

# Liquid handling in Chemical Synthesis- The Celltech approach

Nick Ray - Celltech R&D  
Granta Park, Cambridge



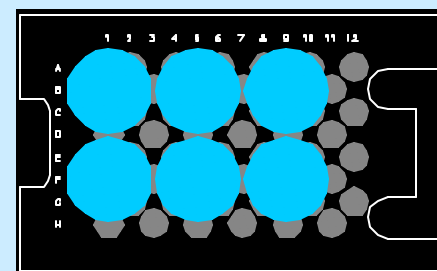
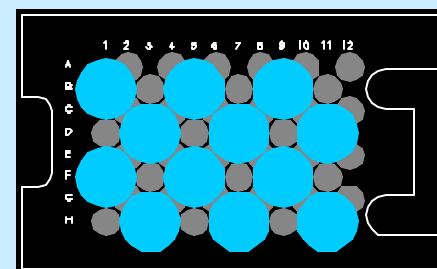
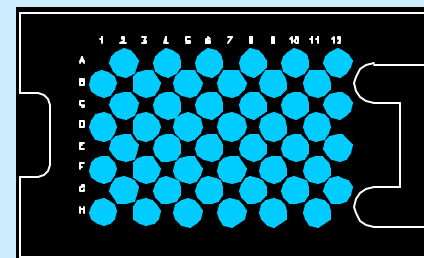
# Liquid handling - why?

- Not for speed
- Economies of scale
  - >10 reactions
- Accuracy
- Boredom!



# What's different about Chemistry?

- Variety of organic solvents
  - Viscosity
  - Vapour pressure
  - Material suitability
- 'Hard to handle' reagents
- Biphasic mixtures
  - Liquid-liquid
  - Solid-liquid
- Flexibility



# The Tools

- Tecan Genesis ChemSystem
- (Zinsser Calli)



