University of Oxford
Department of Chemistry
South Parks Road
Oxford OX1 3QY

Professor Stephen G. Davies' Group
Dyson Perrins Laboratory
University of Oxford
South Parks Road
Oxford
OX1 3QY

Tel: +44 (0)1865 275662
Fax: +44 (0)1865 275674
http://chem.ox.ac.uk/dp/sgdavies

3rd May 2001

Evaluation of RDT Cooled Carousel Reaction Station™

The RDT Cooled Carousel Reaction Station was evaluated for the following performance criteria:

- The ability to maintain sub-ambient temperatures for a range of cooling mixtures.
- The ease of application to low temperature synthetic methodology: The Horner-Wadsworth-Emmons reaction and the highly diastereoselective conjugate addition of homochiral lithium amides to α,β-unsaturated esters.
- Stirring efficiencies of different RDT magnetic stirring bars

Cooling Performance

The Cooled Carousel was assembled in a standard fume-hood as directed in the user's manual.[1] 12-threaded reaction tubes (RR98061) containing medium cross-shaped stirring bars (RR98091) were charged with THF (15mL) and attached to the gas tight threaded PTFE caps (RR98068) and sealed with Suba Seals[2] (RR98076). Using the dry ice/solvent cooling mixtures listed in the Cooled Carousel user's manual,[3] the Cooled Carousel achieved the desired temperatures in each case (temperature measurements were taken from both the cooling reservoir and from directly inside the reaction tubes using a standard low temperature thermometer). It should be noted however that using the ultra-low temperature cooling mixtures such as dry ice/ethanol and dry ice/acetone, condensation of moisture onto the aluminium reactor head was a problem. This problem could be largely eradicated however with the aid of the Cooled Carousel Cover (RR99915/4) *vide infra*.

The time course over which these temperatures could be sustained when the user is not present to top up the cooling mixture with dry ice and/or solvent (e.g. in the case of an overnight reaction) was also evaluated. This was necessitated since, it was noted that when placed in a standard fume-hood, the increased rate of solvent evaporation from the cooling reservoir resulted in depletion of the cooling mixture after a few hours.[4] This study was conducted using dry ice/acetone as the cooling mixture; the cooling reservoir was charged with dry ice such that the level of the dry ice was level with the rim of the reservoir and acetone was added *via* a wash bottle to give a slurry of the coolant. The temperature of the coolant in the reservoir and that of the reaction solvent (i.e. THF) was then monitored at 60-minute intervals over an 8-hour period. The results are depicted in Table 1.

Table 1:

Evaluation of Temperature vs. Time using Cooled Carousel Reaction Station[a]

Cooling Reservoir Temp/^{o}C	Reaction solvent Temp/^{o}C	Time/h
-83	-81	0[b]
-81	-78	1
-81	-78	2
-81	-78	3
-80	-78	4
-80	-78	5
-76	-73	6
-68	-65	7
-20	-	8

[a] *The evaluation was performed a total of three times to determine the reproducibility of each run. There was little observed deviation in the data between each run.* [b] *Time=0 was taken as 15 minutes after the cooling mixture had been added to the cooling reservoir.*

These results indicate that when the cooling reservoir is fully charged with dry ice/acetone as the coolant, the reaction temperature can be expected to remain at –78^{o}C for a period of 5-6h.

Cooling Performance with Cooled Carousel Cover (RR99915/4)

The problem of condensation forming on the reactor head when using ultra-low temperature cooling mixtures has been addressed by the production of a plastic cover that fits directly over the reactor head, forming a loose seal over the rim of the cooling reservoir, giving the apparatus a UFO-shaped appearance. The cover was designed to be of further utility in that it would insulate the cooling mixture held inside the dome, slowing down the depletion of the cooling mixture, thereby prolonging the time period over which the desired low temperature could be maintained. On receipt of the Cooled Carousel Cover from RDT, the temperature/time course for the dry ice/acetone system was repeated to evaluate the effect of the cover on the

depletion of the cooling mixture (Table 2) in addition to determining the effect, if any, of the level of condensation forming on the reactor head.

Table 2:

Evaluation of Temperature vs. Time using Cooled Carousel with Cover in place[a]

Cooling Reservoir Temp/^{o}C)	Reaction solvent Temp/^{o}C	Time/h
-83	-81	0
-81	-78	1
-81	-78	2
-81	-78	3
-80	-78	4
-80	-78	5
-81	-78	6
-81	-78	7
-77	-75	8

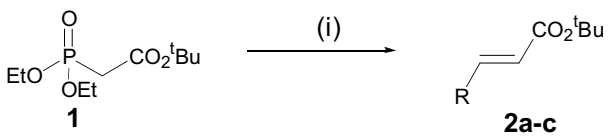
[a] *The evaluation was performed a total of three times to determine the reproducibility of each run*

The data shows that with the Cooled Carousel Cover in place, the temperature of the cooling mixture and reaction solvent remain at –78^{o}C for approximately 40 per cent longer than when the Cooled Carousel is used without the Cover, i.e. 7-8h. Additionally, use of the Cover also led to a dramatic reduction in the amount of condensation forming on the apparatus.

