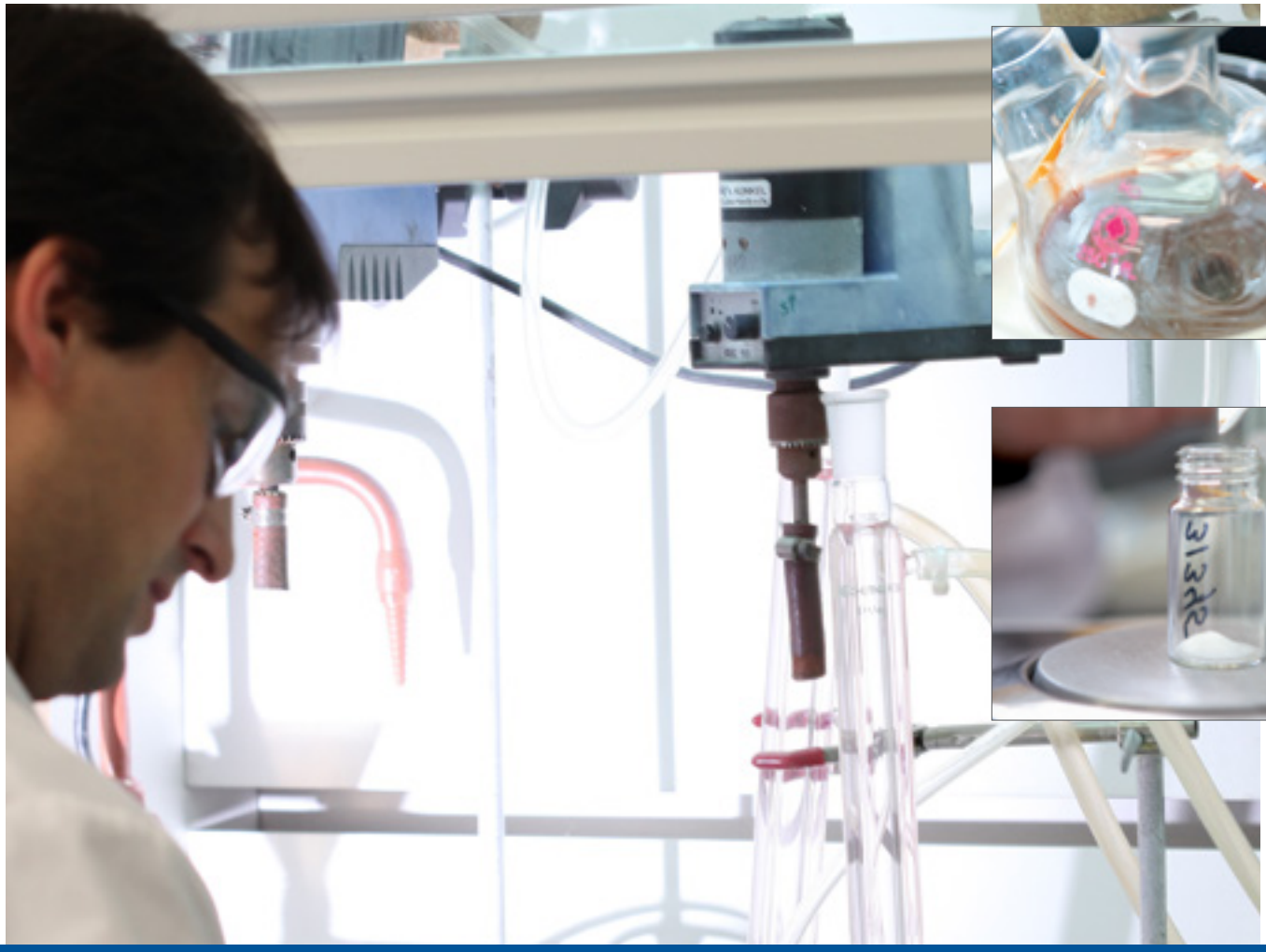
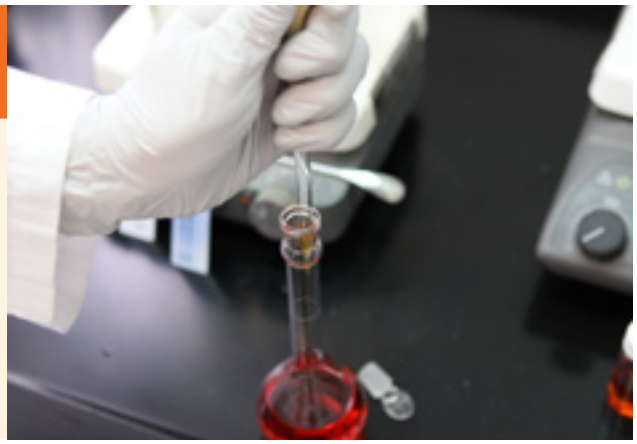


Organic Synthesis

SiliaBond® Reagents & Oxidants

Silica-Based Reagents & Oxidants in Organic Chemistry

Discover How Heterogeneous Reagents & Oxidants Can Optimize your Synthesis



Our heterogeneous supports for chemical synthesis are offered in two different forms:

- **Silia*Bond*** Reagents (*for both catalytic & stoechiometric reactions*)
- **Silia*Bond*** Oxidants

Available Formats: 5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 10 kg, 25 kg, etc.

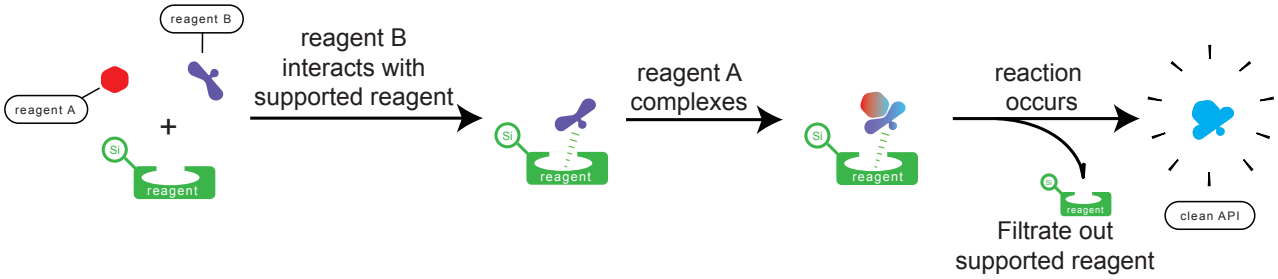
What are Silia*Bond* Heterogeneous Reagents & Oxidants?

Increasingly, the use of heterogeneous reagents in organic synthesis and chemical production is growing in importance. This technology is completely in line with the industries seeking improved sustainability and reduced ecological footprint.

This strong trend is directly derived from the inherent benefits offered by silica-based heterogeneous reagents & oxidants:

- **Extremely easy product / API isolation and purification** (*simple & quick filtration of the heterogeneous support*)
- **Eliminates or strongly reduces the need for laborious purifications**
- **No leaching of silica or catalyst and no cross contamination**
- **Highly suitable for either batch or continuous flow applications**
- Convenient for high throughput medicinal & discovery chemistry
- Improved reactivity & selectivity over homogeneous reagents / catalyst
- Compares very favourably to polymer-based reagents: no swelling, thermally stable, more easily scalabe, faster kinetics, compatible with all solvents and mechanically stable.

Here is the reaction mechanism:



Here are a selection of reactions that can be done using our reagents and oxidants:

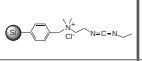
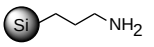
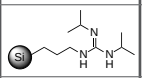
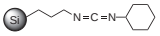
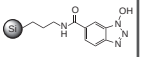
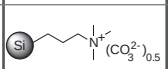
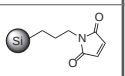
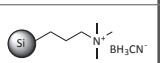
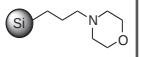
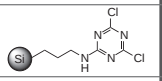
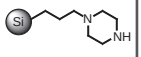
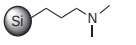
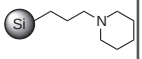
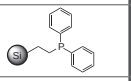
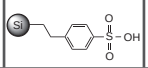
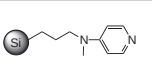
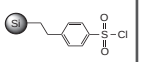
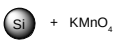
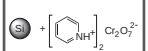
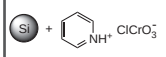
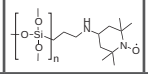
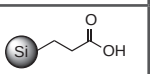
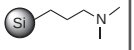
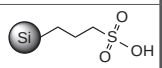
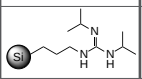
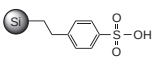
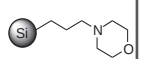
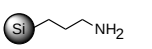
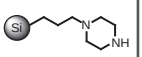
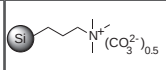
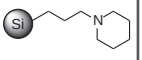
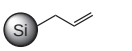
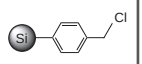
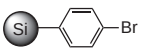
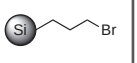
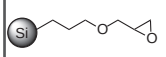
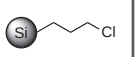
- Acylation / Esterification
- Alkylation / Etherification
- Amide Coupling
- Catalytic Hydrogenation
- Various Cross-Couplings
- Cyanation
- Deprotection of Ethers
- Ether Formation
- Fmoc, Bsmoc Deprotections
- Friedel-Crafts Alkylation
- Fries Rearrangement
- Grubbs Metathesis
- Michael Addition
- Tosylate Formation
- Urea Synthesis
- ***And so many more...***

Complete Overview of all Functionalized Silia*Bond* Reagents

Here is a global recapitulation of all SiliCycle's functionnalized silicas that can be used as reagents in organic synthesis.

- Silia*Bond* Catalysts & Reagents
- Silia*Bond* Oxidants
- Silia*Bond* Acids & Bases
- Silia*Bond* Linkers

