

# SiliaBond<sup>®</sup>

## Reagents



Distributed by

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# SiliaBond Reagents

## Amide Coupling Reagents

The amide bond is the defining molecular structure of proteins and peptides. In addition, a report estimates that as many as 25% of all synthetic pharmaceutical drugs contain an amide group.<sup>1</sup> Therefore, there is an ongoing scientific endeavor to develop efficient amidation methodologies.<sup>2</sup> Usually, the amide bond formation relies on the use of an excess of toxic coupling reagents such as carbodiimides or supernucleophiles. These chemicals produce a large amount of by-products, which tends to complicate the isolation and purification of the desired amide product.

The use of a reagent linked to an insoluble material has become a widely used tool since the introduction of the solid-phase synthesis concept.<sup>3</sup> Solid-phase reagents are valuable for amide coupling with a carboxylic acid because of the decrease of unwanted side products. Other advantages to using solid-supported reagents include improved stability, toxic chemical immobilization, the ability to run multiple transformations in a single pot, and the flexibility to use both batch reactions and flow chemistry.

<sup>1</sup> *J. Comb. Chem.* **1999**, *1*, 55.

<sup>2</sup> *Tetrahedron* **2005**, *61*, 10827.

<sup>3</sup> *J. Am Chem Soc.* **1963**, *85*, 2149.

## SiliaBond Carbodiimide (R70530B)

Loading: 1.0 mmol/g	Endcapping: Yes	Category: Reagent	Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton
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### Description

#### SiliaBond Carbodiimide (Si-DCC)

1,3-Dicyclohexylcarbodiimide (DCC) has arguably become the most commonly used reagent in peptide synthesis and other amide bond-forming reactions of primary and secondary amines with carboxylic acids.<sup>1</sup> The major drawback associated with using DCC is the formation of the urea by-product (DCU) which remains in solution and requires additional purification steps to remove. However, by using covalently bonded DCC on silica, it is possible to avoid problematic purifications. Only a simple filtration step is needed to remove the unwanted DCU.

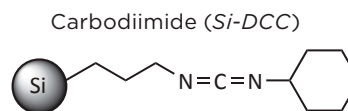
<sup>1</sup> *Chem. Rev.* **1981**, *81*, 589.

### Solvent compatibility

- Aprotic Solvent

### Prolonged storage

- Keep cool (< 8 °C) and dry, store under argon





## SiliaBond Ethyl-Dimethylamino Carbodiimide (EDC) (R70630B)

Loading: 0.8 mmol/g | Endcapping: Yes | Category: Reagent | Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton

### Description

#### SiliaBond Ethyl-Dimethylaminopropyl Carbodiimide (Si-EDC)

A recent literature review shows that 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) has become recognized as one of the best reagents for amide coupling reactions. Unfortunately, using the EDC basic tertiary amine results in the formation of urea, which has to be separated from the product by acidic aqueous extractions.<sup>1</sup> By attaching EDC to silica, it is possible to avoid this potentially problematic work-up without sacrificing the useful carbodiimide reactivity. In fact, SiliaBond EDC behaves in a similar fashion as EDC in solution, but the by-product remains on the solid support.

<sup>1</sup> *The Peptides: Analysis, Synthesis, Biology; Academic: New York, 1979, 1, 241.*

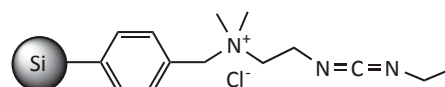
### Solvent compatibility

- Aprotic Solvent

### Prolonged storage

- Keep cool (< 8 °C) and dry, store under argon

Ethyl-Dimethylaminopropyl Carbodiimide (Si-EDC)



## SiliaBond Dichlorotriazine (R52230B)

Loading: 0.7 mmol/g | Endcapping: Yes | Category: Reagent | Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton

### Description

#### SiliaBond Dichlorotriazine (Si-DCT)

2,4,6-Trichloro[1,3,5]triazine (cyanuric chloride) has been used as a versatile reagent in alkyl chloride and acid chloride synthesis. This triazine has been especially useful as a coupling reagent for amide selective formation.<sup>1</sup> However, cyanuric chloride is toxic, corrosive, and a severe eye, skin and respiratory tract irritant. By anchoring cyanuric chloride on a silica matrix, it is now possible to use this valuable reagent without worrying about its toxicity profile. SiliaBond DCT reacts in a similar manner as cyanuric chloride. In addition, excess reagent and by-product elimination is reduced to a simple filtration, which is particularly useful for products where toxicity is a concern such as in the synthesis of active pharmaceutical ingredients (API).

<sup>1</sup> *J. Org. Chem. 1997, 62, 982.*

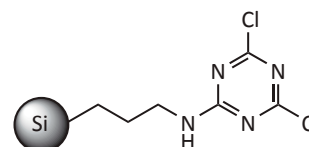
### Solvent compatibility

- Aprotic Solvent

### Prolonged storage

- Keep cool (< 8 °C) and dry, store under argon

Dichlorotriazine (Si-DCT)



## SiliaBond HOBt (R70730B)

Loading: 0.7 mmol/g | Endcapping: Yes | Category: Reagent | Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton

### Description

#### SiliaBond HOBt (*Si-HOBt*)

**NEW  
PRODUCT**

Hydroxybenzotriazole (*HOBt*) has been used for increasing yield and decreasing racemization during chiral amide synthesis. However, dry *HOBt* can undergo exothermic decomposition. Bonding *HOBt* to silica eliminates this risk of explosion. SiliaBond *HOBt* can be easily activated and should ideally be used with a base such as *N,N*-diisopropylethylamine in the same condition as in homogeneous solution. Moreover, this supported reagent can be reused a few times without adversely affecting its performance.

