Frequently Asked Questions about SynPhase™ Lanterns

1. What are SynPhase™ Lanterns?

SynPhase Lanterns are discrete, modular and quantized solid supports optimized for the synthesis of small organic compounds, peptides, and the scavenging of excess reagents from solution-phase reactions. The SynPhase Lantern offers synthesis characteristics comparable to, or better than, commonly available low-cross-linked resins, whilst at the same time delivering the ultimate in handling convenience. There is no need for time-consuming tasks such as weighing and filtering with SynPhase Lanterns. The modular design makes SynPhase Lanterns adaptable to any type of synthesis strategy such as parallel array handling or tagged split and pool techniques. In many ways a SynPhase Lantern can be thought of as a large, stable, polystyrene resin bead.

At the core of SynPhase technology is a mobile surface polymer grafted onto a rigid unreactive base polymer. This provides a solid framework for reliable handling of the solid phase during all stages of synthesis. The unique "Lantern" shape provides maximized surface area, free flow-through of reactants and rapid drainage of wash solutions.

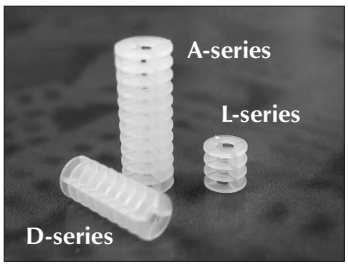

Fig 1

The SynPhase Lantern family

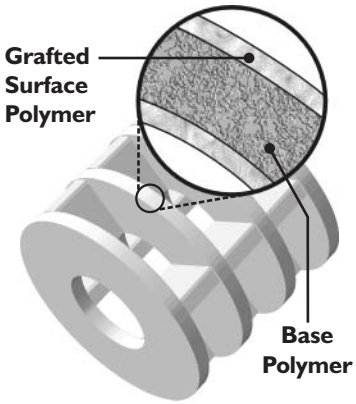

Fig 2

Schematic representation of the SynPhase Lantern surface

Our specialized grafting process yields a uniform 50μm polymer graft, delivering high performance reaction kinetics with minimal batch-to-batch variation in loading. The mobile phase may consist of polystyrene (PS) or polyamide (PA), the former being suitable for general small molecule organic synthesis while the latter is preferable for hydrophilic applications.

2. What are the physical dimensions of SynPhase™ Lanterns?

The SynPhase Lantern is cylindrical in appearance, with dimensions as shown in Table 1. These properties make the SynPhase Lantern compatible with a wide range of reaction vessels and synthesizers.

Table 1 | Physical dimensions of SynPhase Lanterns

Property	L-series	D-series	A-series
Height (mm)	5	12.5	17
Diameter (mm)	5	5	6
Surface Area (cm^2)	1.7	3.6	7.2
Void Volume (μL)	98	245	480

3. What is the fundamental difference between SynPhase™ Lanterns and Resins?

The primary difference between SynPhase Lanterns and resins is the modular, easy handling nature of SynPhase Lanterns, based on a structure of a rigid polymeric support beneath a grafted mobile phase. This gives rise to a number of unique features which lead to significant fundamental advantages over conventional resins. These are detailed in Table 2.

SynPhase Lantern Property	Advantages over resin
Surface polymer chain structure only requires solvent wetting	Transfer of reagents to reaction sites is faster Vigorous agitation is not required
Low gelling tendency of the surface polymer	Easy removal of unreacted reagents and by-products
Modular design with defined loading	Does not require weighing
Macroscopic, modular support	Easy manual handling No filtration Simple washing techniques No resin shattering No fines remaining on vessels Easily accommodates tags (colored, or radio frequency transponders) Allows rapid reaction optimization
Each Lantern series has same loading per unit surface area and per unit working volume	Chemistry translates between L-, D- and A-Series Lanterns without re-optimization
Closely controlled manufacturing process	Minimal batch to batch or within batch variation (refer to Question 5).
Optimized surface and shape	Loading per unit working volume similar to resin (0.15mmol/mL) Uniform reaction rates Minimizes working volumes Rapid drainage of reagents Compatible with automated synthesizers

Table 2 | The advantages of SynPhase Lanterns over resin

4. Are there any special storage requirements with SynPhase™ Lanterns?

There are no special requirements for short-term storage. SynPhase Lanterns can be kept in their original vacuum sealed ziplock bag. However, for prolonged storage, we recommend that SynPhase Lanterns be kept cool and dry at 8°C. The storage container must always be kept tightly closed when cold and must be allowed to reach room temperature before opening to prevent condensation. SynPhase Lanterns should only be used with dried solvents in dry glassware and apparatus. Avoid rough handling or abrasion of the dry Lanterns.