Global Recapitulation of Silia*Bond* Reagents

	Name & Product Number	Structure	Loading (mmol/g) / Density (g/ml)	Name & Product Number	Structure	Loading (mmol/g) / Density (g/ml)
Catalysts & Reagents	Silia*Bond* $AlCl_3$ (*R74530B*)		≥ 1.60 0.781	Silia*Bond* EDC (*R70630B*)		≥ 0.32 0.770
	Silia*Bond* Amine (*R52030B*)		≥ 1.20 0.700	Silia*Bond* Guanidine (*R68230B*)		≥ 0.80 0.732
	Silia*Bond* Carbodiimide (*R70530B*)		≥ 0.91 0.751	Silia*Bond* HOBt (*R70730B*)		≥ 0.56 0.766
	Silia*Bond* Carbonate (*R66030B*)		≥ 0.46 0.608	Silia*Bond* Maleimide (*R71030B*)		≥ 0.64 0.644
	Silia*Bond* Cyanoborohydride (*R66730B*)		≥ 0.87 0.705	Silia*Bond* Morpholine (*R68030B*)		≥ 0.99 0.666
	Silia*Bond* Dichlorotriazine (*R52230B*)		≥ 0.60 0.781	Silia*Bond* Piperazine (*R60030B*)		≥ 0.83 0.671
	Silia*Bond* Dimethylamine (*R45030B*)		≥ 1.14 0.705	Silia*Bond* Piperidine (*R71530B*)		≥ 1.03 0.660
	Silia*Bond* Diphenylphosphine (*R39030B*)		≥ 0.75 0.588	Silia*Bond* Tosic Acid (*R60530B*)		≥ 0.54 0.698
	Silia*Bond* DMAP (*R75630B*)		≥ 0.53 0.674	Silia*Bond* Tosyl Chloride (*R44030B*)		≥ 0.63 0.761
Oxidants	Silia*Bond* $KMnO_4$ (*R23030B*)		10 % w/w 0.593	Silia*Bond* PDC (*R24530B*)		20 % w/w 0.651
	Silia*Bond* PCC (*R24030B*)		20 % w/w 0.693	Silia*Cat* TEMPO (*R723-100*)		≥ 0.70 0.550 - 0650
Acids & Bases	Silia*Bond* Carboxylic Acid (*R70030B*)		≥ 0.92 0.687	Silia*Bond* Dimethylamine (*R45030B*)		≥ 1.14 0.705
	Silia*Bond* Propylsulfonic Acid (*R51230B*)		≥ 0.63 0.728	Silia*Bond* Guanidine (*R68230B*)		≥ 0.80 0.732
	Silia*Bond* Tosic Acid (*R60530B*)		≥ 0.54 0.698	Silia*Bond* Morpholine (*R68030B*)		≥ 0.99 0.666
	Silia*Bond* Amine (*R52030B*)		≥ 1.20 0.700	Silia*Bond* Piperazine (*R60030B*)		≥ 0.83 0.671
	Silia*Bond* Carbonate (*R66030B*)		≥ 0.46 0.608	Silia*Bond* Piperidine (*R71530B*)		≥ 1.03 0.660
Linkers	Silia*Bond* Allyl (*R53530B*)		≥ 1.08 0.613	Silia*Bond* Phenylmethylchloride (*R56530B*)		≥ 1.14 0.637
	Silia*Bond* Bromophenyl (*R55030B*)		≥ 0.99 0.742	Silia*Bond* Propyl Bromide (*R55530B*)		≥ 1.39 0.748
	Silia*Bond* Glycidoxy (*R36030B*)		≥ 0.82 0.662	Silia*Bond* Propyl Chloride (*R59030B*)		≥ 1.39 0.751

Silia*Bond* Reagents & Oxidants Typical Reactions Selection Table

Here is a quick view of typical reaction examples in which SiliCycle functionalized silicas can be used as a quick, trendy and easy synthetic strategy.

Pure product can either be obtained by:

- using leach-free supported reagents, catalysts or oxidants
- purifying a reaction mixture, contaminated by excess homogeneous reagent or by a metal after using an homogeneous metal-based catalyst

Silia*Bond* Reagents & Oxidants Typical Reactions Selection Table

Typical Reactions in Organic Synthesis			Best Silia*Bond* Reagent or Oxidant for Synthesis OR Best Silia*Cat* Catalyst for Catalysis	
Acylation / Esterification			Silia*Bond* DMAP Silia*Bond* $AlCl_3$	Silia*Bond* Tosic Acid
Alkylation / Etherification			Silia*Bond* Guanidine	Silia*Bond* $AlCl_3$
Amide Coupling	With acids, acid chlorides and amines		Silia*Bond* Carbodiimide Silia*Bond* Dichlorotriazine	Silia*Bond* EDC
	Using HOBt		-	
Catalytic Hydrogenation			Silia*Cat* Pd^0	Silia*Cat* Pt^0
Coupling Reactions Buchwald Amination, Heck Coupling, Kumada Coupling, Negishi Coupling, Sonogashira Coupling, Stille Coupling Suzuki Coupling and more...			Silia*Cat* DPP-Pd Silia*Cat* Pd^0 Please see Silia*Cat* section p. 27 for detailed protocoles and information	
Deprotection of Aromatic Ether			Silia*Bond* Tosic Acid	
Ether Formation			Silia*Bond* $AlCl_3$	Silia*Bond* Tosic Acid
Fmoc, Bsmoc Deprotection of Amino Acid			Silia*Bond* Piperazine	
Friedel-Crafts Alkylation			Silia*Bond* $AlCl_3$	
Fries-Speier Esterification			Silia*Bond* Tosic Acid	
Grubbs Metathesis			-	
Knoevenagel Condensation			Silia*Bond* Amine Silia*Bond* Dimethylamine	Silia*Bond* Piperidine Silia*Bond* Piperazine
Michael Addition			Silia*Bond* Dimethylamine	Silia*Bond* Guanidine
Nitro-Aldol (*or Henry*) Reaction			Silia*Bond* Carbonate	
Oxidation	Alcohols to acids		Silia*Bond* $KMnO_4$	
	Alcohols to ketones / aldehydes		Silia*Cat* TEMPO	Silia*Bond* PCC & PDC
Reduction (*Reductive Amination, Alkylation, etc.*)			Silia*Bond* Cyanoborohydride	
Sharpless Dihydroxylation			-	
Sulfonamide Synthesis			Silia*Bond* Dichlorotriazine Silia*Bond* EDC	
Tosylate Formation			Silia*Bond* Tosyl Chloride	
Urea Synthesis			Silia*Bond* DMAP	
Williamson Ether Synthesis			Silia*Bond* Guanidine	

Silia*Bond* Reagents & Oxidants Typical Reactions Selection Table			
Best Silia*Bond* Organic Scavenger to Remove Excess Reagent OR Best Silia*MetS* Metal Scavenger to Remove Excess Metal from Catalyst	**Typical Reactions**		
Various Silia*Mets* Metal Scavenger to remove metallic residues from homogeneous catalyst	**Acylation / Esterification**		
Various Silia*Mets* Metal Scavenger to remove metallic residues from homogeneous catalyst Silia*Bond* Carbonate to remove excess homogeneous HOBt	**Alkylation / Etherification**		
Silia*Bond* Amine to remove excess acid chloride Silia*Bond* Isocyanante or Tosic Acid to remove excess amine	With acids, acid chlorides and amines	**Amide Coupling**	
Silia*Bond* Carbonate to remove excess homogeneous HOBt	Using HOBt		
Silia*MetS* Thiol, Thiourea or DMT to remove Pd Silia*MetS* DMT, Diamine or Triamine to remove Pt Silia*MetS* DMT, DOTA, Imidazole or TAAcONa to remove Ni	**Catalytic Hydrogenation**		
Silia*Bond* Isocyanante or Tosic Acid to remove excess amine Silia*MetS* Thiol, Thiourea or DMT to remove Pd Silia*MetS* DMT, DOTA, Imidazole or TAAcONa to remove Ni Silia*MetS* DOTA, Imidazole or TAAcONa to remove Cu Please see Silia*MetS* section p. 161 for detailed protocoles and information	**Coupling Reactions** Buchwald Amination, Heck Coupling, Kumada Coupling, Negishi Coupling, Sonogashira Coupling, Stille Coupling, Suzuki Coupling and more...		
-	**Deprotection of Aromatic Ether**		
-	**Ether Formation**		
Silia*Bond* Amine, DMAP, Piperazine, Silia*MetS* Diamine or Triamine to remove excess FMOC-Cl or Bsmoc-Cl	**Fmoc, Bsmoc Deprotection of Amino Acid**		
-	**Friedel-Crafts Alkylation**		
-	**Fries Rearrangement**		
Silia*MetS* DMT or Cysteine to remove Ru	**Grubbs Metathesis**		
-	**Knoevenagel Condensation**		
Silia*MetS* TAAcONa to remove Li Silia*MetS* Thiol, Thiourea or DMT to remove Pd	**Michael Addition**		
Silia*MetS* DOTA, Imidazole or TAAcONa to remove Cu	**Nitro-Aldol (*or Henry*) Reaction**		
-	Alcohols to acids	**Oxidation**	
-	Alcohols to ketones / aldehydes		
Silia*Bond* Tosic Acid to remove excess borohydride or excess amine	**Reduction (*Reductive Amination, Alkylation, etc.*)**		
Silia*MetS* Thiol, DMT, Cysteine, Imidazole, TAAcOH or TAAcONa to remove Os	**Sharpless Dihydroxylation**		
Silia*Bond* Amine to remove excess sulfonyl chloride	**Sulfonamide Synthesis**		
-	**Tosylate Formation**		
Silia*Bond* Amine to remove excess isocyanate	**Urea Synthesis**		
-	**Williamson Ether Synthesis**		

Typical Reactions in Organic Synthesis

Silia*Bond* Acids & Bases Typical Reactions Selection Table
Silia*Bond* Linkers Typical Reactions Selection Table

Here is a quick view of typical reaction examples in which SiliCycle functionalized silicas can be used as a quick, trendy and easy synthetic strategy.

Silia*Bond* Reagents & Oxidants Typical Reactions Selection Table

	Classification	Best Silia*Bond* Acids & Bases
Acids & Bases	**Acids**	Silia*Bond* Carboxylic Acid
		Silia*Bond* Propylsulfonic Acid
		Silia*Bond* Tosic Acid
	Bases	Silia*Bond* Amine
		Silia*Bond* Carbonate
		Silia*Bond* Dimethylamine
		Silia*Bond* Guanidine
		Silia*Bond* Morpholine
		Silia*Bond* Piperazine
		Silia*Bond* Piperidine
Linkers	**Synthesis of homemade functionalized silicas according to your very own application**	SiliaBond Allyl
		SiliaBond Bromophenyl
		SiliaBond Glycidoxy
		SiliaBond Phenylmethylchloride
		SiliaBond Propyl Bromide

SiliaBond Reagents & Oxidants Typical Reactions Selection Table

Typical Reactions & Applications Examples		
Acids & Bases	• Nucleophilic acyl substitutions such as esters hydrolysis, Fisher esterifications, amides hydrolysis, etc.	• A chromatographic phase week cation exchanger at pH ≥ 6.8 that can be eluted at a pH ≤ 2.8 (*please see p. 232*)
	• Nucleophilic acyl substitutions such as transesterifications, etc.	• Carbon-carbon coupling reactions
	• A chromatographic phase strong cation exchanger that is permenently negatively charged (*pKa < 1*) • Ionic scavenging (*please see p. 232)*	• Deprotections of aromatic ethers • Fries rearrangements
	• Organic scavenging of electrophiles (*please see p. 156 - 159)* • Ionic scavenging (*please see p. 156 - 159)*	• Nucleophilic-catalyzed reactions • Acid-catalyzed reactions such as Aldol reactions, Retro-Claisen reaction, Mannich reactions, etc.
	• Ionic scavenging (*please see p. 156 - 159)* • Nitro-Aldol (*Henry*) reactions & Michael additions	• Amine free-basing • Compatible with solvent-free conditions
	• Knoevenagel condensations	• Catch and release purification of compounds bearing a permanent negative charge such as salts of sulfonic acids
	• Alkylations • Strecker-type reactions • Etherifications such as Williamson synthesis	• Michael additions and more generally speaking 1,4 addition reactions • Ionic scavenging (*please see p. 156 - 159)* • Deprotonates moderately acidic hydrogens
	• Acid sponge • Enamine formations • Mannich condensations	• Less nucleophilic and less basic than piperidine hence forming stable chloramines
	• Deprotecting and scavenging agent for Fmoc and Bsmoc amino protecting groups	• Knoevenagel condensations • Ionic & nucleophile scavenger
	• Deprotecting and scavenging agent for Fmoc and Bsmoc amino protecting groups • Knoevenagel condensations	• Ketones to enamines conversions • Production of dipiperidinyl dithiuram tetrasulfide (*rubber vulcanization accelerator*)
Linkers	• Allylic oxidations • Ene reactions	• Tsuji-Trost reactions • Rancidification
	• Introduction of phenyl groups via Pd-catalyzed couplings	• Synthesis of Grignard reagents
	• Immobilization of molecules bearing amino, hydroxy, mercapto and thiocarboxylic acid groups • Ring-opening reactions & hydrolysis	• Reduction with tungsten hexachloride • Reduction with lithium aluminum hydride
	• Nucleophilic substitutions for introduction of phenyl linker	
	• Nucleophilic substitutions for introduction of n-propyl linker	