Application of low temperature synthetic methodology to the Cooled Carousel Reaction Station

In order to evaluate the utility of the Cooled Carousel Reaction Station, the ease by which two low temperature synthetic reactions routinely employed within this laboratory could be transferred from standard glassware onto the Cooled Carousel apparatus was investigated. This was tested firstly by the synthesis of an array of (*E*)-α,β-unsaturated *tert*-butyl esters **2a-c** by the Horner-Wadsworth-Emmons reaction[5] of diethyl *tert*-butylphosphonoacetate **1** with three aromatic aldehydes (Scheme 1), this protocol being representative of a standard C-C bond forming reaction.

Scheme 1:



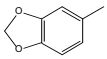
1 **2a-c**

Reagents and conditions: (i) RCHO, *n*-BuLi, THF, -78^{o}C to rt.

The three (*E*)-unsaturated *tert*-butyl esters **2a-c** were obtained in good isolated yields with >95% selectivity for the (*E*)-diasteroisomer (Table 3).

Table 3:

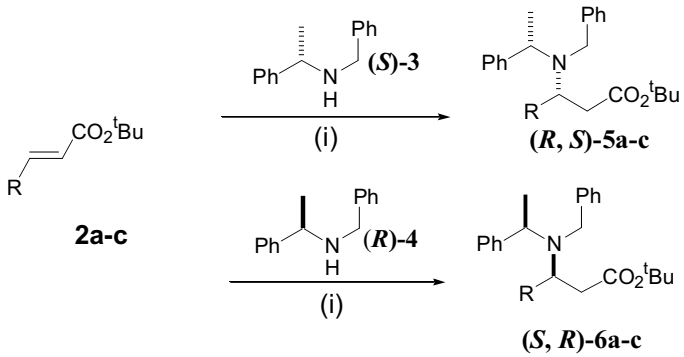
Yields for HWE reaction of diethyl *tert*-butylphosphonoacetate with aromatic aldehydes

product	R	Yield (%)[a,b]
2a	Ph	86
2b		60
2c		88

[a] Yields refer to those obtained after chromatography and or recrystallisation; [b] >98% d.e. as determined by 500MHz ^{1}H NMR analysis of the crude reaction products.

Conversion of these three Michael acceptors to an array of six diastereomeric β--amino acid precursors **(*R,S*)-5a-c** and **(*S,R*)-6a-c** by the highly stereoselective conjugate addition of each enantiomer of the chiral auxiliary *N*-benzyl-α-methylbenzyl lithium amide[6] (Scheme 2) was then performed in parallel using the Cooled Carousel. THF solutions of the Michael acceptors **2a-c** at -78^{o}C were cannulated onto THF solutions of the lithium amide, generated by addition of *n*-butyl lithium to **(*S*)-3** and **(*R*)-4** also at –78^{o}C under an atmosphere of argon.

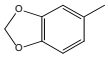
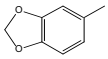
Scheme 2:



Reagents and conditions: (i) *n*-BuLi, THF, -78^{o}C.

In each case the crude reaction product was obtained as a single detectable diastereoisomer (>95% d.e.) and in excellent isolated yield following flash chromatography (Table 4).

Table 4

Entry	R	Abs. config. of Li amide	Yield (%)[a]	Major product	d.e. (%)[b]
1	Ph	(*S*)	89	**(*R*, *S*)-5a**	>95
2	Ph	(*R*)	93	**(*S*, *R*)-6a**	>95
3		(*S*)	91	**(*R*, *S*)-5b**	>95
4		(*R*)	92	**(*S*, *R*)-6b**	>95
5		(*S*)	88	**(*R*, *S*)-5c**	>95
6		(*R*)	90	**(*S*, *R*)-6c**	>95

[a] *Yields refer to those obtained after chromatography and or recrystallisation;*
[b] *Determined by 500MHz ^{1}H NMR using (S)-(+)-O-acetyl mandelic acid as chiral shift reagent.*

The results of these two experiments are directly comparable to those obtained when the analogous reactions were performed in standard laboratory glassware[7] and serve to illustrate the ease by which standard synthetic protocols may be transferred onto the Cooled Carousel.

