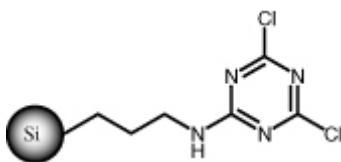
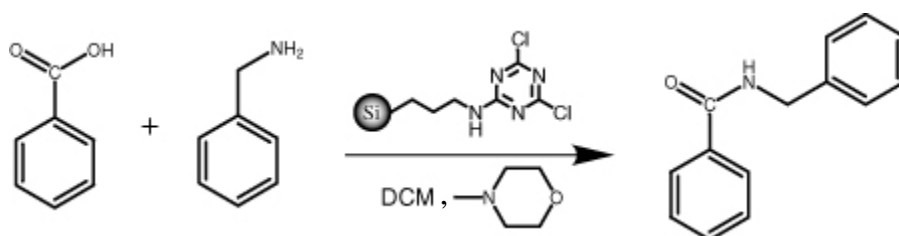


## Use of SiliaBond<sup>®</sup> Dichlorotriazine (Si-DCT)



**SiliaBond<sup>®</sup> DCT** must be activated with *N*-methylmorpholine (NMM) to give a morpholinium salt that can react with the carboxylic acid to form the activated ester. It may then be reacted with an amine to form the amide or safely stored for use at a later date. **Si-DCT** may also be used for synthesis of Weinreb amides and sulfonamides. **Si-DCT** provides a fast clean route to generating amides with complete conversion in a little more than an hour compared to most bound coupling reagents, which require overnight incubation.



### Sample Procedure

#### In Bulk

In a flask, **Si-DCT** (loading: 0.6 mmol/g, 2.0 g, 2.0 eq., 1.2 mmol) was placed in suspension in 10 mL of anhydrous DCM along with *N*-methylmorpholine (NMM, 101.15g/mol, 0.1821g, 3.0 eq., 1.8 mmol), the acid (1.5 eq., 0.9 mmol), and the amine (1.0 eq., 0.6 mmol). The solution was stirred at room temperature for 1 hour or until the amine disappeared (TLC). To this mixture, **SiliaBond<sup>®</sup> Tosic Acid** (loading: 0.8 mmol/g, 3.75g, 5.0 eq., 3.0 mmol) and **SiliaBond<sup>®</sup> Amine** (loading: 1.6 mmol/g, 0.75g, 2.0 eq., 1.2 mmol) were added to scavenge the excess amines (starting amine and NMM) and excess acid. Total volume of the mixture was adjusted to have a maximum ratio of 1 g/5 mL silica/solvent. Scavengers were allowed to react for 1 h at room temperature prior to filtration, washing with anhydrous DCM (3 × 10 mL), and evaporation of the solvent under vacuum. The corresponding amides were analyzed by NMR or GC-MS. Yield corresponds to the mass of isolated product. Purity was determined by GC-FID. THF (anhydrous and inhibitor free) may be used instead of DCM.

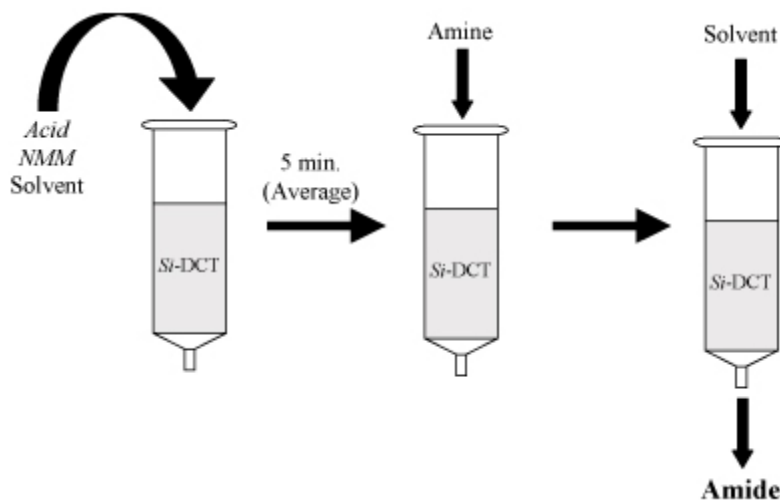
#### In Cartridges

**SiliaPrep<sup>™</sup> Dichlorotriazine** (loading: 0.6 mmol/g, 2.0 g, 6 mL, 2.0 eq., 1.2 mmol) was placed on a vacuum manifold equipped with individual valves. The valves were closed so that the liquid stayed on the **SiliaPrep<sup>™</sup> DCT** bed. NMM (101.15g/mol, 0.1821g, 3.0 eq., 1.8 mmol) and the acid (1.5 eq., 0.9 mmol) were mixed together in the minimum volume of anhydrous DCM to convert all the silica bed. The total volume of the mixture to be incubated must not exceed the bed volume of the cartridge (~1.5-1.6 mL). The resulting solution was inserted into the cartridge and left to react for 1-5 minutes (or sometimes a bit longer for less reactive acids). The valve was opened to drain the solution and rinsing with 2 column volume of anhydrous DCM to convert all the silica bed (~1.5-1.6 mL). The valve was opened while maintaining the vacuum on so that the cartridge was allowed to dry. The valve was closed and the amine (1.0 eq., 0.6 mmol, in the minimum volume of anhydrous DCM) was dripped onto the SPE cartridge and incubated for a time ranging from a few minutes to overnight. The cartridge was drained and rinsed with 2 column volume of anhydrous DCM to collect the amide. Solvent was evaporated under vacuum. Amides were characterized as described in previous example. THF (anhydrous and inhibitor free) may be used instead of DCM.