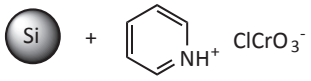
Oxidations

SiliaBond Pyridinium Chlorochromate (*R24030B*)
SiliaBond Pyridinium Dichromate (*R24530B*)

Description

SiliaBond Pyridinium Chlorochromate (*Si-PCC*)

Commonly used for the oxidation of alcohols to carbonyl compounds, selective oxidation of allylic and benzylic alcohols, organometallic oxidations, oxidative transpositions, oxidative cleavages, allylic and benzylic oxidation and oxidative cyclizations.[1-4] Using PCC immobilized onto silica gel provides anhydrous conditions that minimize the risk of side reactions and reduced yields. It greatly facilitates removal of polymeric reduced chromium by-products and is compatible with acid-sensitive protecting groups.[5,6] When used in conjunction with ultrasounds, kinetics are increased and the amount of oxidant required to complete the reaction is decreased.[7-9]



Category: Oxidant

Typical Application: Oxidation of alcohols to aldehydes / ketones

Loading: 20 % w/w	**Density**: 0.693 g/mL	**Endcapping**: No

Solvent Compatibility: Anhydrous CH_2Cl_2

Storage: Keep cool (< *8°C*) and dry

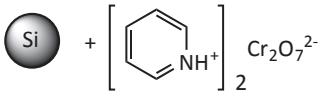
[1] *Org. Chem.*, **1989**, *54*, 5387
[2] Tetrahedron Lett., **2001**, *42*, 2141
[3] Synlett, **1999**, *10*, 1630
[4] Synth. *Commun.*, **1996**, *26*, 225
[5] *J. Org.Chem.*, **1993**, *58*, 2509
[6] *J. Chem. Educ.*, **1999**, *76*, 974
[7] *J. Org. Chem.*, **1983**, *48*, 666
[8] *Liebigs Ann. Chem.*, **1993**, 173
[9] *J. Org. Chem.*, **1992**, *57*, 3867

Description

SiliaBond Pyridinium Dichromate (*Si-PDC*)

Great alternative to *Si*-PCC in nucleoside and carbohydrate oxidation, particularly for fragile molecules.[1] SiliaBond PDC can also be used in conjunction with *tert*butylhydroperoxide for a variety of oxidative transformations.[2]

Si-PDC is a very convenient and effective reagent for oxidizing allylic and benzylic alcohols, saturated with acid-sensitive groups, such as cyclopropane rings or ketal functions.[3]



Category: Oxidant

Typical Application: Oxidation of alcohols to aldehydes / ketones

Loading: 20 % w/w	**Density**: 0.651 g/mL	**Endcapping**: No

Solvent Compatibility: Anhydrous CH_2Cl_2

Storage: Keep cool (< *8°C*) and dry

[1] *J. Chem. Soc. Perkin Trans. I*, **1982,** 1967
[2] *J. Chem. Soc. Chem. Commun.*, **1993**, *7*, 651
[3] *Tetrahedron*, **1979**, *35*, 1789

SiliaBond Potassium Permanganate (*R23030B*)

Description

SiliaBond Potassium Permanganate (*Si-KMnO$_4$*)

This product is a strong oxidant that will oxidize alcohols and aldehydes to carboxylic acids. SiliaBond Potassium Permanganate increases recovery, facilitates work-up and expands the scope of the chemistry because it can be used in all organic solvents eliminating solubility issues.[1] With SiliaBond Potassium Permanganate, the manganese salt by-products stay adsorbed onto the silica.

Category: Oxidant

Typical Application: Oxidation of alcohols and aldehydes to acids

Loading: 10 % w/w	**Density**: 0.593 g/mL	**Endcapping**: No

Solvent Compatibility: Anhydrous CH_2Cl_2

Storage: Keep dry

[1] *Synlett*, **2001**, *10,* 1555

Amide Coupling Reactions

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.[1] Therefore, there is an ongoing scientific endeavor to develop efficient amidation methodologies.[2] 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.[3] Solid-phase reagents are valuable for amide coupling with a carboxylic acid because they generate less unwanted side products. Other advantages of 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 batch reactions, microwave irradiation and flow chemistry.

[1] *J. Comb. Chem.,* **1999**, *1*, 55 [2] *Tetrahedron,* **2005**, *61*, 10827 [3] *J. Am Chem Soc.,* **1963**, *85*, 2149

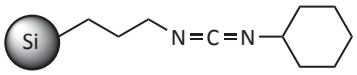
SiliaBond Carbodiimide (*R70530B*)

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.[1] 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.

[1] *Chem. Rev.*, **1981**, *81*, 589



Category: Reagent

Typical Application: Amide coupling with acids, acyl chlorides and amines

Loading: ≥ 0.91 mmol/g	**Density**: 0.751 g/mL	**Endcapping**: Yes

Solvent Compatibility: Aprotic solvents

Storage: Keep cool (< *8°C*), dry and under argon

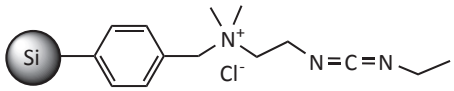
SiliaBond Ethyl-Dimethylamino Carbodiimide (*R70630B*)

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.[1] 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.

[1] *The Peptides: Analysis, Synthesis, Biology; Academic: New York*, **1979**, *1*, 241



Category: Reagent

Typical Application: Amide coupling with acids, acyl chlorides and amines

Loading: ≥ 0.32 mmol/g	**Density**: 0.770 g/mL	**Endcapping**: Yes

Solvent Compatibility: Aprotic solvents

Format: Keep cool (< *8°C*), dry and under argon

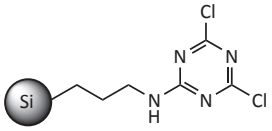
Silia*Bond* Dichlorotriazine (*R52230B*)

Description

Silia*Bond* 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.[1] 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. Silia*Bond* 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*).

[1] *J. Org. Chem.*, **1997**, *62*, 982



Category: Reagent

Typical Application: Amide coupling with acids, acyl chlorides and amines

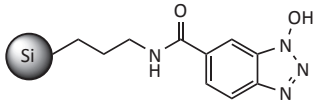
Loading: ≥ 0.60 mmol/g	**Density**: 0.781 g/mL	**Endcapping**: Yes
Solvent Compatibility: Aprotic solvents		
Storage: Keep cool (< *8°C*), dry and under argon		

Silia*Bond* HOBt (*R70730B*)

Description

Silia*Bond* HOBt (*Si-HOBt*)

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. Silia*Bond* HOBt can be easily activated and should ideally be used with a base such as *N,N*-diisopropylethylamine in the same conditions as in homogeneous solution. Moreover, this supported reagent can be reused a few times without adversely affecting its performance.



Category: Reagent

Typical Application: Avoiding or reducing racemization during chiral amide synthesis

Loading: ≥ 0.56 mmol/g	**Density**: 0.766 g/mL	**Endcapping**: Yes
Solvent Compatibility: Aprotic solvents		
Storage: Keep dry		

Reductive Aminations

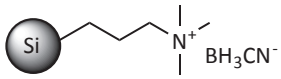
Reductive amination involves the conversion of a carbonyl group, most of the time a ketone or an aldehyde, to an amine via an intermediate imine or iminium. The intermediate imine is reduced by sodium cyanoborohydride. This is known as direct reductive amination and is carried out with reducing agents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

Silia*Bond* Cyanoborohydride (*R66730B*)

Description

Silia*Bond* Cyanoborohydride (*Si-CBH*)

Silia*Bond* 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. However, when using the solution phase equivalent, cyanide contamination of the product is a concern. 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 Silia*Bond* Cyanoborohydride was slurried 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 work-up required only a filtration and HCN nor NaCN were liberated during work-up.



Category: Reagent

Typical Application: Reductive amination

Loading: ≥ 0.87 mmol/g	**Density**: 0.705 g/mL	**Endcapping**: Yes

Solvent Compatibility: All solvents, aqueous and organic

Storage: Keep cool (< *8°C*), dry and under argon

Nitro-Aldol (*or Henry*) Reaction

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, α-nitro ketones by oxidation and β-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 Cannizarro reactions.

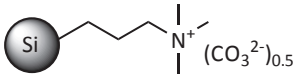
Silia*Bond* Carbonate (*R66030B*)

Description

Silia*Bond* Carbonate (*Si-CO_3*)

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

Silia*Bond* Carbonate is also an excellent product for amine free-basing. Please see p. 112 for more information.



Category: Reagent or Catalyst

Typical Application: Nitro-Aldol reaction (*Henry reaction*), free basing of amines

Loading: ≥ 0.46 mmol/g	**Density**: 0.608 g/mL	**Endcapping**: Yes
Solvent Compatibility: Aprotic solvents		
Storage: Keep dry		

Silia*Bond* Piperazine (*R60030B*)

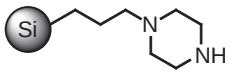
Description

Silia*Bond* Piperazine (*Si-PPZ*)

Silia*Bond* Piperazine (*Si-PPZ*) is a very useful solid-phase Knoevenagel catalyst. According to the results of a study, Si-PPZ is superior to its polystyrene-based equivalent.[1-3]

Silia*Bond* Piperazine is a useful deprotecting and scavenging agent for Fmoc and Bsmoc amino protecting groups, as well as a great electrophile scavenger.

Please see p. 157 for more information on Silia*Bond* Piperazine scavenging capabilities.



Category: Reagent or Catalyst

Typical Application: Knoevenagel synthesis, Fmoc and Bsoc deprotection, organic scavenger.

Loading: ≥ 0.83 mmol/g	**Density**: 0.671 g/mL	**Endcapping**: Yes
Solvent Compatibility: All solvents, aqueous and organic		
Storage: Keep cool (< *8°C*) and dry		

[1] *J. Org. Chem.*, **1983**, *48*, 666
[2] *J. Org. Chem.*, **1999**, *64*, 4324
[3] *J. Org. Chem.*, **2010**, *51*, 6670

Acylation & Esterification Reactions

Acylations are the addition of an acyl group (*RCO*) via electrophilic substitution, whereas esterifications are the formation of esters (*RCOOR*) from a derived carboxylic acid.

The typical acylation reaction is the Friedel-Crafts, and other acyl transfers include the Boekelheide, Kostanecki, Passerini reactions, the Pummerer rearrangement, etc. The typical esterification reaction is the Fischer reaction, and other ester synthesis include the Fisher-Speier modification, Mitsunobu reaction, the Steglich esterification, etc.

For both reactions DMAP (*4-dimethylaminopyridine*) is well-known as an acyl-transfer catalyst, to increase speed and yield of alcohol and phenol acylations over acetic and benzoic anhydrides. Tosic Acid, on the other hand, is a very popular acid catalyst for esterification & transesterification of esters and $AlCl_3$ is probably one of the most commonly used Lewis acid as a catalyst for Friedel-Crafts reactions.

Silia*Bond* Aluminum Chloride (*R74530B*)

Description

Silia*Bond* Aluminum Chloride (*Si-AlCl$_3$*)

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

- It is a milder Lewis acid. $AlCl_3$ is so reactive that it often lacks selectivity and causes the formation of unwanted by-products.
- Si-$AlCl_3$ 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.

Silia*Bond* 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 and is no longer reactive.