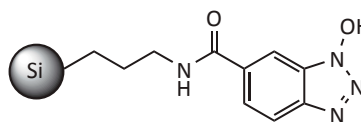
### Solvent compatibility

- Aprotic Solvent

### Prolonged storage

- Keep cool (< 8 °C) and dry, store under argon

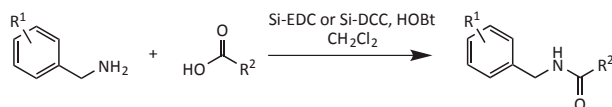
HOBt (*Si-HOBt*)





## Synthesis of Capsaicin Analogues

Capsaicin's potential clinical use as an analgesic and peripheral anti-inflammatory effects, as well as the discovery of an ultra-potent analogue (*resiniferatoxin*) has attracted significant interest in finding capsaicin synthesis routes.



### General Procedure

The acid (*0.5 mmol*) was placed in an oven-dried reaction vial with anhydrous  $\text{CH}_2\text{Cl}_2$  (*10 mL*) under  $\text{N}_2$ . The HOBT (*1.0 mmol*) and the SiliaBond Carbodiimide or SiliaBond EDC were added to the solution, which was then stirred briefly (*5 min*). The amine (*0.5 mmol*) was then added to the reaction tube, and the mixture was then stirred for 16 h at room temperature. Finally, the reaction was followed by GC-MS.

### Capsaicin Analogues Reaction Results

Entry	Product	Yield <sup>a</sup> (Purity <sup>b</sup> )	
		Si-DCC	Si-EDC
1		99% (> 98%)	81% (> 98%)
2		98% (> 98%)	88% (95%)
3		99% (> 98%)	99% (> 98%)
4		98% <sup>c</sup>	98% <sup>c</sup>

<sup>a</sup>Yield calculated in crude product, <sup>b</sup>Purity determined by GC-MS, <sup>c</sup>Yield determined by GC-MS

## Amine Protection Using Benzylcarbamate Group

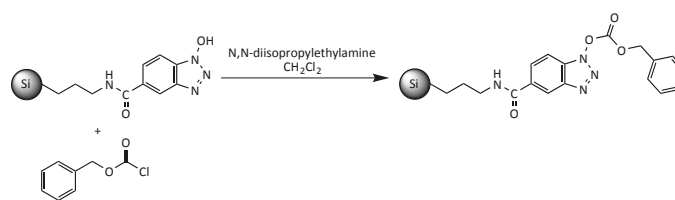
Benzylcarbamate groups are one of the most used amine protecting functions because of the easy deprotection by hydrogenolysis. SiliaBond HOBT, as a key reactive, facilitates the protection manipulation and can be reused a few times without loss of reactivity.

### General Procedure

SiliaBond HOBT (*1 g* or *1 eq.*) was introduced in a flask (*oven-dried*) containing anhydrous  $\text{CH}_2\text{Cl}_2$ . Benzylchloroformate (*4 eq.*) was added to the suspension, followed by *N,N*-diisopropylethylamine *4 eq.* The reaction mixture was stirred for 60 minutes at room temperature. Then, the suspension mixture was filtered, and washed with  $\text{CH}_2\text{Cl}_2$  (*2 x 10 mL*), and the SiliaBond HOBT was oven-dried.

The dried, activated SiliaBond HOBT was placed in a flask containing anhydrous  $\text{CH}_2\text{Cl}_2$  under  $\text{N}_2$ . To this suspension, *0.8 eq.* of amine was added, and the reaction mixture was stirred for 4 to 16 h at room temperature. The reaction suspension was filtered and washed with  $\text{CH}_2\text{Cl}_2$  (*2 x 10 mL*).

### Activation Reaction



### Activation and recycling Results

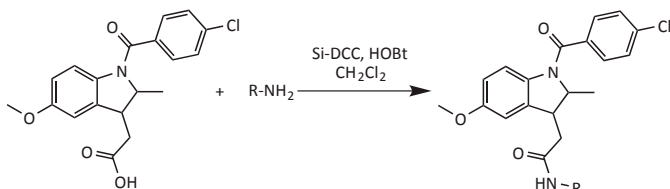
Entry	Yield <sup>a</sup>
Activation	96%
1 <sup>st</sup> Recycling	86%
2 <sup>nd</sup> Recycling	95%
3 <sup>rd</sup> Recycling	96%

<sup>a</sup>Conversion determined by GC-MS

## Synthesis of Amide Derivatives of Indomethacin

A report<sup>1</sup> has shown that indomethacin primary and secondary amide analogues are potent compounds for human COX-2 specific inhibition. SiliaBond Carbodiimide can be used as a key reagent in its synthesis.

<sup>1</sup> *J. Med. Chem.* **2000**, 2860.



### General Procedure

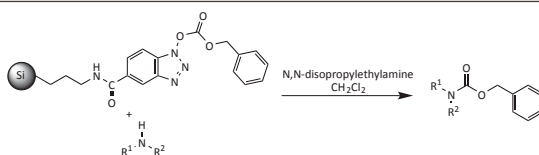
The indomethacin (*0.56 mmol*) was placed in an oven-dried reaction vial in anhydrous dichloromethane (*5 mL*) under  $N_2$ . HOBt (*0.95 mmol*) and the SiliaBond Carbodiimide (*1.12 mmol*) were added, and the mixture was stirred briefly (*5 minutes*). Then, the amine (*0.56 mmol*) was added to the vial, and the reaction was stirred at room temperature for 16 h. Then, the crude product was directly purified on a short plug of silica gel (*hexane/EtOAc 1/1*) to yield pure amide.