Notes:

- 1) If using Fmoc protected amino acid (or any compound bearing base sensitive groups), pass the NMM in solution first, wash, and then load the acid.
- 2) If using Boc protected amino acid (or any compound bearing acid sensitive groups), mix all products together in a minimum of DCM. Apply the solution to the cartridge and let incubate for a few minutes before washing with DCM. Add scavengers.

The following scheme shows how **SiliaPrep™ DCT** is used for amide synthesis.



**Table 1 : Results of Amide Bond Formation Using Si-Dichlorotriazine (Si-DCT) (1g, 12mL)**

#	Acid	Amine	% Yield (% Purity <sup>a</sup> )	
			Bulk	Cartridge
1	Benzoic acid	Aniline	100.0 (98.9) <sup>C</sup>	100.0 (98.5) <sup>D</sup>
2	"	Benzyl amine	100.0 (97.8)	99.6 (96.7)
3	"	Phenylethylamine	100.0 (98.4)	99.9 (96.5)
4	Phenoxyacetic acid	<i>Tert</i> -Butylamine	99.5 (99.0)	92.7 (95.3) <sup>E</sup>
5	"	1,2,3,4-Tetrahydro-isoquinoline	91.1 (92.0)	70.0 (94.0) <sup>E</sup>
6	Boc-Phe-OH (L)	Phenylethylamine	99.8 (97.9)	91.1 (95.4)
7	Fmoc-Phe-OH (D) <sup>H</sup>	"	100.0 (>95 <sup>B</sup> )	100.0 (>95 <sup>B</sup> )
8	Z-Val-OH	"	100.0 (>95 <sup>B</sup> )	98.3 (>95 <sup>B</sup> )
9	3-Iodobenzoic acid	Benzylamine	100.0 (99.0)	99.9 (98.9)
10	Heptanoic acid	Ethanolamine	78.2 (68.0) <sup>F</sup>	53.2 (95.0) <sup>G</sup>

A : Determined by GC-FID; B : Determined by <sup>1</sup>H NMR; C : 3 h reaction time; D : Amine overnight incubation; E : Acid overnight incubation; F : Use 4 eq. of acid and let react for 1 h before adding amine; G : Use 4 eq. of acid; H : Do not use scavengers which would deprotect the amine.

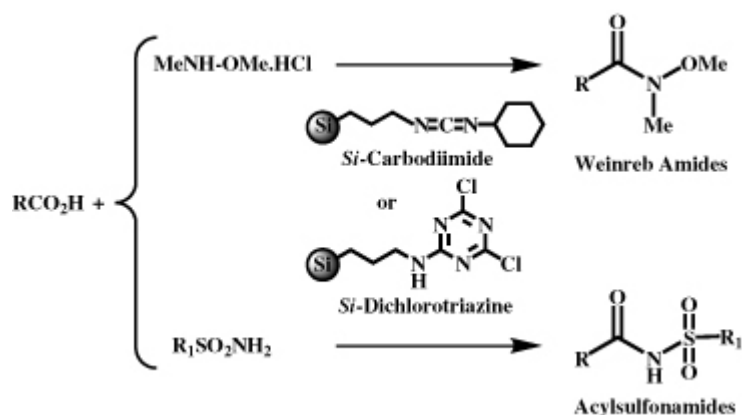
Conditions : As described in the sample procedure unless stated otherwise.

### Si-DCT in cartridges or in bulk?

Using **SiliaPrep™ DCT** offers certain advantages over bulk functionalized silica. They can be summarized as follow:

- Shorter reaction times (few minutes compared to 1 h);
- No need for use of supported scavengers (saves an additional step and costs);
- Amenable to automation.

Applications and uses of **SiliaBond® Dichlorotriazine** are not restricted to standard amides. As a matter of fact, it has been successfully used for the synthesis of Weinreb amides and acylsulfonamides as represented in the following scheme.



### Sample procedure

#### Weinreb Amide in bulk

Same procedure as described above with the exception that the reaction time is overnight.

Table 2 : Weinreb Amide Synthesis with SiliaBond® DCT		
Acid	Amine	% Yield (% Purity)
Benzoic acid	<i>N,O</i> -Dimethylhydroxylamine hydrochloride	96.4 (94.0)
<i>t</i> -Cinnamic acid		81.9 (70.0)
2-Nitrobenzoic acid		92.4 (79.0)

Purity determined by GC-FID.

*Acylsulfonamide in cartridges*

Same as described above with the exception that the amine is incubated overnight.

<b>Table 3 : Acylsulfonamide synthesis with SiliaPrep™ DCT</b>		
Acid	Amine	% Yield (% Purity)
Benzoic acid	Benzenesulfonamine	98.0 (90.0)
	Methanesulfonamine	71.4 (82.0)
Purity determined by GC-FID.		