Category: Reagent or Catalyst

Typical Application: Acylations, esterifications		
Loading: ≥ 1.60 mmol/g	**Density**: 0.781 g/mL	**Endcapping**: No
Solvent Compatibility: Anhydrous, degassed and organic solvents		
Storage: Keep cool (< *8°C*), dry and under argon		

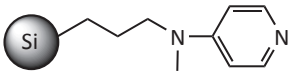
[1] *Acc. Chem. Res.*, **2002**, *35*, 791
[2] *Org. Proc. Res. Dev.*, **1998**, *2*, 221
[3] *J. Catal.*, **2000**, *195*, 237
[4] *J. Catal.*, **2000**, *195*, 412
[5] *Chem. Rev.*, **2003**, *103*, 4307
[6] *Tetrahedron*, **2003**, *59*, 1781

Silia*Bond* DMAP (*R75630B*)

Description

Silia*Bond* DMAP (*Si-DMAP*)

Silia*Bond* DMAP is the heterogeneous 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. Silia*Bond* DMAP has an advantage over its free counterpart as it can be removed by a simple filtration.



Category: Reagent or Catalyst

Typical Application: Acylations, esterifications

Loading: ≥ 0.53 mmol/g	**Density**: 0.674 g/mL	**Endcapping**: Yes

Solvent Compatibility: All solvents, aqueous and organic

Storage: Keep cool (< *8°C*), dry and under argon

Silia*Bond* Tosic Acid (*R60530B*)

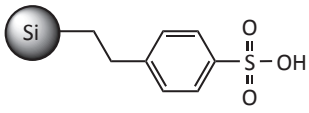
Description

Silia*Bond* Tosic Acid (*Si-SCX*)

Silia*Bond* Tosic 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.

Silia*Bond* Tosic Acid used as an acid catalyst for Fischer-Speier esterification provides excellent conversion.

Silia*Bond* Tosic Acid can also be used as a metal scavenger. Please refer to page 151 for more details.



Category: Reagent or Catalyst

Typical Application: Esterification, deprotection of aromatic ethers

Loading: ≥ 0.54 mmol/g	**Density**: 0.698 g/mL	**Endcapping**: Yes

Solvent Compatibility: All solvents, aqueous and organic

Storage: Keep dry

Alkylation & Etherification Reactions

Alkylation reactions are the transfer of an alkyl group from one molecule to the other via alkylating agents, that may have an electrophilic or nucleophilic character. Etherifications are a type of C-O bond formation reaction, usually from the S_N2 reaction between an organohalide and an alcohol.

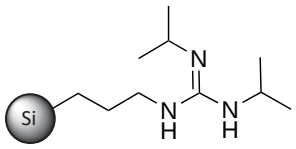
Just like for acylation reactions, the most common type of alkylation is the Friedel-Crafts reaction and the typical etherification reaction is the Williamson synthesis.

Silia*Bond* Guanidine (*R68230B*)

Description

Silia*Bond* Guanidine (*Si-GUA*)

Silia*Bond* Guanidine is a silica-bound guanidine moiety that is sufficiently basic to deprotonate moderately acidic hydrogens. It is most commonly used in Williamson synthesis, 1,4 addition reactions, Strecker-type reactions, etc.



Category: Reagent

Typical Application: Williamson ether synthesis, Strecker-type reactions, 1,4 addition reactions

Loading: ≥ 0.80 mmol/g	**Density**: 0.732 g/mL	**Endcapping**: Yes

Solvent Compatibility: All solvents, aqueous and organic

Storage: Keep dry

Silia*Bond* Aluminum Chloride (*R74530B*)

Description

Silia*Bond* Aluminum Chloride (*Si-AlCl$_3$*)

As shown on the previous page, Silia*Bond* Aluminum Chloride is the silica-supported version of the widely used Lewis acid, aluminum chloride.[1] It is an effective catalyst for Friedel-Crafts alkylations[2-4] and acylations. It also catalyzes the formation of ethers. The silica supported product has several advantages over the free catalyst:[5,6]

- It is a milder Lewis acid. Homogeneous $AlCl_3$ 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.

Silia*Bond* 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 and is no longer reactive.

Category: Reagent or Catalyst

Typical Application: Acylations, esterifications

Loading: ≥ 1.60 mmol/g	**Density**: 0.781 g/mL	**Endcapping**: No

Solvent Compatibility: Anhydrous, degassed and organic solvents

Storage: Keep cool (< *8°C*), dry and under argon

[1] *Acc. Chem. Res.*, **2002**, *35*, 791
[2] *Org. Process Res. Dev.*, **1998**, *2*, 221
[3] *J. Catal.*, **2000**, *195*, 237
[4] *J. Catal.*, **2000**, *195*, 412
[5] *Chem. Rev.*, **2003**, *103*, 4307
[6] *Tetrahedron*, **2003**, *59*, 1781

SiliaBond Reagents Compatibility with Different Technologies

Organic synthesis has traditionally been performed in batch: round-bottom flasks, test tubes, or closed vessels.

The general strategies and synthetic protocols used to construct organic molecules have remained relatively unchanged over the last few decades despite the many conceptual and technological advances that have arisen.

However, certain key enabling technologies, such as microwave heating and flow-based chemical processing, have seen rapid adoption and are greatly impacting on the synthetic routes used to prepare many of today's new chemical entities.

Nowadays, many existing syntheses have been re-examined and improved through the judicious application of modern chemical engineering principles.

In the following section, flow-based applications are identified by the following logo:

and microwave-based applications are identified by the following logo:

Flow Chemistry

What is Flow Chemistry?

Flow chemistry is a simple yet powerful technique: a chemical reaction is run in a continuously flowing stream, in opposition to a static volume contained in a vessel. Fluids containing the various reagents are pumped to join into a mixer and be submitted to different experimental conditions (*such as heating, cooling, pressure etc.*), in order to react.

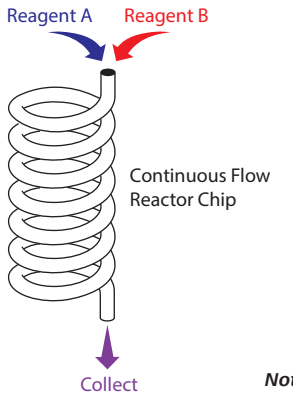
The main advantage of this new concept is that molecules enter, react and leave the system hence avoiding sustained exposition to conditions that would eventually lead to side reactions, by-products or impurities formation, etc.

In terms of reactivity, the strength of flow chemistry originates from the mixing. At large scale, mixing becomes much more powerful and heat exchange surface much more favorable than in a batch operation.

Doubling reaction size multiplies the surface by only 4, but the volume by 8. This volume-surface ratio is specially critical when hot spots arise (*low temperature reactions*), or when build-up next to the vessel's walls (*high temperature reactions*): temperature of the fluids is thus homogeneous.

Using silica-supported products in flow chemistry applications will ensure the following:

- Increase in R&D and manufacturing productivity
- Much higher reproducibility during scale-up because there is no issue of volume:surface ratio
- Precise control of mixing & temperature
- Minimal risk associated with hazardous reagents
- Separation of the catalyst from the products alleviates the need for any filtration (*or further handling*)
- Silia*Bond*, Silia*Cat* and Silia*MetS* can be used without degradation



***Note**: a reactor is needed*

Importance of Flow Chemistry

Flow chemistry is a relatively new technique that is being used more and more for large scale manufacturing because it only requires a small investment but enables the production of large quantities in shorter time and less space.

The use of supported catalysts in flow chemistry is even more recent. Supported catalysts are available on different supports such as polymers, charcoal, alumina and silica. They offer many advantages over the traditional homogeneous catalysts, including ease of handling and purification.

Silica presents many advantages such as no swelling, good mechanical and thermal stability and ease of scalability. SiliCycle has developed innovative silica-based catalysts (*Silia*Cat*, please see appropriate section p. 15*), reagents (*Silia*Bond*) and metal scavengers (*Silia*MetS*, *please see appropriate section p. 137*) that can be used in flow chemistry.

Microwave Applications

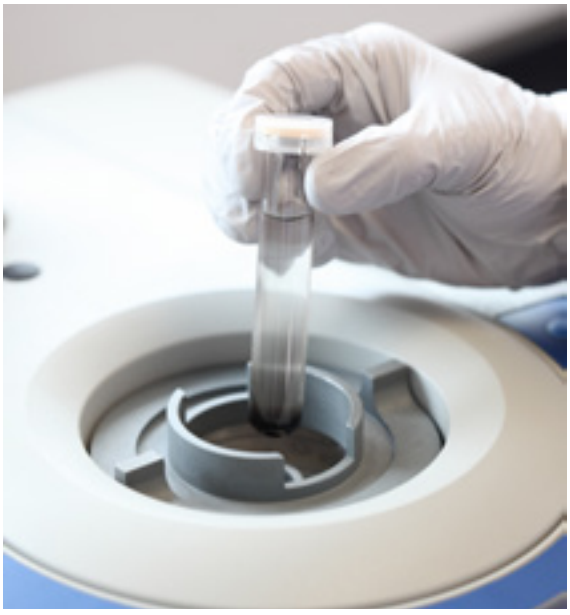
What is Microwave Chemistry?

It's been a while since chemists have known that molecules undergo excitation when exposed to electromagnetic radiations

Use of microwave or dielectric heating in organic chemistry has lead to extraordinary reaction rate enhancements. More recently the use of microwave radiation for heating reactions has even been expanded to inorganic and materials chemistry.

In the background of green chemistry, microwave irradiation provides an alternative to the conventional methods, for heating or introducing energy into the system. It utilizes the ability of mobile electric charges present in liquid or conducting ions in solid to transform electromagnetic energy into heat. Microwave-assisted reactions are fast, clean, economic and eco-friendly. This technique has frequently been proposed as the "technology of tomorrow".

- Faster kinetics: only a few minutes per reaction
- Higher yields and excellent purity
- Compatibility with many solvents
- Silia*Bond*, Silia*Cat* and Silia*MetS* can be used without degradation
- Wide variety of reactions and applications



Importance of Microwave-Assisted Synthesis

In last 2 decades, microwave synthesizer have taken organic chemistry by strom. Fast kinetics, higher yields, excellent purity, wide compatibility of solvents and their applicability to a variety of reactions and applications, make them very useful tools in the laboratory. After their introduction, chemists started to use supported reagents for solution-phase synthesis. The polymer-supported reagents commonly used, although very useful, have drawbacks in microwave synthesizers, namely swelling and heat instability. The high temperatures generated inside these synthesizers put stress on the resins. Also, because of the small reaction volumes, the swelling of the resins can be problematic. Silica-based products on the other hand, do not suffer from such shortcomings. They are heat resistant and they do not swell. In the following pages, we present different reactions (*amide synthesis, reductive amination, Henry reaction*) using Silia*Bond* Reagents as well as an electrophile and nucleophile that demonstrate the effectiveness of these reagents for microwave applications.

Application Notes and Case Studies

We have selected a few application cases to help understanding how our functionalized silicas can be introduced in your daily synthetic strategies.

Application Notes

You can read through our “Application Notes” section to learn more about different SiliCycle applications that were developed in our labs, but don’t take our word for granted and also check out customers Case Studies.

In the following section, application notes are identified by this logo:

Case Studies

Discover and learn what some of our customers are doing with our technology in the “Case Studies” section.

In the following section, case studies and applications developed by our customers are identified by this logo:

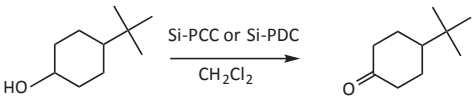
Nothing speaks more than lab examples and real-life experiences!