### Amide Derivatives of Indomethacin Results

Entry	Amine	Yield <sup>a</sup>
1		90%
2		82%
3		94%
4		78%

<sup>a</sup>Conversion determined by GC-MS

### Amine Protection Reaction



### Amine Protection Results

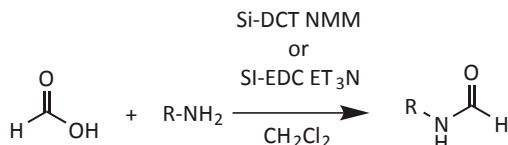
Entry	Product	Conversion <sup>a</sup>
1		98% (4 h)
2		94% (4 h) 96% (16 h) 86% (16 h) <sup>b</sup>
3		81% (16 h)
4		93% (4 h) 98% (16 h)
5		98% (4 h)
6		93% (16 h)

<sup>a</sup>Conversion determined by GC-MS, <sup>b</sup>Polymer HOBt



## Synthesis of Formylated Amino Acids

N-formylamino acid esters are useful derivatives for preparing selected N-formylamino acids, incorporating polyfunctional amino acids into peptides, and for other useful starting material preparation. Formylated amino acids have been prepared in high yields by using SiliaBond Dichlorotriazine (DCT) and SiliaBond Ethyl-Dimethylaminopropyl Carbodiimide (EDC).



### General Procedure

Formic acid (0.90 mmol) was placed in an oven-dried reaction vial in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) under  $\text{N}_2$ . To this solution was added triethylamine (0.90 mmol) and either the SiliaBond EDC (2.25 mmol) or N-methylmorpholine (0.90 mmol) and SiliaBond DCT (2.25 mmol). Then, the mixture was stirred briefly (5 minutes). The amine (0.45 mmol) was then added to the vial and the reaction was stirred at room temperature for 16 h. Conversion to the desired formamide was followed by GC-MS. Upon completion, the SiliaBond EDC or SiliaBond DCT was filtered and washed with 2 x 10 mL of  $\text{CH}_2\text{Cl}_2$ . Evaporation of the solvent yielded the desired product.

### Synthesis of Formylated Amino Acids Results

Entry	Product	Conversion <sup>a</sup>	
		Si-DCT	Si-EDC
1		99%	93%
2		99%	100%
3		99%	99%
4		98%	95%

<sup>a</sup>Conversion determined by GC-MS

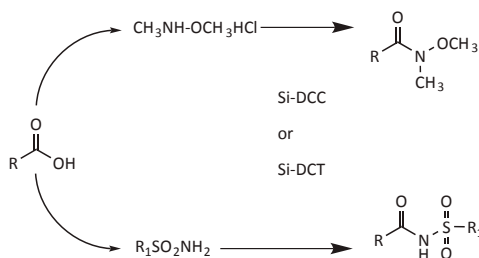
## Weinreb and Acylsulfonamide Synthesis

Weinreb synthesis is a reaction often used in medicinal chemistry to produce amides. These functional groups are present in natural products and can be reliably reacted to form new carbon-carbon bonds or converted to other functions. In normal conditions, Weinreb synthesis can tolerate a large variety of functional groups such as N-protected amines, sulfonates, alpha-beta saturation and silyl ethers.

### Weinreb Synthesis Results

Acid	Amine	Yield (Purity) <sup>a</sup>	
		Si-DCC	Si-DCT
Benzoic Acid	N,O-Dimethylhydroxyamine Hydrochloride	99% (96%)	96% (94%)
t-Cinnamic Acid		87% (95%)	82% (70%)
2-Nitrobenzoic Acid		> 99% (93%)	92% (79%)

<sup>a</sup>Yield and purity determined by GC-MS



### Acylsulfonamide Synthesis Results

Acid	Sulfonamide	Yield (Purity) <sup>a</sup>	
		Si-DCC	Si-DCT
Benzoic Acid	Benzenesulfonamide	96% (71%)	98% (90%)
	Methanesulfonamide	79% (53%)	71% (82%)

<sup>a</sup>Yield and Purity determined by GC-MS





## SiliaBond Cyanoborohydride for Reductive Aminations

Reductive amination involves the conversion of a carbonyl group, most of the time a ketone or an aldehyde, to an amine by an intermediate imine or iminium. The intermediate imine is reduced by sodium cyanoborohydride. This is known as direct reductive amination, and is carried out with reducing agents that are more reactive toward protonated imines than ketones and are stable under moderately acidic conditions.

### General Procedure

To 1 mmol of SiliaBond Cyanoborohydride 5 mL of solvent, 0.5 mmol of aldehydes or ketones and 0.6 mmol of amines were added. The reaction mixture was stirred at room temperature for 16 h. Each solution was then analysed by GC-MS.

### SiliaBond Cyanoborohydride (R66730B)

Loading: 1.0 mmol/g	Endcapping: Yes	Category: Reagent	Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton
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#### Description

#### SiliaBond Cyanoborohydride (Si-CBH)

SiliaBond Cyanoborohydride is the silica-bound equivalent of sodium cyanoborohydride. Bound cyanoborohydride is very useful in reductive amination and in the reduction of imines and aldehydes. Cyanide contamination of the product is a concern, however, when using the solution phase equivalent. This problem is minimized with the use of silica-bound materials since the toxic cyanide residue remains on the silica. To see if any cyanide ion was leaching from the silica, 1 g of SiliaBond Cyanoborohydride was washed in 10 mL of methanol for 24 h. Cyanide strips indicated less than 3 ppm in each test performed. In addition to providing superior conversions, acetic acid was not needed (*eliminating issues with acid labile groups*), the workup required only a filtration, and HCN and NaCN were not liberated during workup.