Evaluation of RDT PTFE magnetic stirrer bars

The following six types of PTFE magnetic stirrer bars, available from RDT, were evaluated in the Cooled Carousel for their stirring efficiency:

1. Large octagonal PTFE magnetic stirrer bar (RR98070)
2. Small octagonal PTFE magnetic stirrer bar (RR98071)
3. Small cross shape PTFE magnetic stirrer bar (RR98075)
4. Rare earth medium cross shape PTFE magnetic stirrer bar (RR98091)
5. Rare earth small elliptical PTFE magnetic stirrer bar (RR98096)
6. Rare earth large elliptical PTFE magnetic stirrer bar (RR98097)

The reaction tubes containing the six-types of stirrer bar were charged with THF (15mL) and their relative performances rated from stirring speed calibration positions 5-10 on the Carousel Stirring Hotplate (RR98072) according to the vortex generated by the stirrer bar. The results are illustrated in Table 5.

Table 5

	Stirring speed/depth of vortex created[a]					
Stirrer Type	5	6	7	8	9	10
1	+	+ +	+ +	+ +	+ + +	+ + +
2	- -	-	+	+	+	+ +
3	- - -	-	+	+	+	+ +
4	+	+ +	+ + +	+ + +	+ + +	- - -
5	- - -	-	+	+	+	+
6	+	+	+	+ +	+ +	+ +

[a] *Key to table:* - - - *poor stirring/no vortex*
+ + + *efficient stirring/deep vortex*

This study demonstrates that for chemistry performed in RDT Reaction Tubes the large octagonal PTFE stirrer bar (Table 5, type 1) and the rare earth medium cross shape PTFE stirrer bar (Table 5, type 4) gave the deepest vortex at medium to high stirrer speeds, although it was observed at maximum speed the medium cross shape bar tended to cease stirring. The smaller stirrer bars generally gave poorer stirring performances, most notably the small cross shape stirrer bar and the rare earth small elliptical bar (Table 5, types 3 and 5 respectively) performed the worst across the range of stirrer speeds.

Comment

The RDT Cooled Carousel Reaction Station, like its forerunner the Carousel Reaction Station, has been quickly assimilated into the daily chemistry operations within this laboratory for both parallel synthesis and for rapid reaction development and optimisation. Undergraduate, Graduate and Postdoctoral workers alike use the Cooled Carousel routinely, itself being testament to the convenience of operation and the ease by which standard methodology may be transferred onto the apparatus.

References

1. RR99900 Cooled Carousel Reaction Station users manual.
2. It was found that once pierced with a needle, these Suba Seals do not afford an adequate gas tight seal. Additionally, these Suba Seals were observed to be readily degraded with aggressive reagents such as TFA or trifluoromethanesulfonic acid. Standard natural rubber Suba Seals (size 13) are routinely used in place of the clear silicone Suba Seals in this laboratory and have been found to afford excellent seals with the PTFE cap and considerably better chemical resistance.
3. Cooling Mixture Appendix, page 10
4. The rate of depletion of the cooling mixture will of course depend on the solvent employed in the cooling mixture and the velocity of airflow in the fume hood. The airflow velocity is dictated by the height of the front sash, airflow being fastest when the sash is raised, hence lowering the sash will slow depletion of the cooling mixture.
5. Horner, L.; Hoffman H.; Wippel, H.G.; Khlare, G.; *Chem. Ber*., **1959**, *92*, 2499; Wadsworth Jr., W.S.; Emmons, W.D.; *J. Am. Chem. Soc*., **1961**, *83*, 1733; Wadsworth Jr., W.S.; *Org React*. **1977**, *25*, 73
6. For selected examples see: Davies, S.G.; Ichihara, O.; *Tet. Lett*. **1999**, *40*, 9319; Davies, S.G.; Chernega A.N.; Lewis, C.N. and Todd, R.S. *J. Chem. Soc., Perkin Trans*. 1 **1999**, *24*, 3603; Davies, S.G.; Smyth, G.D.; Chippendale A.M.; *J. Chem. Soc., Perkin Trans*. 1 **1999**, *21*, 3089; Davies, S.G.; Dixon D.J.; *J. Chem. Soc., Perkin Trans*. 1 **1998**, *17*, 2635; Davies, S.G.; Ichihara, O.; *Tet. Lett.*, **1998**, *39*, 6045; Davies, S.G.; Smyth, G.D.; *J. Chem. Soc., Perkin Trans*. 1 **1999**, *21*, 2467.
7. Davies, S.G. and Wright, A.J.; *unpublished results*.

Evaluation and report compiled by Dr. Andy Mulvaney and Miss Angela Wright