash in next cleaning cycle. Spread out cleaned caps, internal side up, on a paper towel to dry in the hood.

Cleaning vessels: Leave vessels in the Bill-Board. Tap dried resin into waste disposal vessel. Rinse out vessels with solvent from a squirt bottle, one time with DMF and two times with acetone. The DMF rinse and first acetone rinse (collected separately) can be recycled for rinse use after filtering off any small amounts of resin. Allow to air dry.

Questions or comments?

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(Updated February 2015)

1)Distributed Drug Discovery, Part 1: Linking Academia and Combinatorial Chemistry to Find Drug Leads for Developing Word Diseases, Journal of Combinatorial Chemistry, 2009, 11, 3-13, William Scott and Martin J. O-Donnell

2) Distributed Drug Discovery, Part 2:Gobal Rehearsal of Alkylating Agents for the Synthesis of Resin-Bound Unnatural Amino Acids and Virtual D^3 Catalog Construction,
Journal of Combinatorial Chemistry, 2009, 11,14-33, William Scott, Jordi Alsina, Christopher O. Audu, Evgenii Babaev, Linda Cook, Jeffery L. Dage, Lawrence A. Goodwin, Jacek G. Martynow,
Dariusz Matosiuk, Miriam Royo, Judith G. Smith, Andrew T. Strong, Kirk Wickizer, Eric M. Woerly, Ziniu Zhou and Martin J. O'Donnell.