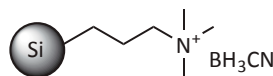
#### Solvent compatibility

- All solvents, aqueous and organic

#### Prolonged storage

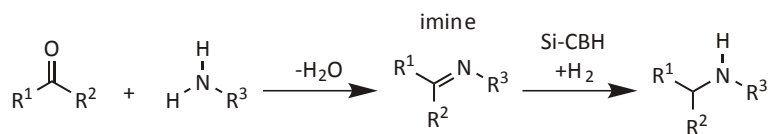
- Keep cool (< 8 °C) and dry, store under argon


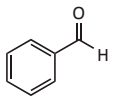
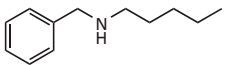
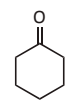
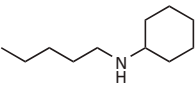

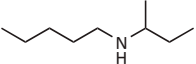
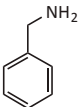
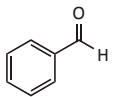
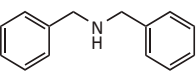

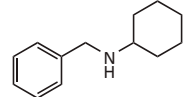

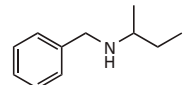

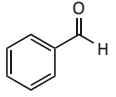
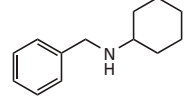

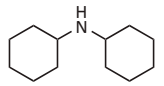

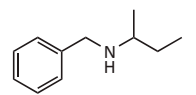
Cyanoborohydride (Si-CBH)



## SiliaBond Cyanoborohydride for Reductive Aminations

## Reduction of Primary Amines

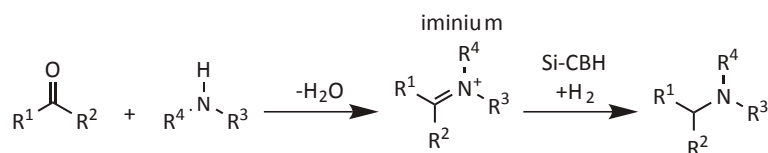


Reduction of Primary Amine Results								
1° Amine	Carbonyl	Conditions (RT 16 h) Product	Acetonitrile		Ethanol		Methylene Chloride	
			Conversion Product (%) <sup>a</sup>	Imine (%) <sup>b</sup>	Conversion Product (%) <sup>a</sup>	Imine (%) <sup>b</sup>	Conversion Product (%) <sup>a</sup>	Imine (%) <sup>b</sup>
			27	25	64	11	69	12
			97	0	95	5	92	8
			92	0	84	7	78	9
			61	20	71	23	73	24
			92	2	83	17	81	13
			88	3	90	7	91	6
			66	21	97	0	100	0
			91	5	93	5	93	6
			90	0	92	6	86	7

<sup>a</sup>Conversion determined by GC-MS, <sup>b</sup>Unreacted imine was determined by GC-MS



## Reduction of Secondary Amines



### Reduction of Secondary Amine Results

2° Amine	Carbonyl	Conditions (RT 16 h) Product	Acetonitrile		Ethanol		Methylene Chloride	
			Conversion Product (%) <sup>a</sup>	SM <sup>c</sup> (%) <sup>b</sup>	Conversion Product (%) <sup>a</sup>	SM <sup>c</sup> (%) <sup>b</sup>	Conversion Product (%) <sup>a</sup>	SM <sup>c</sup> (%) <sup>b</sup>
			90	2	71	0	91	0
			92	5	79	17	93	3
			79	8	79	21	93	2
			94	6	67	0	79	0
			77	23	77	20	87	3
			70	25	61	26	44	2
			97	3	80	0	83	1
			85	15	69	19	88	6
			81	9	70	21	55	2

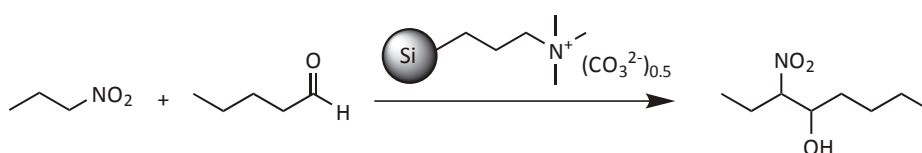
<sup>a</sup>Conversion determined by GC-MS, <sup>b</sup>Unreacted imine was determined by GC-MS, <sup>c</sup>Starting Material

## SiliaBond Carbonate for Henry Reactions

The Henry reaction is commonly used to form carbon-carbon bonds by addition of nitroalkanes over aldehydes. This reaction is a useful technique in organic chemistry due to the synthetic utility of its corresponding products, as they can be easily converted to other useful synthetic intermediates such as nitroalkenes by dehydrogenation, alpha-nitro ketones by oxidation and  $\beta$ -amino alcohols by reduction. Usually, the Henry reaction is carried out in presence of bases in homogeneous solution, giving low yield due to side reactions such as retroaldol and Cannizzaro reactions.

### General Procedure

1-nitropropane (1 eq.) was added to a solution containing THF (5 mL) and valeraldehyde (1 eq.). SiliaBond Carbonate (0.1 eq.) was added, and the mixture was stirred at room temperature for 6 h. The reaction mixture was then filtered and washed with THF and the crude product was evaporated. Finally, pure product was obtained after flash chromatography purification using a mix of hexane/ethylacetate (80/20).



### Henry Reaction Results

Entry	Solvent	Reaction Conditions	Conversion <sup>a</sup>
1	THF	0.1 eq. Si-CO <sub>3</sub> room temperature, 6 h	92% (83%) <sup>b</sup>
2	CH <sub>2</sub> Cl <sub>2</sub>		76%
3	Ethanol		90%
4	Propanol		95%
5	None		92%
6	THF	0.1 eq. Si-CO <sub>3</sub> $\mu$ wave 100 W, 100°C 10 min	89%

<sup>a</sup>Conversion determined by GC-MS, <sup>b</sup>Purity determined from the isolated product

## SiliaBond Carbonate (R66030B)

Loading: 0.7 mmol/g | Endcapping: Yes | Category: Reagent | Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton

### Description

#### SiliaBond Carbonate (Si-CO<sub>3</sub>)

Used as a heterogenous catalyst in the Henry reaction, SiliaBond Carbonate is replacing the use of expensive and toxic heterogeneous catalysts. SiliaBond Carbonate in catalytic amounts drive the reaction forward to high yield with or without solvent.