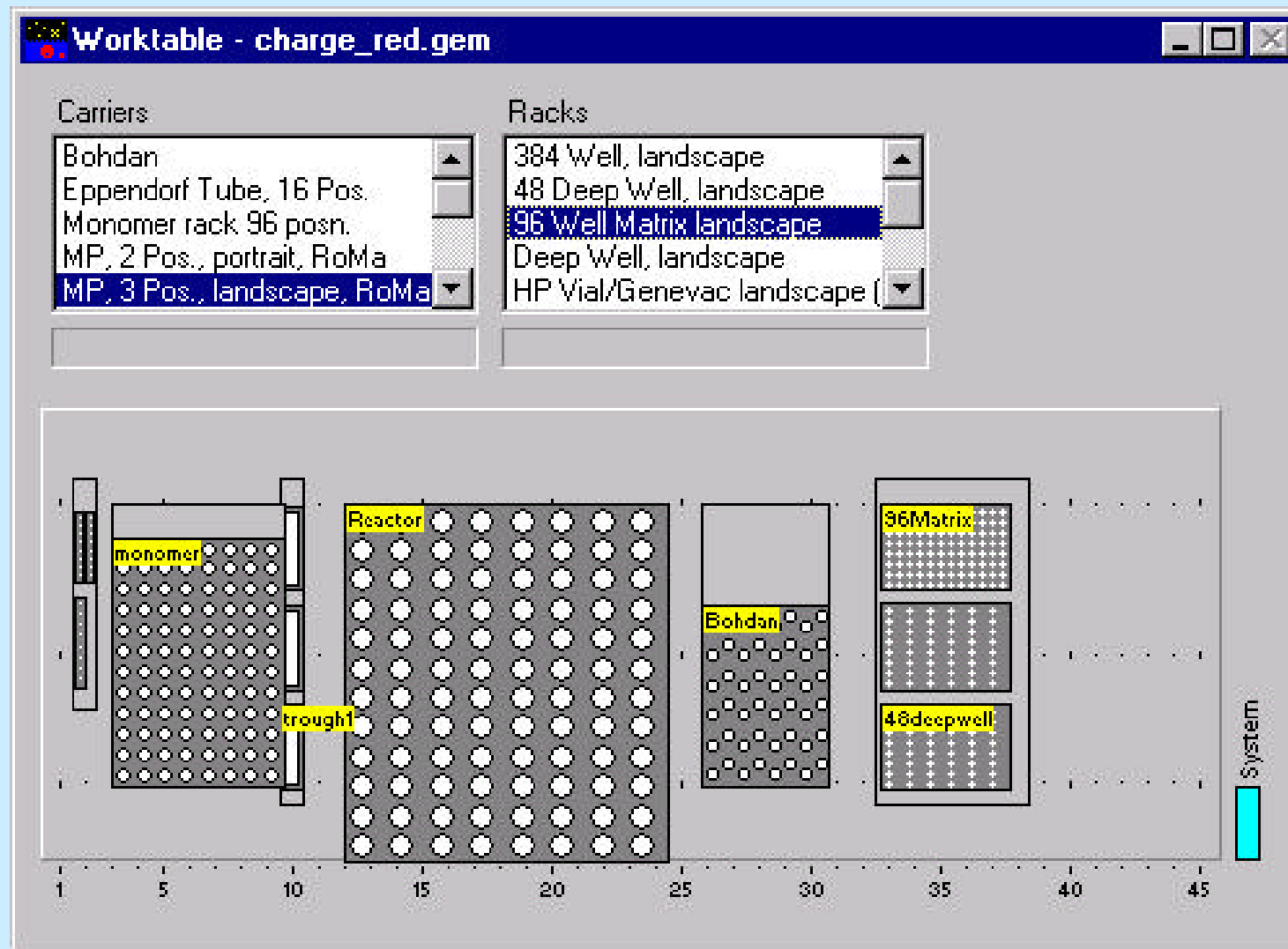
# Tecan features

- Chemically Inert fittings
- 6 Independent solvent lines via switching valve
- Co-axial septum piercing tips (8)
- Flexible software
- Good deck capacity (150cm, 200cm)
- Good Z-clearance

# Programming the Tecan




















- Button-driven, drag & drop, cut & paste
- Sub-routines pre-defined for;
  - Aspirate, dispense, mix, replicates, copy, serial diln., merge
- Ability to program loops, variables, system fluid changes, waste switching, time delays
- Other features
  - Cherry picking
  - liquid class selection
  - Turn inerting on/off
  - Control of 3rd party devices (reaction block)

# Worktable






# Protocols

charge_phenols.gem			
3		System	Heptane (10.0ml)
4		Wash Tips	 2.0 + 1.0 ml
5		Comment	make-up monomer standards
6		Worklist	 Load Worklist "H:\Libraries\starting materials\Tecan files\phenols.
7		Worklist	Execute loaded worklist(s)
8		Worklist	 Load Worklist "H:\Libraries\starting materials\Tecan files\phenols.
9		Worklist	Execute loaded worklist(s)
10		Wash Tips	 2.0 + 1.0 ml
11		User Prompt	"OK to continue?" sound : no
12		Comment	transfer monomers
13		Begin Loop	3 times "dispense"
14		Aspirate	 800 $\mu$ l >> Ethanol << "monomer" (Col. 1, Rows 1-8) , 1 option
15		Dispense	 400 $\mu$ l Ethanol "reactor" (Col. 1, Rows 1-8) , 1 option

**Aspirate**

Tip Selection

 1-8

☒ ☒ ☒ ☒ ☒ ☒ ☒ ☒

All tips First tip

Volume

800  $\mu$ l

Individual Volumes

Liquid Class

>> DMSO <<

Editor Customize

Loop Options

1 option

Loop Options

Location

Tip Spacing 1

"monomer"

Grid of circles (10x10):

- Row 1: 8 green, 2 white
- Row 2: 8 green, 2 white
- Row 3: 8 green, 2 white
- Row 4: 8 green, 2 white
- Row 5: 8 green, 2 white
- Row 6: 8 green, 2 white
- Row 7: 8 green, 2 white
- Row 8: 8 green, 2 white
- Row 9: 10 white
- Row 10: 10 white