5. What is the typical loading capacity of SynPhase™ Lanterns?

Nominal loading values for the polystyrene graft are typically 15 μmol for SynPhase L-Series Lanterns, 35μmol for SynPhase D-Series Lanterns, and 75μmol for SynPhase A-Series Lanterns.

The variation in loading within a particular batch, say for polystyrene, is typically less than 0.6μmol for SynPhase L-Series Lanterns, less than 1.5μmol for SynPhase D-Series Lanterns, and less than 3 μmol for SynPhase A-Series Lanterns.

Product yields of 7-8mg for SynPhase PS L-Series Lanterns, 17-

19mg for SynPhase PS D-Series Lanterns, and quantities up to 40mg can be expected for the SynPhase PS A-Series Lanterns, based upon a compound of 500 MW and a yield of close to 100%.

The batch-to-batch variation in loading of 47 consecutive batches of SynPhase PS D-Series Lanterns is presented in Fig 3. The average loading for each batch was determined by quantitative Fmoc analyses on 10 SynPhase PS D-Series aminomethylated Lanterns, coupled with Fmoc- -Alanine (120mM Fmoc- -Alanine, DIC/HOBt activation).

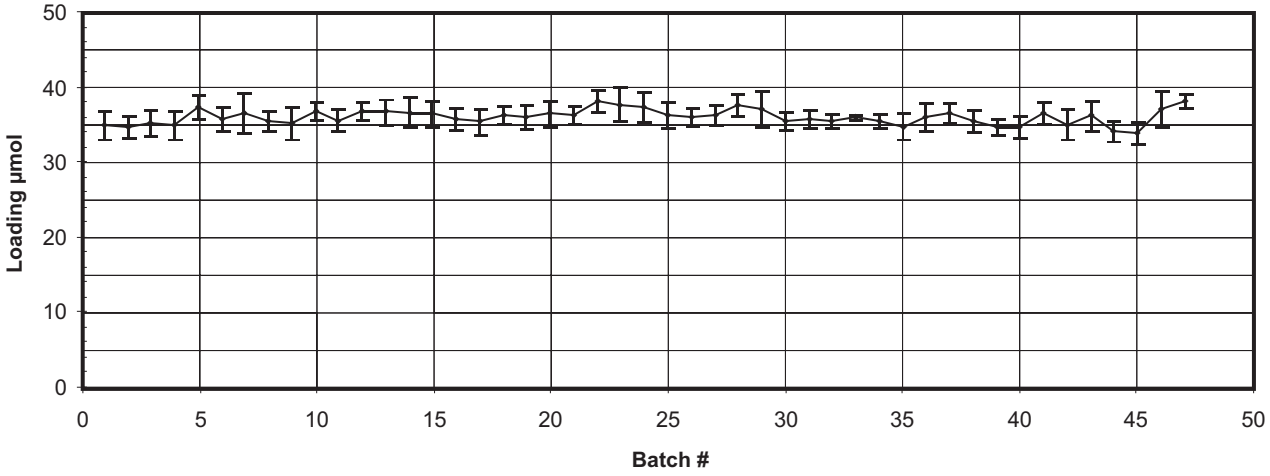

Fig 3 | Batch to batch loading variation for 47 consecutive batches of SynPhase D-Series aminomethylated Lanterns. The average loading of the 47 batches was 35.8μmol with a standard deviation of 1.0μmol.

6. What linkers are available with SynPhase™ Lanterns?

SynPhase Lanterns are available with a variety of derivatized surfaces and preformed linkers (refer to Table 3) enabling you to access a wide range of templates and chemistries.

Alternatively you can add your own proprietary linker, or we can perform custom linker attachment to meet your specific requirements.