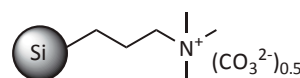
### Solvent compatibility

- Aprotic solvents

### Prolonged storage

- Keep dry

Carbonate (Si-CO<sub>3</sub>)





## SiliaBond DMAP for Baylis-Hillman and Acylation Reactions

### Baylis-Hillman Reaction

Coupling of activated alkenes, generally alpha, 1-beta-unsaturated, with aldehydes is named the Baylis-Hillman reaction. This reaction is well known for the formation of carbon-carbon bonds under soft conditions and its compatibility with several functional groups. Furthermore, an organic base can be used to catalyze this reaction with similar success to using transition metals.

### Acylation Reaction

It is well-known that DMAP used as a catalyst increases speed and yield of alcohol and phenol acylations over acetic and benzoic anhydrides.

### SiliaBond DMAP (R75530B)

Loading: 0.8 mmol/g	Endcapping: Yes	Category: Reagent	Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton
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#### Description

#### SiliaBond DMAP (Si-DMAP)

SiliaBond DMAP is the heterogenous catalyst equivalent of 4-dimethylaminopyridine, which is used as a nucleophilic catalyst in a wide variety of reactions such as acylations and Baylis-Hillman reactions. These reactions are well known in organic synthesis and are very useful in various applications. SiliaBond DMAP has an advantage over its free counterpart as it can be removed by a simple filtration.

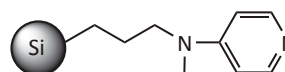
#### Solvent compatibility

- All organic solvents

#### Prolonged storage

- Keep cool (< 8 °C) and dry, store under argon

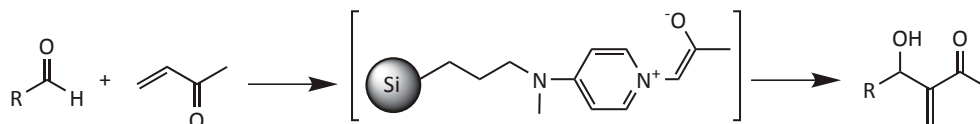
DMAP (Si-DMAP)

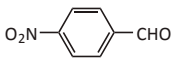

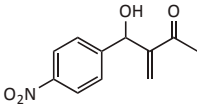
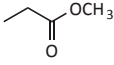
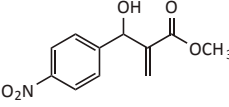
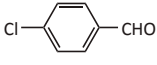

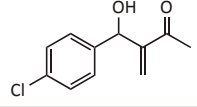


## SiliaBond DMAP for Baylis-Hillman Reaction

### General procedure

Aldehyde (1 mmol) was placed in a flask, and THF, SiliaBond DMAP (0.10 mmol), water and enone (2 mmol) were added. The mixture was stirred at room temperature for 6 to 96 h.



Baylis-Hillman Reaction Results					
Aldehyde	Enone	Conditions	Product	Yield <sup>a</sup>	
				Si-DMAP	Polymer
		THF/H <sub>2</sub> O (3/1) room temperature, 6 h 10% Si-DMAP		81%	37%
		DMF/H <sub>2</sub> O (3/1) room temperature, 90 min 10% Si-DMAP		75%	14%
		CH <sub>2</sub> Cl <sub>2</sub> room temperature, 24 h 10% Si-DMAP		74%	37%
		No solvent room temperature, 96 h 24% Si-DMAP		71%	58%
		THF/H <sub>2</sub> O (3/1) room temperature, 96 h 19% Si-DMAP		63%	15%

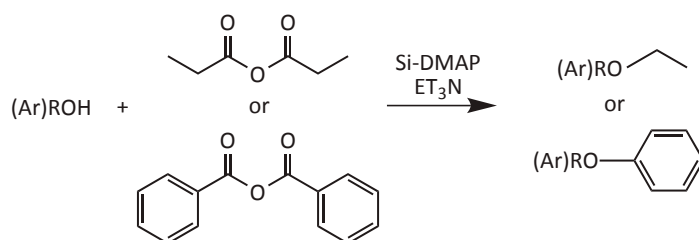
<sup>a</sup>Yield determined from the isolated product



## SiliaBond DMAP for Acylation Reactions (*Acylation of 1-phenyl-1-propanol*)

### General procedure

A mixture of 2 mmol of alcohol, acetic anhydride (1.3 eq.), triethylamine (1.5 eq.), and 5% SiliaBond DMAP in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature for 90 min. The reaction was quenched by the addition of 0.5 mL of methanol, diluted with Et<sub>2</sub>O, and washed twice with saturated aqueous NaHCO<sub>3</sub> and once with brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the solution was filtered and evaporated to give a colorless oil in quantitative yield.