Ok Cancel Help



# Liquid classes

**Edit liquid classes**

**DEFAULT CLASSES**

- ☒ DMSO
  - Standard <3 - 15µl>
  - Standard <15 - 200µl>
  - Standard <all volumes>
  - DITI <3 - 15µl>
  - DITI <15 - 200µl>
  - DITI <all volumes>
  - Std. & Low Vol. <0.5 - 3µl>
  - Std. & Low Vol. <3 - 15µl>
  - Std. & Low Vol. <15 - 300µl>
- ☒ Ethanol
- ☒ Micro DMSO
- ☒ Micro Priming Liquid (2-Propanol)
- ☒ Micro Water
- ☒ Serum
- ☒ Water
- ☒ Water on liquid level

**CUSTOM CLASSES**

- ☒ Organic

**Type** **Aspirate** **Dispense** **Calibration**

	Single Pipetting	Multi Pipetting
Aspiration Speed	150 µl / s	150 µl / s
Delay	300 ms	300 ms
System Trailing Airgap	20 µl	20 µl
Leading Airgap	0 µl	0 µl
Trailing Airgap	10 µl	0 µl
Excess Volume	0 µl	50 µl
Conditioning Volume	0 µl	30 µl
Use Pinch Valve	<input type="checkbox"/> yes	<input type="checkbox"/> yes

**Single Pipetting**

System  
STAG  
Vol.  
TAG

**Multi Pipetting**

System  
STAG  
Excess  
Vol.  
Cond.

Use Liquid Detection ☒ yes

Aspiration Position liquid level ± offset, with tracking 2 mm X: center

On Detection Error user prompt

Use Clot Detection ☐ yes

On Clot Error user prompt

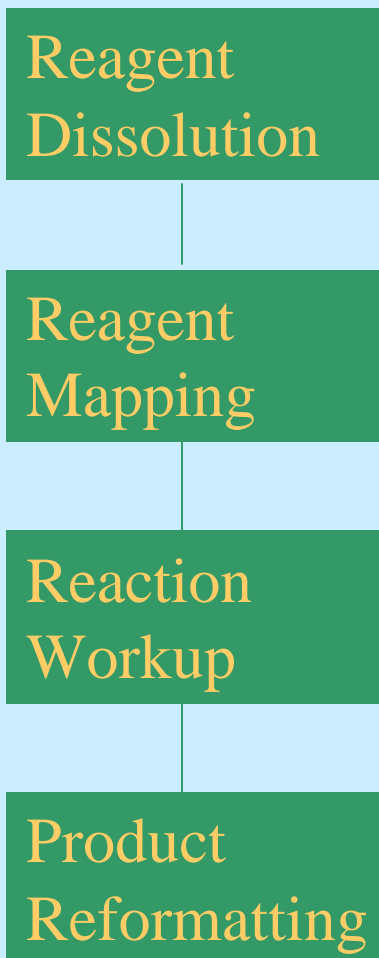
Mix before Aspiration ☐ yes 1 x 100 µl at selected position, no tracking 0 mm

Retract Tips to liquid level -5 mm

Retract Speed 20 mm / s

OK Cancel Help

# The Chemical Synthesis Process



# Reagent Dissolution

- Preparation of equimolar solutions
- Link to weighing station
- Max/Min permissible volumes
- Air-sensitive reagents

Accord for Escal - dilution template.xls [Read-Only]

	A	B	C	D	E	F	G	H	I
1									
2				Desired concentration mM			10		
3									
4	CHEMISTRY	Mol Wt	mass (mg)	Dilution volume (µl)					
5	Chemistry 1	122.123	0.6951						
6	Chemistry 2	220.268	9.4086						
7	Chemistry 3	112.088	10.8922						
8	Chemistry 4	114.144	11.9637						