Derivatized Surfaces/Preformed Linkers		Description of use
Solid Phase Synthesis	Aminomethylated	Allows derivatisation with a cleavable linker of choice (PS only)
	Non Functionalized	Allows derivatisation with a cleavable linker of choice (PA only)
	Chloromethylated	Equivalent to Merrifield resins
	Hydroxymethylated	Alternative to chloromethylated, for linking carboxylic acids
	Rink Amide linker	Links carboxylic acids. Cleaves to give primary amides
	Hydroxymethylphenoxy linker	Links carboxylic acids, alcohols, phenols and amines
	Trityl Alcohol linker	Links carboxylic acids, alcohols, phenols, amines and thiols
	Hyperlabile linker	Links carboxylic acids, alcohols, phenols and amines
	Backbone Amide linker	Links amines via reductive amination
Solution Phase Applications	Sulfonic Acid	Scavenges primary, secondary and tertiary amines by quarternary salt formation
	Aminomethylated	Scavenges acid chlorides, sulphonyl chlorides, isocyanates and other electorphiles
	TMI Isocyanate	Scavenges primary and secondary amines but does not scavenge anilic type aromatic amines
	N-Methyl Morpholine	Supported tertiary amine base for acylations and sulfonylations
	o-Nitrophenol	Solid supported active ester used for synthesis of amides and sulfonamides
	Benzaldehyde	Scavenges various nucleophiles including amines, hydrazines and carbon based nucleophiles such as phenylmagnesium halides

Table 3 | Derivatized surfaces and preformed linkers available on SynPhase Lanterns

7. How does the performance of SynPhase™ Lanterns compare to conventional resins?

SynPhase Lanterns provide yields and purities comparable to commonly used resins such as 100-200 mesh polystyrene resin. The design and shape of the Lantern maximizes surface area and allows free-flow of reagents to deliver high and uniform reaction rates, without the need for agitation.

The data in Fig 4 shows the optimized reaction of a support bound aniline with an isocyanate to form a urea on SynPhase PS Lanterns and two common polystyrene resins.

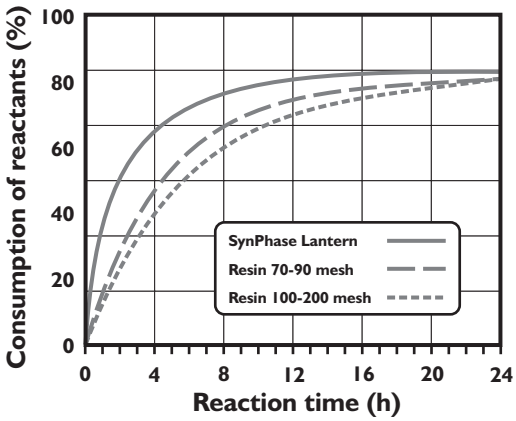

Fig 4 | Optimized reaction of support bound aniline with isocyanate on SynPhase PS- Lanterns and 2 common polystyrene resins

8. Does chemistry on resin transfer directly to SynPhase™ Lanterns?

In direct comparisons between polystyrene resin and Lanterns, experimental chemistry protocols have been found to be fully transferable. In addition, kinetics have often proved to be faster on SynPhase Lanterns. The higher and more uniform reaction rates can be attributed to the structure of the surface polymer, which allows better diffusion of the reactive species inside the matrix due to the low level of cross-linking in the grafted layer.

The improvements in reaction kinetics also apply to the kinetics of the washing step. Removal of excess reagents and side-products is very fast and economical. For example, removal of palladium salts (post-Suzuki coupling chemistry) is a straightforward procedure on Lanterns whereas on resin, long and tedious washes are required to ensure complete removal of salts.

A range of published chemistries utilizing linkers such as Rink, HMP, BAL and Trityl have been performed with SynPhase Lanterns and published as SynPhase Chemistry Notes*. These syntheses were selected from peer-reviewed literature where the chemistry had been performed on polystyrene resin and led to "structurally interesting", non-peptidic organic compounds of molecular weight <500.

**SynPhase Chemistry Notes can be obtained by downloading them in PDF format from http://www.mimotopes.com/combichem/tech.html or by requesting copies from your regional Mimotopes office.*

9. What solvents are compatible with SynPhase™ Lanterns? What are the swelling characteristics of SynPhase™ Lanterns in various solvents?

The physical properties of SynPhase Lanterns ensure compatibility with most solvents at temperatures in the range of -80°C to +100°C. The maximum recommended temperature for use of Lanterns under any conditions is +100°C.