### Acylation Results

Alcohol	Catalyst	Anhydride	Reaction Conditions	Conversion <sup>a</sup>
	None	1.4 eq. Ac <sub>2</sub> O	18 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	25%
	5% <i>Si</i> -DMAP	1.2 eq. Ac <sub>2</sub> O	2 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	> 98%
	None	1.3 eq. Bz <sub>2</sub> O	24 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	11%
	5% <i>Si</i> -DMAP	1.3 eq. Bz <sub>2</sub> O	24 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	91%
	None	1.3 eq. Ac <sub>2</sub> O	18 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	50%
	5% <i>Si</i> -DMAP	1.3 eq. Ac <sub>2</sub> O	40 min, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	> 98%
	None	1.3 eq. Bz <sub>2</sub> O	18 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	29%
	5% <i>Si</i> -DMAP	1.3 eq. Bz <sub>2</sub> O	2 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	91%
	None	1.3 eq. Ac <sub>2</sub> O	19 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	18%
	5% <i>Si</i> -DMAP	1.3 eq. Ac <sub>2</sub> O	40 min, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	> 98%
	None	1.3 eq. Bz <sub>2</sub> O	24 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	6%
	5% <i>Si</i> -DMAP	1.3 eq. Bz <sub>2</sub> O	24 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	88%
	None	1.3 eq. Ac <sub>2</sub> O	3 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	89%
	5% <i>Si</i> -DMAP	1.3 eq. Ac <sub>2</sub> O	25 min, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	> 99%
	None	1.3 eq. Bz <sub>2</sub> O	4 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	63%
	5% <i>Si</i> -DMAP	1.3 eq. Bz <sub>2</sub> O	4 h, CH <sub>2</sub> Cl <sub>2</sub> , room temperature	94%
	None	1.3 eq. Ac <sub>2</sub> O	24 h, PhH, 80 °C	49% <sup>b</sup>
	5% <i>Si</i> -DMAP	1.3 eq. Ac <sub>2</sub> O	24 h, PhH, 80 °C	80% <sup>b</sup>

<sup>a</sup>Conversion determined from the isolated product, <sup>b</sup>Determined by GC-FID

## SiliaBond Tonic Acid in Fischer-Speier Esterifications

The Fischer-Speier reaction is a classic organic process where a carboxylic acid is reacted with an alcohol in the presence of an acidic catalyst to form an ester. All carboxylic acids and only primary and secondary aliphatic alcohols can be used in this reaction. The most commonly used catalysts for this reaction are highly toxic such as  $\text{H}_2\text{SO}_4$ , tosic acid and scandium triflate. Also, a large excess of one of the reagents is used to push the equilibrium towards the product.

### SiliaBond Tonic Acid (R60530B)

Loading: 0.8 mmol/g	Endcapping: Yes	Category: Reagent	Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton
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#### Description

#### SiliaBond Tonic Acid (Si-SCX)

SiliaBond Tonic Acid is in a class of strong acids used in different fields of synthetic organic chemistry. The aromatic ring makes it slightly more acidic than other supported sulfonic acids. It will not dissolve in methanol or any other solvents.

SiliaBond Tonic Acid used as an acid catalyst for Fischer-Speier esterification provides excellent conversion.

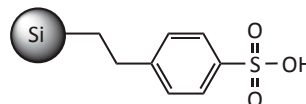
#### Solvent compatibility

- All solvents, aqueous and organic

#### Prolonged storage

- Keep dry

Tonic Acid (Si-SCX)







## SiliaBond Tonic Acid for Fischer-Speier Esterifications

### General procedure

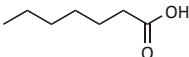
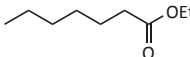
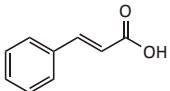
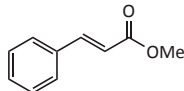
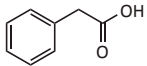
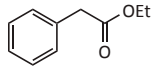

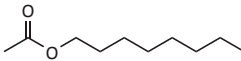

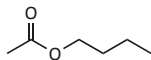

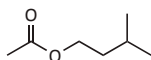
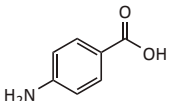
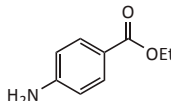
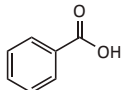
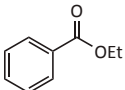
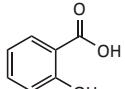
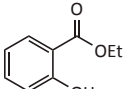
#### Method A

1.5 mmol of carboxylic acid was added to a mixture of alcohol (10 mL) and SiliaBond Tonic Acid (0.1 eq.). The reaction mixture was maintained at reflux under magnetic agitation for 16 h.

#### Method B

In a 250 mL round-bottom flask with a magnetic stirrer and a Dean-Stark apparatus, 16.3 mmol of a carboxylic acid was added to alcohol (4 eq.) and SiliaBond Tonic Acid (0.1 eq.). The mixture was then heated to reflux for 20 to 24 h under magnetic agitation.

Fischer-Speier Esterification Results

Alcohol	Carboxylic Acid	Method	Ester	Conversion <sup>a</sup>
Ethanol		A		100%
Methanol		A		98%
Ethanol		A		100%
1-Octanol		A		100%
1-Butanol		A		100% (99%) <sup>b</sup>
3-Methylbutanol		A		100%
Ethanol		A (72 h)		40% <sup>c</sup>
Ethanol		B		94% <sup>c</sup>
Methanol		B		89% <sup>c</sup>

<sup>a</sup>Conversion determined by GC-MS, <sup>b</sup>Si-SCX reused 3 times, <sup>c</sup>Conversion determined from the isolated product

## SiliaBond TBD for Williamson Etherifications

The Williamson etherification is a standard reaction to synthesize asymmetric ethers from alcoholates, prepared from primary and secondary alcohols or phenols with base, in the presence of primary alkyl halides. Because of the high reactivity of alcoholates, they need to be produced during the reaction by strong bases.

### SiliaBond TBD (R68530B)

Loading: 0.9 mmol/g	Endcapping: Yes	Category: Reagent	Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton
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#### Description

##### SiliaBond TBD (Si-TBD)

SiliaBond TBD is a silica-bound bicyclic guanidine moiety that is sufficiently basic to deprotonate moderately acidic hydrogens. It is most commonly used in Williamson ether synthesis.