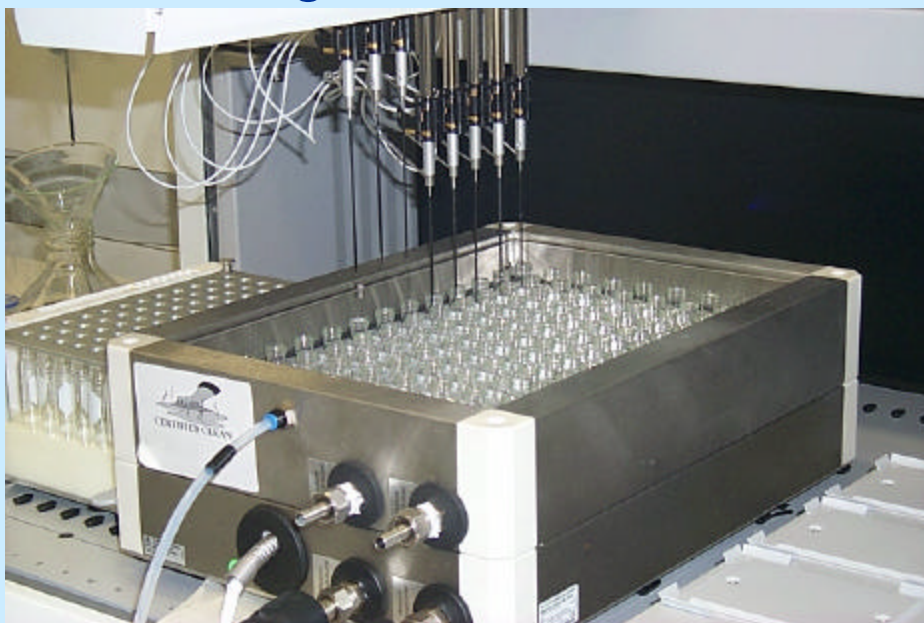
phenols.gwl - Notepad

```

File Edit Search Help
A;System;;;1;;2020
D;monomer;;;1;;2020
W;
A;System;;;1;;1847
D;monomer;;;2;;1847
W;
A;System;;;1;;2155
D;monomer;;;3;;2155
W;
A;System;;;1;;3287
D;monomer;;;4;;3287
W;
A;System;;;1;;2178
D;monomer;;;5;;2178
W;
A;System;;;1;;1496
D;monomer;;;6;;1496
W;
A;System;;;1;;2084
D;monomer;;;7;;2084
W;
    
```

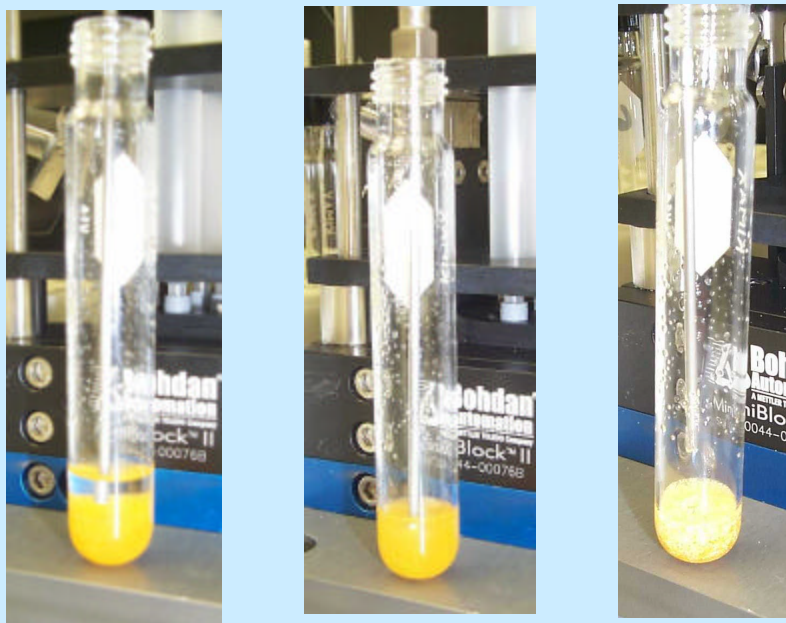
# Reagent Mapping

- What goes where?
- Variety of block designs/layouts
- Variety of reaction protocols
- Tracking via Excel