Oxidations

Oxidation of Alcohols to Ketones and Aldehydes (*Si-PDC or Si-PCC*)

General Procedure

Silia*Bond* PCC or Silia*Bond* PDC (*8.00 mmol; 2.0 equiv*) and acetic acid (*4.00 mmol; 1.0 equiv*) were added to a solution of alcohol in CH_2Cl_2 (*7.5 mL*). The resulting mixture was stirred for 6 h at room temperature. Ether (*15 mL*) was added and after stirring for another 2 min, the solution was filtered and the solids were washed with ether (*4 x 9 mL*). Concentration under vacuum afforded the desired product without further purification.



Oxidation of Alcohols Results		
Silia*Bond* Oxidant	Conditions	Conversion[a] (%)
Silia*Bond* PCC	6 h, r.t.	100
Silia*Bond* PDC		100

[a] Conversion determined from GC-MS

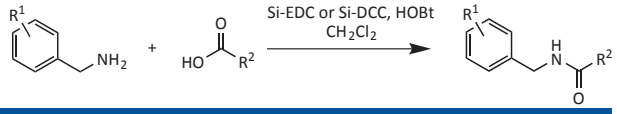
Amide Coupling Reactions

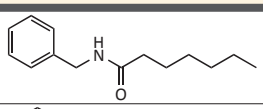
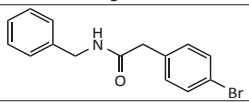
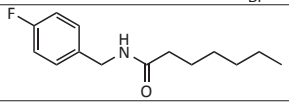
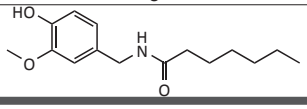
Synthesis of Capsaicin Analogues (*Si-DCC or Si-EDC*)

Capsaicin's potential clinical use as an analgesic and for its 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 (*1.00 mmol; 1.0 equiv*) was placed in an oven-dried reaction vial with anhydrous CH_2Cl_2 (*10 mL*) under nitrogen. HOBt (*1.00 mmol; 1.0 equiv*) and Silia*Bond* DCC or Silia*Bond* EDC (*1.50 mmol; 1.5 equiv*) were added to the solution, which was then stirred briefly (*5 min*). The amine (*0.50 mmol; 0.5 quiv*) was then added to the reaction tube and the mixture was then stirred for 16 h at room temperature. Reaction was followed by GC-MS, and work-up consisted in a simple filtration on Büchner and washing with CH_2Cl_2 (*3 x 10 mL*). Solvent was evaporated to yield pure amide.

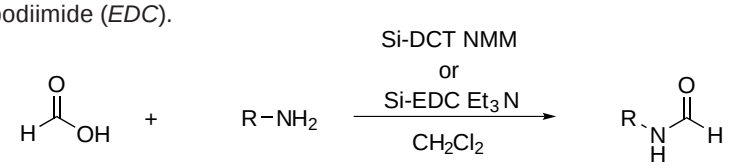


Capsaicin Analogues Reaction Results (*in %*)		
Product	Yield[a] (*Purity*[b])	
	Si-DCC	*Si*-EDC
	99 (> *98*)	81 (> *98*)
	98 (> *98*)	88 (*95*)
	99 (> *98*)	99 (> *98*)
	98[c]	98[c]

[a] Yield calculated in crude product [b] Purity determined by GC-MS [c] Yield determined by GC-MS

Synthesis of Formylated Amino Acids (*Si-DCT or Si-EDC*)

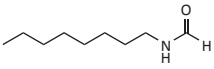
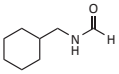
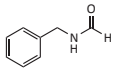
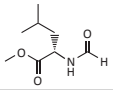
N-formylamino acid esters are useful derivatives for preparing selected *N*-formylamino acids, incorporating polyfunctional amino acids into peptides and for other useful starting material preparation. Formylated amino acids have been prepared in high yields by using Silia*Bond* Dichlorotriazine (*DCT*)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



General Procedure

Formic acid (*0.90 mmol; 1.0 equiv*) was placed in an oven-dried reaction vial in anhydrous CH_2Cl_2 (*10 mL*) under nitrogen. To this solution was either added *[N-methylmorpholine (0.90 mmol; 1.0 equiv) and Silia*Bond* DCT (2.25 mmol; 2.5 equiv)]* or *[triethylamine (0.90 mmol; 1.0 equiv) and Silia*Bond* EDC (2.25 mmol; 2.5 equiv)]*. The mixture was then stirred briefly (*5 min*), and the amine (*0.45 mmol; 0.5 equiv*) was added to the vial and the reaction was stirred at room temperature for 16 h. Conversion to the desired formamide was monitored by GC-MS. Upon completion, the Silia*Bond* DCT or EDC was filtered and washed with 2 x 10 mL of CH_2Cl_2 to yield product.
No further purification was required.

Synthesis of Formylated Amino Acids Results (*in %*)

Product	Conversion[a] Si-DCT	Conversion[a] Si-EDC	Product	Conversion[a] Si-DCT	Conversion[a] Si-EDC
	99	93		99	99
	99	100		98	95

[a] Conversion determined by GC-MS

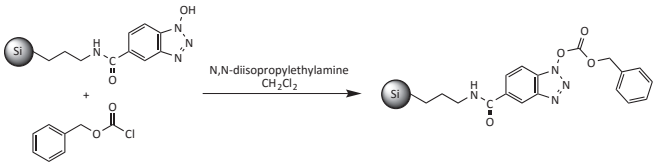
Amine Protection Using Benzylcarbamate Group (*Si-HOBt*)

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

General Procedure

Silia*Bond* HOBt (*0.80 mmol; 1.0 equiv*) was introduced in an oven-dried flask containing anhydrous CH_2Cl_2. Benzylchloroformate (*3.20 mmol; 4.0 equiv*) was added to the suspension, followed by *N,N*-diisopropylethylamine (*3.20 mmol; 4.0 equiv*). The reaction mixture was stirred for 60 min at room temperature. Then, the suspension mixture was filtered, washed with CH_2Cl_2 (*2 x 10 mL*) and the Silia*Bond* HOBt was oven-dried for reuse.

Activation Reaction



Activation and Recycling Results (*in %*)

Entry	Yield[a]
Activation	96
1st Recycling	86
2nd Recycling	95
3nd Recycling	96

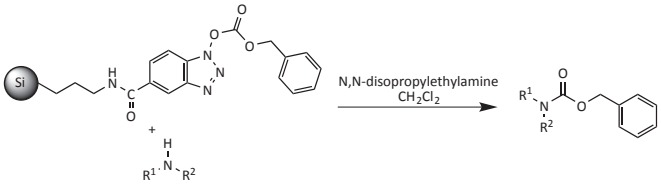
[a] Yield determined by GC-MS

Amine Protection Reaction (*Si-HOBt*)

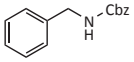
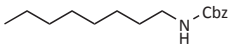
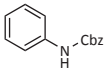
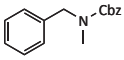
General Procedure

Same as previous

The dried, activated Silia*Bond* HOBt (*0.80 mmol; 1.0 equiv*) was placed in a flask containing anhydrous CH_2Cl_2 under nitrogen. To this suspension, the amine (*0.64 mmol; 0.8 equiv*) was added, and the reaction mixture was stirred for 4 to 16 h at room temperature.
The reaction suspension was filtered and washed with CH_2Cl_2 (*2 x 10 mL*).



Amine Protection Results (*in %*)

Product	Yield[a]	Product	Yield[a]
	98 (*4 h*)		93 (*4 h*) 98 (*16 h*)
	94 (*4 h*) 96 (*16 h*)		98 (*4 h*)
	81 (*16 h*)		93 (*16 h*)

[a] Yield determined from isolated product

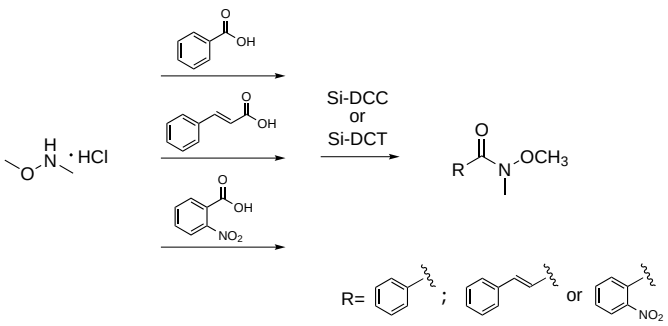
Weinreb and Acylsulfonamide Synthesis (*Si-DCC or Si-DCT*)

The 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, the Weinreb synthesis can tolerate a large variety of functional groups such as *N*-protected amines, sulfonates, alpha-beta saturation and silyl ethers.

General Procedure for Weinreb Synthesis

The acid (*0.21 mmol; 3.0 equiv*), DMAP (*0.21 mmol; 0.3 equiv*), pyridine (*0.25 mmol; 3.5 equiv*), *N,O,*-dimethylhydroxylamine hydrochloride (*0.07 mmol; 1.0 equiv*) and Silia*Bond* DCC or DCT (*0.32 mmol; 4.5 equiv*) in 10 mL of DCM were added to a dry vessel and stirred overnight at room temperature Excess acid was scavenged with Silia*Bond* Amine (*0.29 mmol; 4.0 equiv*) and excess amine, DMAP and pyridine were scavenged with Silia*Bond* Tosic Acid (*1.00 mmol; 14.0 equiv*).

Total volume of the mixture was adjusted to keep a ratio silica / solvent of 1 g / 5 mL. Scavengers were allowed to react for 1 h at room temperature prior to filtration, washing with DCM and evaporation of solvent.



Weinreb Synthesis Results (*in %*)

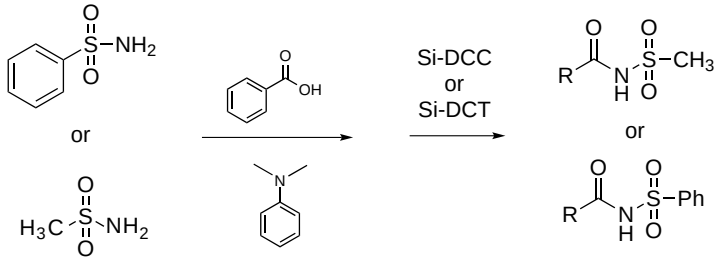
Amine	Acid	Yield[a] (*Purity*)[b]	
		Si-DCC	Si-DCT
N,O-Dimethylhydroxyamine Hydrochloride	Benzoic Acid	99 (*96*)	96 (*94*)
	t-Cinnamic Acid	87 (*95*)	82 (*70*)
	2-Nitrobenzoic Acid	> 99 (*93*)	92 (*79*)

[a] Yield determined from isolated product
[b] Purity determined by GC-MS

General Procedure for Acylsulfonamide Synthesis

Benzoic Acid (*0.27 mmol; 3.0 equiv*), DMAP (*0.27 mmol; 3.0 equiv*), sulfonamide (*0.09 mmol; 1.0 equiv*) and Silia*Bond* DCC or DCT (*0.41 mmol; 4.5 equiv*) were added to a 10 mL of (*4:1*) DCM / DMF mixture in a dry reaction vessel and stirred 24 h at room temperature Excess amine and DMAP were scavenged with Silia*Bond* Tosic Acid (*1.08 mmol; 12.0 equiv*).

Total volume of the mixture was adjusted to keep a ratio silica / solvent of 1 g / 5 mL. Scavengers were allowed to react for 2 h at room temperature prior to filtration, washing with DCM and evaporation of the solvent.