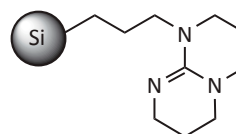
#### Solvent compatibility

- All solvents, aqueous and organic

#### Prolonged storage

- Keep cool (< 8°C) and dry, store under argon

TBD (Si-TBD)

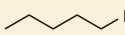
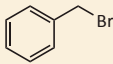


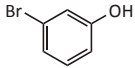
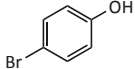
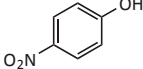
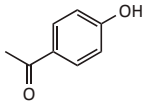
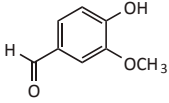
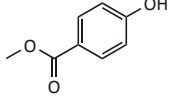
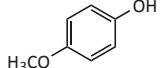




## SiliaBond TBD for Williamson Etherifications

### General procedure

0.15 mmol of alcohol was added to 4 mL of acetonitrile and SiliaBond TBD (0.3 eq.). The solution was stirred for 1 h at room temperature. Next, 0.12 mmol of the alkyl halide was transferred to the reaction mixture, which was again stirred for 16 h at 60°C. Finally, the mixture was filtered and washed with 2 mL of acetonitrile. Conversion was measured by GC-MS.

Williamson Etherification Results		
Alcohol	Alkyl Halide	
		
	83%	89%
	89%	88%
	81%	88%
	80%	80%
	59%	86%
	79%	88%
	87%	94%
	78%	86%
	76%	75%

## SiliaBond Aluminum Chloride Used as a Catalyst for Friedel-Crafts Alkylations and Acylations

For decades, sulfonated linear alkylbenzenes (LABs) have been among the most prolific detergents. LAB synthesis is carried out by Friedel-Crafts alkylation of benzene by linear olefins using hydrogen fluoride or aluminum chloride as catalyst. The use of these catalysts presents severe problems, however. For example, aluminum chloride is difficult to separate after reaction and produces a large amount of waste effluent.

### SiliaBond Aluminium Chloride (R74530B)

Loading: 1.6 mmol/g	Endcapping: No	Category: Reagent	Format: 5g, 10g, 25g, 50g, 100g, 250g, 500g, 1kg, 10kg, 25kg, ..., Multi-Ton
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#### Description

#### SiliaBond Aluminum Chloride (Si- $AlCl_x$ )

SiliaBond Aluminum Chloride is the silica-supported version of the most widely used Lewis acid, aluminum chloride.<sup>1</sup> It is an effective catalyst for Friedel-Crafts alkylations<sup>2-4</sup> and acylations. It also catalyzes the formation of ethers. The silica supported product has several advantages over the free catalyst.<sup>5,6</sup>

- It is a milder Lewis acid.  $AlCl_3$  is so reactive that it often lacks selectivity and causes the formation of unwanted by-products.
- The steric bulk of the silica reduces over alkylation and increases shelf life.

*Execution of the reaction is easier. The reagent is removed by a simple filtration, avoiding the destructive water quench which produces large amounts of hazardous waste.*

SiliaBond Aluminum Chloride's activity can be determined by its color. The material should only be used when it's yellow or violet. The product turns white in presence of moisture.

<sup>1</sup> Acc. Chem. Res., 2002, 35, 791

<sup>2</sup> Org. Process Res. Dev., 1998, 2, 221

<sup>3</sup> J. Catal., 2000, 195, 237

<sup>4</sup> J. Catal., 2000, 195, 412

<sup>5</sup> Chem. Rev., 2003, 103, 4307

<sup>6</sup> Tetrahedron, 2003, 59, 1781

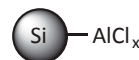
#### Solvent compatibility

- All anhydrous organic solvents

#### Prolonged storage

- Keep cool (< 8°C) and dry, store under argon

Aluminum Chloride (Si- $AlCl_x$ )



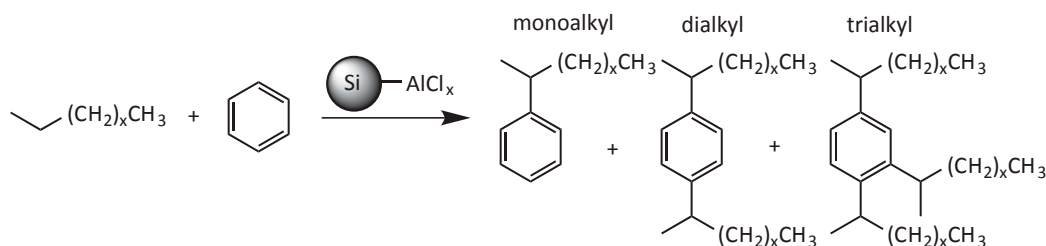


## SiliaBond Aluminum Chloride as a Catalyst for Friedel-Crafts Alkylations

### General procedure

SiliaBond Aluminum Chloride (0.03 eq.) is stirred into anhydrous benzene (Typical reaction solvent volume: 5 mL/g of SiliaBond Aluminium Chloride). Add the alkene (1.0 eq.) slowly (a small exothermic reaction should be observed).

After the addition is completed, remove the catalyst by filtration.



### Friedel-Crafts Alkylation Results

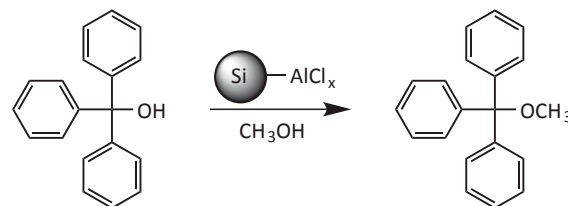
Alkene	Catalyst	Alkene Conversion <sup>a</sup>	Selectivity Towards Alkylbenzene		
			% Mono	% Di	% Tri
1-Hexene	$\text{AlCl}_3$	100%	58.6	31.1	10.3
1-Hexene	$\text{Si}-\text{AlCl}_x$	100%	71.0	28.0	1.0
1-Decene	$\text{AlCl}_3$	100%	68.5	22.5	9.0
1-Decene	$\text{Si}-\text{AlCl}_x$	100%	80.0	20.0	0