Table 4 lists the swelling characteristics of Lanterns in several common solvents and reagents at 40°C, 70°C and 100°C.

10. What are the recommended volumes and concentrations of reagents for use with SynPhase™ Lanterns?

SynPhase Lanterns require relatively small working volumes, typically 250µL for SynPhase L-Series Lanterns, 500µL for SynPhase D-Series Lanterns, and 1000 µL for SynPhase A-Series Lanterns. However, the actual working volume is dependent upon the shape of the reaction vessel used for synthesis.

Since SynPhase Lanterns require minimal volumes of solvent, reagent concentrations can be kept relatively high in order to quickly drive reactions to completion. Based upon the nominal loading capacity and recommended working volumes, the number of µmol and the number of equivalents for a given concentration can be derived for SynPhase Lanterns, as shown in Table 5.

Solvent	40°C	70°C	100°C
Acetic acid	L	L	L
Acetic anhydride	L	L	L
Acetone	L	-	-
Acetonitrile	L	L	-
Benzyl alcohol	L	L	L
Benzylamine	L	M	M
Bromobenzene	M	H	H
t-Butanol	L	L	-
t-Butyl acetate	L	M	H
t-Butyl methyl ether	M	-	-
Carbon disulfide	H	-	-
Chloroform	H	H	-
Cyclohexane	H	H	-
Cyclohexanone	L	M	H
1,2-Dichloroethane	L	M	-
Dichloromethane	M	-	-
Dibutyl ether	M	H	H
Diethylene glycol diethyl ether	L	L	M
Diethyl ether	M	-	-
Diisopropyl ether	M	M	-
1,2-Dimethoxyethane	L	M	-
Dioxane	L	M	H
Dimethyl formamide (DMF)	L	L	M
Dimethyl sulfoxide (DMSO)	L	L	M
Ethanol	L	L	-
Ethanolamine	L	L	L
Ethoxy ethanol	L	L	L
Ethyl acetate	L	L	-
Formamide	L	L	L
Formic acid	L	L	L
Heptane	M	H	H
n-Hexane	M	H	-
Hexamethylphosphoric acid (HMPA)	L	L	M
Methanol	L	L	-
4-Methyl morpholine	M	H	H
1-Methyl-2-pyrolidinone	L	L	M
Nitrobenzene	L	L	L
Piperidine	M	H	H
Propane-1,2-diol	L	L	L
Propan-2-ol	L	L	-
Pyridine	L	M	H
Trifluoroacetic acid (TFA)	L	L	-
Tetrahydrofuran (THF)	H	H	-
1,1,2,2-Tetrachloroethane	M	H	H
Toluene	H	H	H
1,1,1-Trichloroethane	H	H	-
Water	L	L	L
m-Xylene	M	H	H

L : Low (<5%) **M** : Medium (5%-10%) **H** : High (>10%) **-** : Data not obtained

Table 4 Relative degree of swelling of SynPhase Lanterns in various solvents. This table should be used as a guide and it is recommended that some preliminary trials be performed to assess the degree of swelling prior to synthesis.

As with resins, the reagent concentration (or the number of equivalents) required can vary widely depending on the nature of the chemistry. When the optimum reaction conditions are unknown, we suggest that 3 different concentrations are used during the optimization, spanning the concentration range 0.1M to 2M.

Reagent Concentration (M)	L-Series		D-Series		A-Series	
	No. of μmol per 250μL	Equivalents per Lantern	No. of μmol per 500μL	Equivalents per Lantern	No. of μmol per 1000μL	Equivalents per Lantern
0.1	25	1.67	50	1.43	100	1.34
0.2	50	3.33	100	2.86	200	2.67
0.3	75	5.0	150	4.29	300	4.0
0.35	87.5	5.83	175	5.0	350	4.67
0.5	125	8.33	250	7.14	500	6.67
1.0	250	16.7	500	14.3	1000	13.33
2.0	500	33.3	1,000	28.6	2000	26.67

Table 5 | The number of μmol and equivalents for a given reagent concentration for SynPhase Lanterns, based upon nominal loading and recommended working volumes.