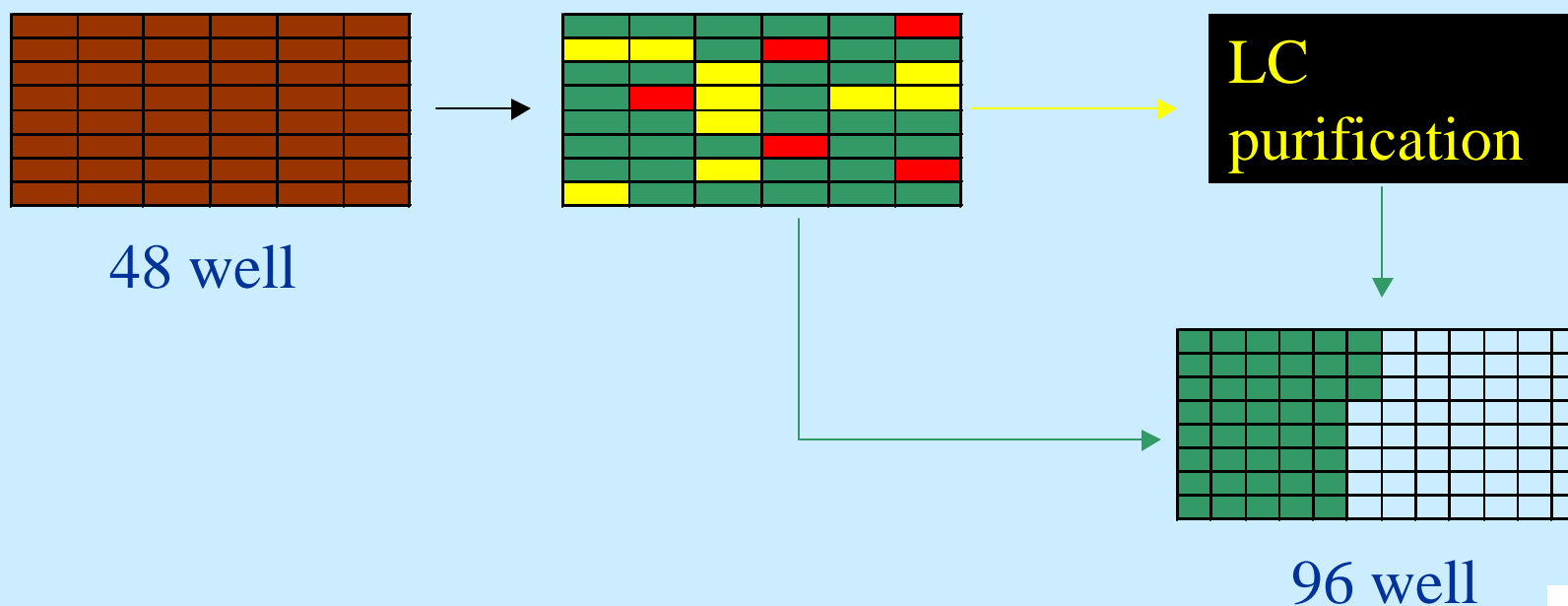
# Reaction work-up and product isolation

- Reaction quench with aqueous acid
- Separation of layers
- Separation of solids (resins)
- Distribution to analysis/purification plates



# Product Reformating

- Re-uniting purified/non-purified samples
- Reconstitution to standard molarity
- Replating





# Summary

- A liquid handler for chemistry must:
  - Be chemically robust
  - Be flexible
    - Deck
    - Programming
  - Allow the use of multiple solvents
  - Use a common interface (Excel)
- Optionally it should:
  - Allow septum-piercing
  - Allow inerting
  - Be multi-tipped

Tecan was our choice, but there are other machines available.....