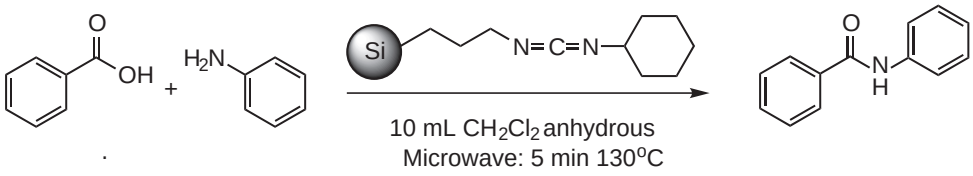
Acylsulfonamide Synthesis Results (*in %*)

Acid	Sulfonamide	Yield[a] (*Purity*)[b]	
		Si-DCC	Si-DCT
Benzoic Acid	Benzenesulfonamide	96 (*71*)	98 (*90*)
	Methanesulfonamide	79 (*53*)	71 (*82*)

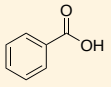
[a] Yield determined from isolated product
[b] Purity determined by GC-MS

Coupling of Benzoic Acid with Aniline (*Si-DCC*)

In the amide coupling between benzoic acid and aniline catalyzed by Si-DCC using 2 different synthetic approaches, better yields were acheived in both strategies, albeit with a little less purity in crude compound before further purification.



Amide Coupling Yield[a] (*Purity*)[b] in %

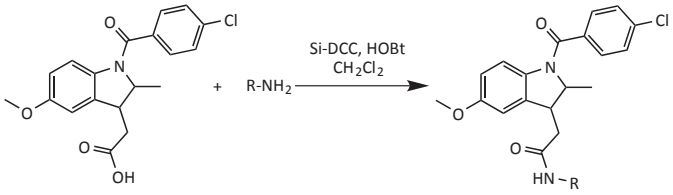
		*Si*-Carbodiimide (*Si-DCC*)	Microwave	Bulk (*room temperature, 24 h*)
1.5 equiv	1.0 equiv	2.0 equiv	73 (*88*)	53 (*99*)
2.0 equiv		3.0 equiv	95 (*95*)	81 (*98*)

[a] Determined from GC-FID,
[b] Refers to the isolated product

Synthesis of Amide Derivatives of Indomethacin (*Si-DCC*)

A report has shown that indomethacin primary and secondary amide analogues are potent compounds for human COX-2 specific inhibition. Silia*Bond* Carbodiimide can be used as a key reagent in its synthesis.

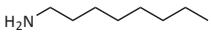
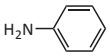
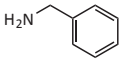
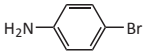
J. Med. Chem., **2000**, *43*, 2860-2870



General Procedure

The indomethacin (*0.56 mmol; 1.0 equiv*) was placed in an oven-dried reaction vial in anhydrous CH_2Cl_2 (*5 mL*) under nitrogen. HOBt (*0.95 mmol; 1.7 equiv*) and the Silia*Bond* Carbodiimide (*1.12 mmol; 2.0 equiv*) were added, and the mixture was stirred briefly (*5 min*). Then, the amine (*0.56 mmol; 1.0 equiv*) 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 Results

Amine	Yield[a] (*in %*)	Amine	Yield[a] (*in %*)
	90		94
	82		78

[a] Yield determined from isolated product

Reductive Amination

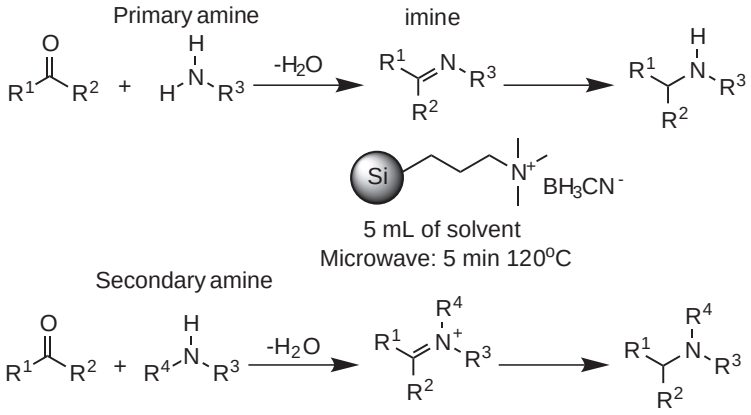
Reductive Aminations (*Si-CBH*)

General Procedure (*conventional - batch*)

In polypropylene tubes with a frit on the bottom, was weighed Silia*Bond* Cyanoborohydride (*1.14 mmol; 1.2 equiv*). The tubes were placed on SiliCycle's MiniBlock and 5 mL of THF was added in each tube. The appropriate ketones / aldehydes (*0.95 mmol; 1.0 equiv*) were added, followed by the amines (*1.90 mmol; 2.0 equiv*). The tubes were sealed with a teflon septum, and the stirring plate was turned on at 650 RPM for 16 hours. The agitation was then stopped, the septum removed and the solutions filtered through the frits, in identified collection tubes. Each solution was analyzed by GC-MS.

General Procedure (*microwave*)

In polypropylene tubes was weighed the carbonyl (*0.95 mmol; 1.0 equiv*), the amine (*1.90 mmol; 2.0 equiv*) and Silia*Bond* Cyanoborohydride (*1.14 mmol; 1.2 equiv*). THF was added (*5 mL*), and the reaction mixture was maintained at 120°C for 5 min in a microwave. The septum was then removed and the solutions filtered through frits, in identified collection tubes. Each solution was analyzed by GC-MS.



Reductive Amination (%) Results				
Amine (*2.0 equiv*)	Carbonyl (*1.0 equiv*)	Microwave (*120°C, 1.2 equiv Si-CBH*)[a] 5 min	Bulk (*r.t., 2.5 equiv Si-CBH*)[a] 1 h	24 h
Piperidine	Benzaldehyde	> 99	80	> 99
N,N-Benzylmethylamine		> 99	97	> 99
3-Phenyl-1-propylamine	Cyclohexanone	> 99	88	87

[a] Conversion determined by GC-MS

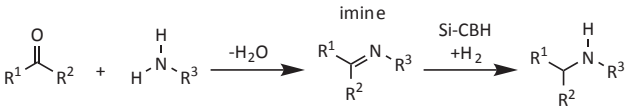
All reactions conducted with the microwave gave conversions that were equivalent to significantly higher, than when using traditional bulk conditions.

Reductive Aminations (*Si-CBH*)

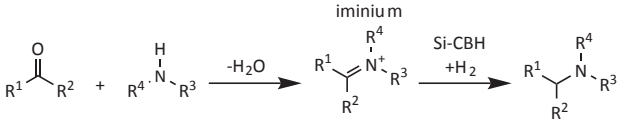
General Procedure

To Silia*Bond* Cyanoborohydride (*1.00 mmol; 2.0 equiv*) was added the solvent (*5 mL*), the aldehyde or ketone (*0.50 mmol; 1.0 equiv*) and the amine (*0.60 mmol; 1.2 equiv*). The reaction mixture was stirred at room temperature for 16 h. Each solution was then analyzed by GC-MS. Upon completion, Silia*Bond* CBH was simply filtered and washed off. Solvent was then evaporated to yield pure amide.

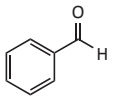
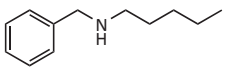
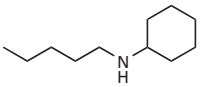
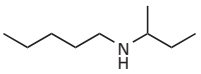
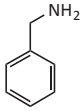
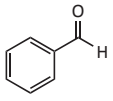
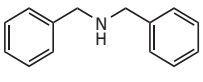
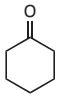
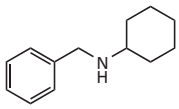
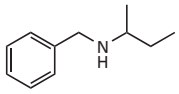
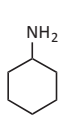
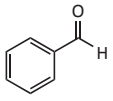
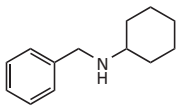
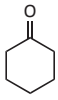
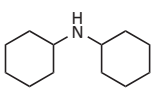
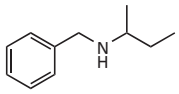
Reduction of Primary Amines



Reduction of Secondary Amines

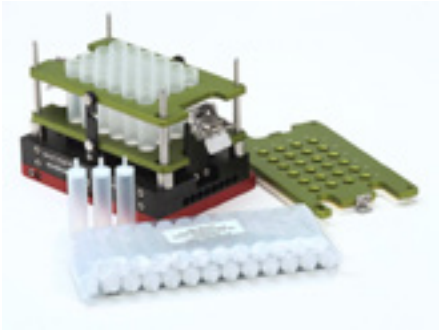


Reduction of Primary Amine Results

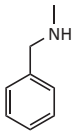
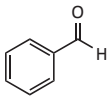
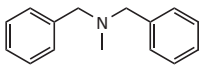
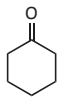
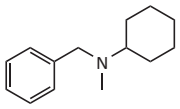
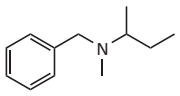
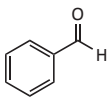
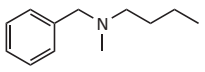
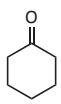
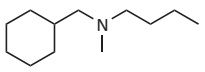
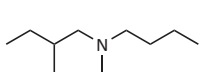
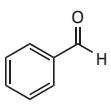
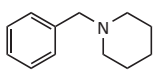
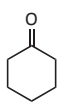
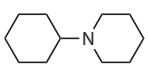
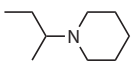
1° Amine	Carbonyl	Conditions (*room temperature, 16 h*) Product	in Acetonitrile		in Ethanol		in Methylene Chloride	
			Conversion Product (%)[a]	Imine (%)[b]	Conversion Product (%)[a]	Imine (%)[b]	Conversion Product (%)[a]	Imine (%)[b]
			27	25	64	11	69	12
			97	0	95	5	92	8
			92	0	84	7	78	9
			61	20	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

[a] Conversion determined by GC-MS, [b]Unreacted imine was determined by GC-MS

All reactions were carried out using SiliCycle MiniBlock, all at once within a timeframe of 16 h.



Reduction of Secondary Amine Results

2° Amine	Carbonyl	Conditions (*room temperature 16 h*) Product	in Acetonitrile		in Ethanol		in Methylene Chloride	
			Conversion Product (%)[a]	SM[c] (%)[b]	Conversion Product (%)[a]	SM[c] (%)[b]	Conversion Product (%)[a]	SM[c] (%)[b]
			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

[a] Conversion determined by GC-MS, [b] Unreacted iminum was determined by GC-MS, [c] Starting Material

Reductive Amination

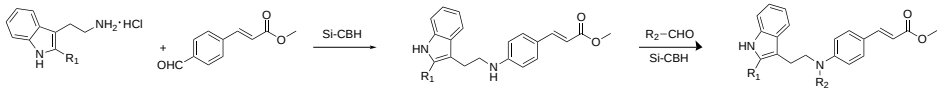
Synthesis of Histone Deacethylase Inhibitors (*Si-CBH*)

Journal of Medicinal Chemistry, **2011**, *54*, 4752-4772

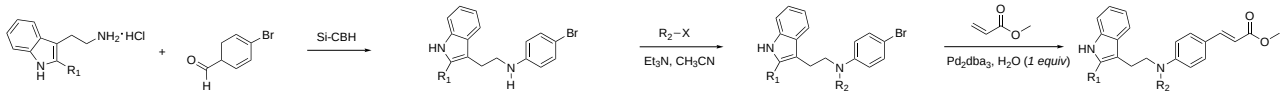
Histone deacethylase (*HDAC*) inhibitors have proven to show interesting potential in the treatment of various forms of cancer. Silia*Bond* Cyanoborohydride was used in the general synthesis of hydroxymate-based HDAC inhibitors:

- An acrylate was reacted with a bromo-benzaldehyde via reductive amination to yield an indole-carboxylic acid ethyl ester, using Silia*Bond* Cyanoborohydride (*route 2*).
- A tryptamine or tryptamine analogue was reacted with a formylcinnamate again via reductive amination to generate substituted amino cinnamates. Subsequent alkylation of the secondary amines in the corresponding tertiary amine was done via reductive amination using Silia*Bond* Cyanoborohydride (*route 1*) or via reaction with previously synthetized arylhalide (*route 2*).