11. What synthesis strategies can be used with SynPhase™ Lanterns?

The modular design of SynPhase Lanterns makes them adaptable to any type of synthesis strategy whether it be parallel array handling or tagged split and pool techniques. SynPhase Lanterns can be easily attached to stems and arranged in an 8x12 array for simple handling which is extremely convenient for simultaneous cleavage. The SynPhase Assembly Workstations can further improve the efficiency of parallel synthesis and cleavage.

When array synthesis is not practical, SynPhase Lanterns can be tagged with a range of SynPhase tagging products for clear identification of compounds throughout the synthesis.

12. Can SynPhase™ Lanterns be used in solution phase applications?

Mimotopes has a range of SynPhase Lanterns designed specifically for use as scavengers in solution-phase chemistry. Just like resin, Lanterns can be used to scavenge excess reagents from solution-phase reactions with all the handling and kinetic advantages of the SynPhase Lantern. Scavenger Lanterns are suitable for a wide range of applications including scavenging of nucleophiles, electrophiles, and various amines.

13. Is there a SynPhase™ Lantern suitable for hydrophilic applications?

SynPhase hydrophilic polyamide (PA) Lanterns are compatible with a wide range of solvents including water, polar alcohols, and typical organic solvents such as methylene chloride and DMF. SynPhase PA Lanterns are available in versions optimized for peptide synthesis and general small molecule organic synthesis.

14. Can SynPhase™ Lanterns be used in automated synthesizers?

The compatibility of SynPhase Lanterns in automated systems is primarily dependent upon the physical dimensions of the reaction vessel of the synthesizer.

Whilst the Lanterns are compatible with a wide range of solvents and chemistries, minimal swelling of the Lanterns may occur, particularly in some solvents at elevated temperatures, see Table 4. Therefore, allowances may need to be made for changes in physical dimensions as a result of swelling of the SynPhase Lantern as with resin.

Vigorous agitation is not required with SynPhase Lanterns as reactants in solution will diffuse rapidly throughout the grafted matrix. Whilst SynPhase Lanterns are stable to stirring, agitation and ultrasonics, these techniques are not required as a general procedure.

A number of laboratories are routinely using SynPhase Lanterns in a range of commercially available synthesizers including those from Advanced ChemTech, Myriad, Bohdan and Argonaut. Significantly, the AutoSort-10K from Discovery Partnerships International has been specifically modified for use with Mimotopes SynPhase Lantern technology.

Fig 5

The IRORI AutoSort™-10K can automatically sort up to 1000 SynPhase Lanterns per hour.

15. How does the cost of SynPhase™ Lanterns compare to resin(s)?

The total synthesis cost of SynPhase Lanterns compares more than favorably with that of resins. The use of SynPhase Lanterns offers significant savings in labor, consumables and equipment as well as intangible cost benefits associated with the rapid development of optimized reaction conditions to deliver high purity compounds.

Initial Start-up Costs

The cost of accessories and equipment for library generation is significantly less for SynPhase Lanterns, given that no special apparatus for synthesis, washing, cleavage and filtration is required. In practical terms, the SynPhase Lanterns themselves are all that is needed for a chemistry laboratory to begin producing small sized libraries, as syntheses can be easily performed in common laboratory glassware.

SynPhase Work Stations are a range of devices that simplify the handling operations with SynPhase Lanterns to provide increased productivity for larger libraries. The initial capital expenditure on SynPhase Work Stations is minimal. In fact, this capital expenditure is as much as an order of magnitude lower than required for an automated synthesizer, which is the only viable option for improving efficiency for synthesis of large libraries with resin.

The Cost of the Solid Phase Support

A single SynPhase Lantern is required for the synthesis of each compound in quantities less than 40mg. For larger scale syntheses, SynPhase Lanterns may be pooled to generate the required quantity of compound. The cost of the solid support, whether it is a SynPhase Lantern or resin, depends upon the type of functionality required for synthesis. The direct cost of SynPhase Lanterns in general terms on a per loading basis ($/mmol) is in the same range as high quality resins.

Reaction Vessels

Reaction, washing and cleavage steps can be easily performed using general laboratory glassware and apparatus during syntheses with SynPhase Lanterns. There is no need for any expensive specialized reaction vessels, which are necessary when performing syntheses with resin due to the requirement to compartmentalize the resin.