<sup>a</sup>Conversion determined by GC-MS

## SiliaBond Aluminum Chloride as Catalyst for Friedel-Crafts Acylation

### Friedel-Crafts Acylation Results

Alcohol	Catalyst	Conversion <sup>a</sup>
Triphenylmethanol	$\text{Si}-\text{AlCl}_x$	95%
	Polymer- $\text{AlCl}_3$	81%
Tert-Butyl Alcohol	$\text{Si}-\text{AlCl}_x$	60%
	Polymer- $\text{AlCl}_3$	0%
Benzyl Alcohol	$\text{Si}-\text{AlCl}_x$	40%
	Polymer- $\text{AlCl}_3$	0%



<sup>a</sup>Conversion determined by <sup>1</sup>H NMR

## SiliaBond Reagents and Scavengers for Typical Coupling Reactions

Coupling Reactions	
Reaction	Reagent / Scavenger
<b>Amide Coupling</b>	
with acid chlorides and amines	SiliaBond Carbodiimide
with acids and amines	SiliaBond Dichlorotriazine SiliaBond Amine (scavenger) - removes excess acid chloride SiliaBond Isocyanate/SiliaBond Tosic Acid - remove excess of amine
using HOBt or pentafluorophenol	SiliaBond Carbonate - removes excess of HOBt
<b>Buchwald Amination</b>	SiliaMetS Metal Scavengers - remove palladium SiliaBond Tosic Acid
<b>Heck Coupling</b>	SiliaCat DPP-Pd, SiliaCat S-Pd and SiliaCat Pd <sup>0</sup> (catalyst) SiliaMetS Metal Scavengers - remove palladium
<b>Sonogashira Coupling</b>	SiliaCat DPP-Pd, SiliaCat S-Pd and SiliaCat Pd <sup>0</sup> (catalyst) SiliaMetS Metal Scavengers - remove palladium, copper
<b>Stille Coupling</b>	SiliaCat DPP-Pd, SiliaCat S-Pd and SiliaCat Pd <sup>0</sup> (catalyst) SiliaMetS Metal Scavengers - remove palladium, tin
<b>Suzuki Coupling</b>	SiliaCat DPP-Pd, SiliaCat S-Pd and SiliaCat Pd <sup>0</sup> (catalyst) SiliaBond Carbonate - removes excess of boronic acid SiliaMetS Metal Scavengers - remove palladium
<b>Kumada Coupling</b>	SiliaCat DPP-Pd, SiliaCat S-Pd and SiliaCat Pd <sup>0</sup> (catalyst) SiliaMetS Metal Scavengers - remove metal residue
<b>Negishi Coupling</b>	SiliaCat DPP-Pd, SiliaCat S-Pd and SiliaCat Pd <sup>0</sup> (catalyst) SiliaMetS Metal Scavengers - remove metal residue



## SiliaBond Reagents and Scavengers for Common Organic Reactions

Common Organic Reactions	
Reaction	Reagent/Scavenger
Acylation/Esterification	SiliaBond DMAP SiliaBond TBD
Deprotection of Aromatic Ether	SiliaBond Tosic Acid
Ether formation	SiliaBond Aluminium Chloride ( <i>catalyst</i> ) SiliaBond Tosic Acid SiliaMetS Metal Scavengers - remove metal catalyst
Fmoc, Bsmoc Deprotection of Amino Acid	SiliaBond Piperazine ( <i>reagent / scavenger</i> ) - Fmoc deprotection
Friedel-Crafts Alkylation	SiliaBond Aluminium Chloride
Fries Rearrangement	SiliaBond Tosic Acid
Knoevenagel Condensation	SiliaBond Amine SiliaBond Dimethylamine SiliaBond TBD SiliaBond Piperidine SiliaBond Piperazine
Michael Addition	SiliaBond Dimethylamine SiliaBond TBD SiliaMetS Metal Scavengers - remove metal catalyst
<b>Oxidation</b>	
alcohols to acids	SiliaBond Potassium Permanganate
alcohols to ketones or aldehydes	SiliaCat TEMPO SiliaBond Pyridinium Chlorochromate (PCC) SiliaBond Pyridinium Dichromate (PDC)
alkanes	SiliaBond Dimethylamine
<b>Reduction</b>	
with borohydride reducing agents	SiliaBond Tosic Acid - removes excess and spent borohydride
Reductive Amination	SiliaBond Cyanoborohydride SiliaBond Tosic Acid - removes excess of amine
Sulfonamide Synthesis	SiliaBond Dichlorotriazine SiliaBond EDC SiliaBond Amine - removes excess of sulfonyl chloride
Tosylate Formation	SiliaBond Tosyl Chloride
Urea Synthesis	SiliaBond Amine - removes excess of isocyanate
Williamson Ether Synthesis	SiliaBond TBD
Grubbs Metathesis	SiliaMetS Metal Scavengers - remove ruthenium
Sharpless Dihydroxylation	SiliaMetS Metal Scavengers - remove osmium
Catalytic Hydrogenation	SiliaCat DPP-Pd, SiliaCat S-Pd and SiliaCat Pd <sup>0</sup> ( <i>catalyst</i> )/ SiliaMetS Metal Scavengers - remove metal catalysts
Cyanation	SiliaCat DPP-Pd, SiliaCat S-Pd and SiliaCat Pd <sup>0</sup> ( <i>catalyst</i> )/ SiliaMetS Metal Scavengers - remove metal catalysts
Hydrogenation	SiliaCat Pt <sup>0</sup> ( <i>catalyst</i> )
Debenzylation of Benzyl protected Groups	SiliaCat Pd <sup>0</sup> ( <i>catalyst</i> )
Hydrosilylation	SiliaCat Pt <sup>0</sup> ( <i>catalyst</i> )