ROUTE 1



ROUTE 2



General Procedure

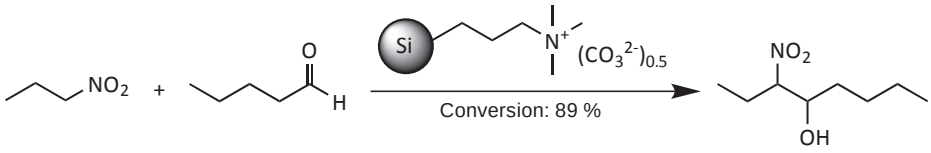
2-Fluoro-ethylamine hydrochloride (*1.10 mmol; 1.0 equiv*) was added to a solution of (*E*)-3-(4-formyl-phenyl)-acrylic acid methyl ester (*1.10 mmol; 1.0 equiv*) and acetic acid in DMF (*1:4*). The mixture was stirred at room temperature for 10 min. Silia*Bond* Cyanoborohydride (*1.10 mmol; 1.0 equiv*) was added and stirred at room temperature for another 10 min. The mixture was then heated via microwave irradiation at 150°C for 5 min, filtered and concentrated under vacuum. Typical total yields were between 7 and 46 %.

Nitro-Aldol (*or Henry*) Reaction

3-Nitrooctan-4-ol Synthesis via a Nitro-Aldol (*Si-CO_3*)

General Procedure

1-nitropropane (*1.12 mmol; 1.0 equiv*) was added to a solution containing THF (*5 mL*) and valeraldehyde (*1.12 mmol; 1 equiv*). Silia*Bond* Carbonate (*0.11 mmol; 0.1 equiv*) 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*).



Nitro-Aldol (*or Henry*) Reaction Results (*in %*)

Entry	Solvent	Reaction Conditions	Conversion[a] (*Purity*)[b]
1	THF	0.1 equiv Si-CO_3 room temperature, 6 h	92 (*83*)[b]
2	CH_2Cl_2		76
3	Ethanol		90
4	Propanol		95
5	None		92
6	THF	0.1 equiv Si-CO_3 microwave 100 W, 100°C, 10 min	89

[a] Conversion determined by GC-MS, [b] Purity determined from the isolated product

Knoevenagel Condensations (*Si-PPZ*)

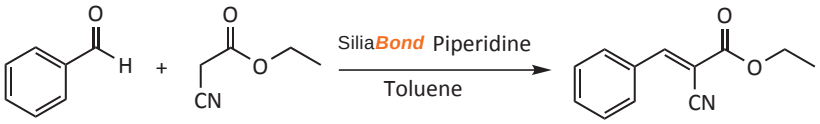
The Knoevenagel condensation between carbonyl compounds and methylene malonic esters produce several important products, including nitriles used in anionic polymerization and unsaturated ester intermediates employed in the synthesis of several therapeutic drugs. Alkali metal hydroxides, pyridine and piperidine are the traditional catalysts used in these reactions.

General Procedure (*conventional - batch*)

A mixture of benzaldehyde (*2.00 mmol; 1.0 equiv*), ethylcyanoacetate (*3.00 mmol; 1.5 equiv*) nd 10 mol % of Silia*Bond* Piperidine (*0.20 mmol; 0.1 equiv*) in 15 mL of toluene were stirred at 110°C for 20 h. The reaction mixture was filtered and the solvent was evaporated. The crude product obtained was analyzed by GC/MS.

General Procedure (*flow*)

The reactor was charged with Silia*Bond* Piperidine (*1.50 mmol; 0.1 equiv*) and heated at 110°C using toluene as solvent. A mixture of benzaldehyde (*15.00 mmol; 1 equiv*), ethylcyanoacetate (*22.50 mmol; 1.5 mmol*) in 110 mL of toluene was stirred at r.t. for 5 min. The mixture was then introduced in a glass bottle directly connected to the pump. Upon completion of the reaction, the reaction mixture was filtered and the crude product analyzed by GC/MS to determine the conversion ratio.



Knoevenagel Condensation Reaction Results

Entry	Catalyst (*mol %*)	Time (*h*)	Flow Conditions			Conversion (*%*) (*Yield %*)
			Flow (*µL/min*)	Vol. Reactor (*mL*)	Residence Time (*min*)	
1	10	20	Conventional (*Batch*)			98 (*80*)
2	55	2	50	0.7	14	99 (*82*)
3	10	20	100	2.4	24	100 (*90*)

At equivalent time reaction and catalyst mol %, flow conditions generate both significantly higher conversion and yields than traditional batch conditions. Higher reaction times were shown to yield better results than higher catalyst mol %. Yet, even in this last option, better conversion and yield were obtained.

Jasminaldehyde Synthesis via Aldol Reaction (*Si-PPZ*)

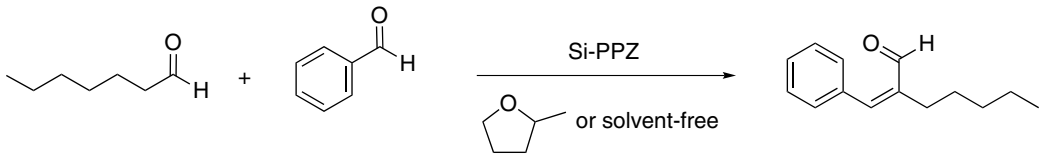
Catalysis Science & Technology, **2013**, *3*, 2732-2736

Jasminaldehyde is usally produced via an aldol C-C bond forming reaction, using typically a base such as NaOH.

One of the major drawback associated with the reaction between heptanal and benzaldehyde is the production of organic waste and by-product formation.

de María *et al.* have reported the synthesis of jasminaldehyde using Silia*Bond* Piperazine as an organocatalyst, both in bio-based solvents (*e.g.: 2-MeTHF*) and solvent-free conditions. Solvent-free conditions provided even better conversion.

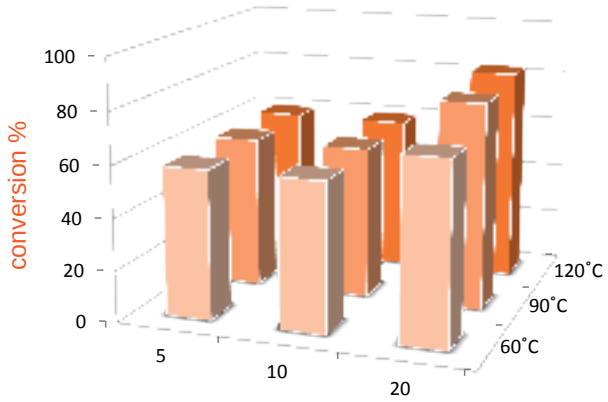
More over, selectivity remained unaltered during catalyst recycling.



General Procedure

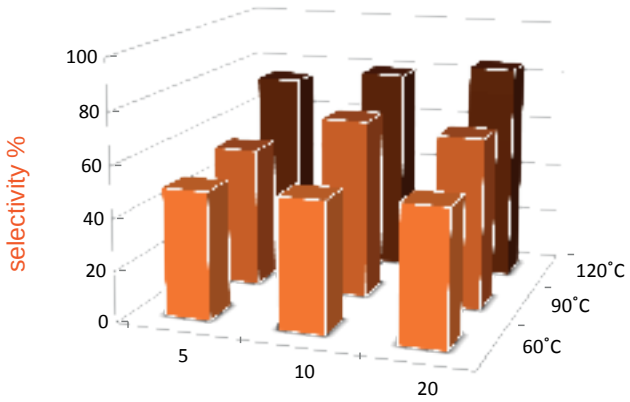
Heptanal (*0.42 mmol; 1.0 equiv*) was mixed with different amounts of benzaldehyde (*2.1 - 8.4 mmol; 5.0 - 20.0 equiv*). Reactions took place mostly in solvent-free conditions at 60 - 120°C, with variable catalyst loadings of Silia*Bond* Piperazine (*0.08 - 0.33 mmol; 0.2 - 0.8 equiv*). Reaction times were set from 8 to 18 h. For the work-up, the suspended catalyst was filtered and the reaction mixture analyzed by ^{1}H NMR to assess conversion and selectivity.

CONVERSION



benzaldehyde - heptanal ratio (*mol:mol*)

SELECTIVITY



benzaldehyde - heptanal ratio (*mol:mol*)

Conclusion

Silia*Bond* Piperazine as organocatalyst for the synthesis of jasminaldehyde was reported for the first time. Under optimized conditions high conversions and selectivities (*> 90 %*) were achieved in solvent-free conditions (*neat substrates*).

The immobilized catalyst proved to be reusable, and high selectivities remained within all catalytic cycles.

Acylation & Esterification Reactions

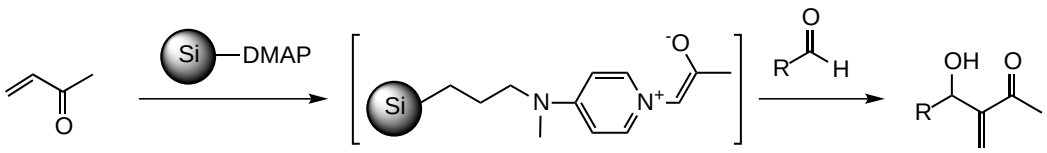
Baylis-Hillman Reaction (*Si-DMAP*): Comparative Study with PS-DMAP

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 mild conditions and its compatibility with several functional groups. Furthermore, an organic base can be used to catalyze this reaction with similar success compared to using transition metals.

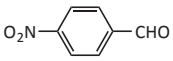
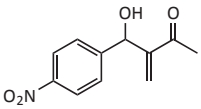
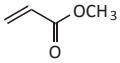
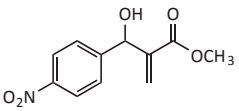
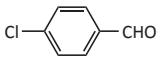
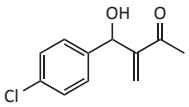
Results using silica-supported DMAP (*Si-DMAP*) were compared to those using polystyrene-bound DMAP (*PS-DMAP*).

General Procedure

Aldehyde (*1.00 mmol; 1.0 equiv*) was placed in a flask and THF, Silia*Bond* DMAP (*or PS-DMAP*) (*0.10 mmol; 0.1 equiv*), water and enone (*2.00 mmol; 1.0 equiv*) were added. The crude reaction mixture was stirred at room temperature for 6 to 96 h and conversion followed by GC-MS. The reaction mixture was then simply filtered on Büchner and washed with solvent to yield pure product after evaporation.