Simple vessels such as test tubes, sealable polypropylene tubes and glass vials, are all suitable for small scale synthesis whilst larger vessels such as beakers, round bottomed flasks and Schott bottles are suitable for large scale syntheses.

Furthermore, the size and dimensions of the SynPhase Lanterns ensures that they will be compatible with most existing reaction blocks or vessels that you have in your laboratory.

Consumables

For general small molecule synthesis, SynPhase Lanterns can be equated to polystyrene resins of approximately 0.5mmol per gram, on a loading per unit mass basis or 1mmol per gram, on a loading per unit volume basis, when the swelling of resin is taken into account.

However, one of the fundamental differences between SynPhase Lanterns and resins is that the SynPhase Lantern has a "wicking" action. This results in solvent/reagent penetration to all parts of the grafted surface without agitation, even though it may not be completely immersed within the solvent or reagent. In contrast, resins need to be completely immersed within the solvent or reagent and require agitation to ensure reagents penetrate to all active sites of the resin. The "wicking" action of the SynPhase Lantern has significant cost advantages as smaller reagent volumes can be used, which is significant when using relatively expensive reagents.

The high washing efficiency of SynPhase Lanterns due to the easy solvation of the grafted surface ensures that ongoing solvent costs are greatly reduced when compared to resin, particularly when the resin is held in a flow-through container. SynPhase Lanterns typically require only half the number of washes and each wash utilizes about one third of the quantity of solvent when compared to resin.

There is also no need for ongoing deep cleaning or replacement of blocked filters and sinters that is required with resin, as there is no filtration step needed with SynPhase Lanterns.

Productivity

The physical nature of SynPhase Lanterns ensures time-consuming tasks are completely eliminated from the synthesis process. At the beginning of synthesis, there is no need for

weighing as the SynPhase Lanterns are quantized; 15μmol for SynPhase L-Series Lanterns, 35μmol for SynPhase D-Series Lanterns and 75μmol for SynPhase PS A-Series Lanterns for instance.

When you need to isolate the solid phase, excess solvent and reagent are easily removed from SynPhase Lanterns, avoiding the need to perform filtrations for each compound in the library.

The modular design allows 96 compounds to be cleaved rapidly in parallel at the conclusion of synthesis. Compare this to the individual handling required for filtration and cleavage with the use of resin. Compounds synthesized with SynPhase Lanterns are cleaved directly into vials or plates in which they will be stored, with no filtration or transfer steps.

Product Purity

High conversions are required in every step of solid phase synthesis to ensure compounds of the required purity are produced. For example, in a four-step solid phase synthesis, 95% conversion is required at each step to get an overall conversion of at least 80%. This requires highly optimized reaction conditions. The development of efficient reaction conditions rather than the library synthesis itself is the critical rate determining step for diverse library synthesis. Optimizing chemistry conditions with SynPhase Lanterns is a rapid process as various reaction conditions can be evaluated concurrently.

Product purity is also enhanced with SynPhase Lanterns as the risk of loss of target compound and contamination, which are associated with every filtration and transfer step using resin, are completely eliminated.

16. Where can I obtain additional information about SynPhase™ Lanterns?

For specific chemistry and equipment queries , please contact SynPhase Support for a rapid response, typically within 24hrs.

SynPhase Support Group

Web: **www.mimotopes.com/contact/techsup.html**
Email: **synphase_support_group@mimotopes.com**

Information regarding our products and services, together with technical information in a downloadable pdf format, is available on our website at www.mimotopes.com.

Additional information regarding any of Mimotopes' products can be obtained from your local Mimotopes office (see details below).

MIMOTOPES

International
Tel : + 61 3 9565 1111
Fax : + 61 3 9565 1199
mimotopes@mimotopes.com

France
Tel : + 33 1 5858 0002
Fax : + 33 1 5858 0006
europe@mimotopes.com

United Kingdom
Tel: +44 151 648 3343
Fax: +44 151 648 3328
uk@mimotopes.com

USA West
Tel : + 1 858 558 5800
Fax : + 1 858 558 5810
Tel : 800 644 1866
Fax : 800 655 1866
uswest@mimotopes.com

USA East
Tel : + 1 919 873 1123
Fax : + 1 919 873 1127
Tel : 800 633 8161
Fax : 800 424 3970
useast@mimotopes.com

http://www.synphase.com http://www.mimotopes.com