Baylis-Hillman Reaction Results

Aldehyde	Enone	Conditions	Product	Yield[a] (*in %*) Si-DMAP	Yield[a] (*in %*) PS-DMAP
		THF / H_2O (*3/1*) room temperature, 6 h 10 % *Si*- or *PS*-DMAP		**81**	37
		DMF / H_2O (*3/1*) room temperature, 90 min 10 % *Si*- or *PS*-DMAP		**75**	14
		CH_2Cl_2 room temperature, 24 h 10 % *Si*- or *PS*-DMAP		**74**	37
		No solvent room temperature, 96 h 24 % *Si*- or *PS*-DMAP		**71**	58
		THF / H_2O (3/1) room temperature, 96 h 19 % *Si*- or *PS*-DMAP		**63**	15

[a] Yield determined from the isolated product

It was thus demonstrated that Silia*Bond* DMAP was clearly superior than the corresponding polystyrene-bound DMAP.

Acylation & Esterification Reactions

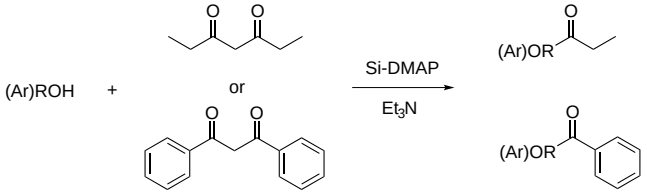
Acylation reactions can generate esters, using activated carboxylic acids (*acids chlorides*) and alcohols, even hindered tertiary alcohols.

General Procedure (*conventional - batch*)

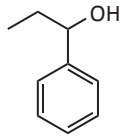
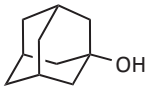
The alcohol (*4.00 mmol; 1.0 equiv*), acetic anhydride (*6.00 mmol; 1.5 equiv*) and triethylamine (*6.00 mmol; 1.5 equiv*) were stirred in 10 mL of CH_2Cl_2 at room temperature for 5 minutes. Two fractions of 5 mL solution were introduced into the reactor charged with Silia*Bond* DMAP (*0.36 mmol; 0.09 equiv*). Upon completion of the reaction, the mixture was analyzed by GC-MS to determine the conversion.

General Procedure (*flow*)

A mixture of the alcohol (*6.00 mmol; 1.0 equiv*), acetic anhydride (*9.00 mmol; 1.5 equiv*), triethylamine (*9.00 mmol; 1.5 equiv*) and Silia*Bond* DMAP (*0.30 mmol; 0.05 equiv*) in 15 ml of CH_2Cl_2 was stirred at room temperature for 90 minutes. The reaction was quenched by the addition of 0.5 mL of methanol, diluted with 25 mL Et_2O and washed twice with saturated aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the solution was filtered and evaporated to give a colorless oil in a quantitative yield.



Acylation Reaction Results

Substrate	Reagent	Catalyst (*equiv*)	Time (*h*)	Flow Conditions: Flow (*µL/min*)	Flow Conditions: Vol. Reactor (*mL*)	Conversion (%) (*Yield %*)
2-Octanol	Ac_2O	5	2	Conventional (*Batch*)		99 (*98*)
		9	2 1	100 200	0.7	100 (*99*) 98 (*99*)
	Bz_2O	10	24	Conventional (*Batch*)		91
		9	14 6	25 12.5	0.7	97 (*95*) 95 (*93*)
	Ac_2O	5	1.5	Conventional (*Batch*)		99 (*98*)
		9	3 2 1	50 100 200	0.7	99 (*97*) 99 (*97*) 99 (*97*)
	Bz_2O	5	24	Conventional (*Batch*)		88
		9	6 3 2	25 50 100	2.38	99 (*97*) 99 (*94*) 98 (*88*)
	Ac_2O	6	24	Conventional (*Batch*)		67
		9	17 7 4	10 25 50	2.38	95 (*61*) 97 (*40*) 97 (*27*)

For all acylation reactions, better or equivalent conversions could be obtained using flow chemistry *vs* conventional batch chemistry and with shorter reaction times. In some cases, the isolated yields using flow chemistry were even higher than simple conversion using batch conditions.

Fischer-Speier Esterifications (*Si-SCX*)

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 H_2SO_4, tosic acid and scandium triflate. Also, a large excess of one of the reagents is used to push the equilibrium towards the product.

General Procedure

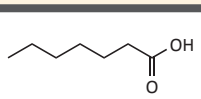
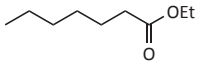
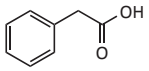
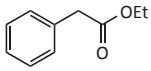
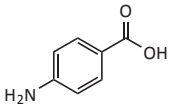
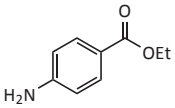
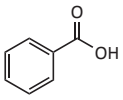
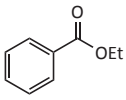
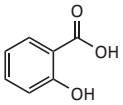
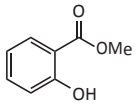
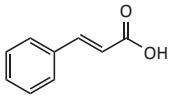
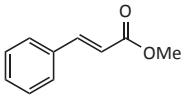
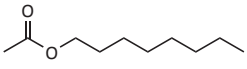
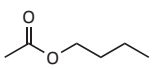
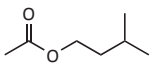
Method A

The carboxylic acid (*1.50 mmol; 1.0 equiv*) was added to a mixture of alcohol (*10 mL*) and Silia*Bond* Tosic Acid (*0.15 mmol; 0.1 equiv*). The reaction mixture was maintained at reflux for 16 h, then simply filtered on Büchner, washed with solvent to yield crude product after evaporation.

Method B

In a 250 mL round-bottom flask equipped with a Dean-Stark apparatus, the carboxylic acid (*16.3 mmol; 1.0 equiv*) was added to an alcohol (*65.20 mmol; 4 equiv*) and Silia*Bond* Tosic Acid (*1.63 mmol; 0.1 equiv*). The mixture was then heated to reflux for 20 to 24 h, then simply filtered on Büchner, washed with solvent to yield crude product after evaporation.

Fischer-Speier Esterification Results

Alcohol	Carboxylic Acid	Method	Ester	Conversion[a] (*in %*)
Ethanol		A		100
				100
		A (*72 h*)		40[c]
		B		94[c]
Methanol				89[c]
		A		98
1-Octanol				100
1-Butanol				100 (*99*)[b]
3-Methylbutanol				100

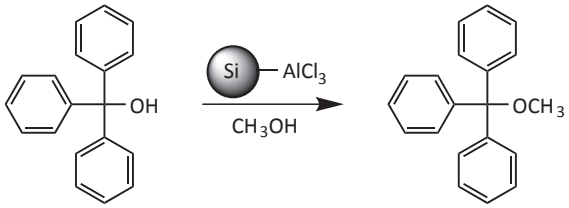
[a] Conversion determined by GC-MS, [b] *Si*-SCX recycled 3 times, [c] Conversion determined from the isolated product

S_{N_1} Acylation of Triphenylcarbinol (*Si-$AlCl_3$*): *Comparative Study with PS-$AlCl_x$*

General Procedure

Triphenylcarbinol (*2.00 mmol; 1.0 equiv*) was added to a solution of Silia*Bond* Aluminum Chloride (*2.30 mmol; 1.15 equiv*) in anhydrous methanol. The mixture was heated to 60°C until completion of the reaction (*followed by TLC, 90 min*). The catalyst was then removed by filtration and the product analyzed by ^{1}H NMR.

*Using the same protocol, a comparison between SiliCycle's silica-supported Silia*Bond* Aluminum Chloride (Si-$AlCl_3$) and the competition's Polymer-bound Aluminum Chloride (PS-$ALCl_x$) was done.*



Friedel-Crafts Acylation Results

Alcohol	Catalyst	Conversion[a] (*in %*)
Triphenylmethanol $(Ph)_3OH$	*Si*-$AlCl_3$	**95**
	PS-$AlCl_x$	81
Tert-Butyl Alcohol $(CH_3)_3OH$	*Si*-$AlCl_3$	**60**
	PS-$AlCl_x$	0
Benzyl Alcohol $PhCh_2OH$	*Si*-$AlCl_3$	**40**
	PS-$AlCl_x$	0

[a] Conversion determined by ^{1}H NMR

Synthesis of pyran-based macrocycles (*Si-DCC*)

Proceedings of the National Academy of Sciences of the United States of America., **2011**, *108*, 6751-6756

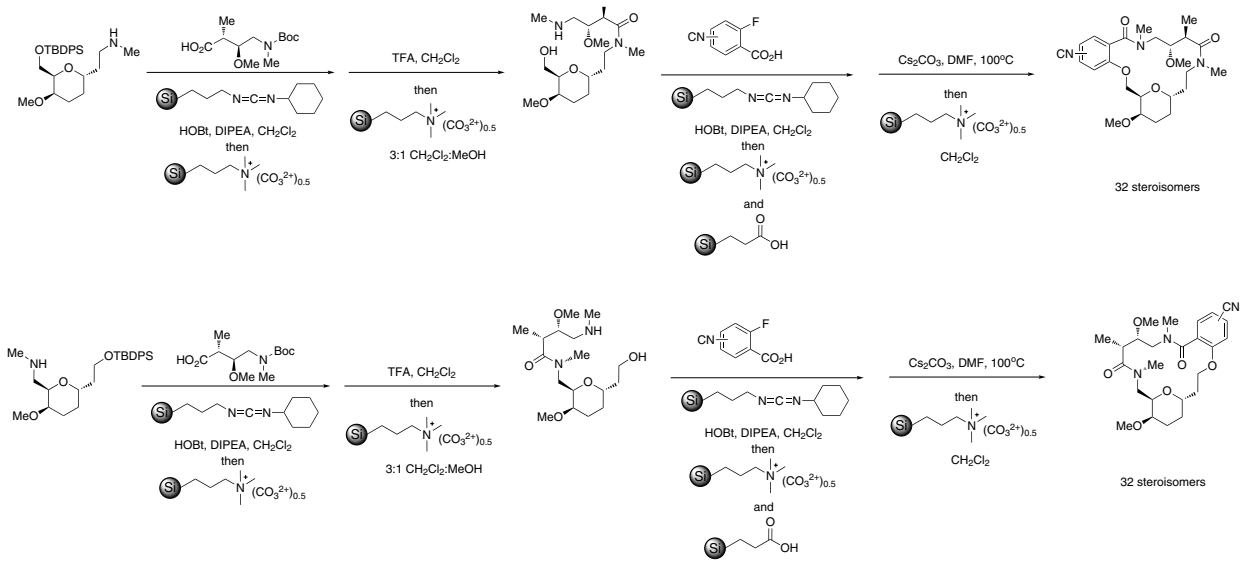
Stereogenic centers in molecules of complex structure are well-known to be key compounds going from discovery to clinical chemistry. In this context, a library of highly structural complex macrocycles with a pyran structure was synthetized with Silia*Bond* Carbodiimide (*Si-DCC*) as a key reagent.

352 macrocycles with ring cycles of 14, 15 and 16 members were produced in parallel synthesis using SiliCycle MiniBlock and MiniBlock XT. Silia*Bond* Carbonate (*Si-CO$_3$*) and Silia*Bond* Carboxylic Acid (*Si-WCX*) were used in the purification process.

The synthetic pathway comprises 2 main steps:

- The acylation of pyran amines with excess of a Boc-protected aminobutanoic acid in the presence of Silia*Bond* Carbodiimide together with homogeneous HOBt. The amino alcohol was deprotected, then unreacted acid was removed using Silia*Bond* Carbonate.
- A selective acylation of the deprotected amino alcohol - again deprotected with Silia*Bond* Carbonate - with either the *ortho*- or *para*- regioisomer of a cyano-fluorobenzoic acid, to yield an S_NAr amide precursor. Again, benzoic acid was scavenged using Silia*Bond* Carbonate and further clean up with Silia*Bond* Carboxylic Acid was done to remove any excess amine or potential o-acylation by-products.

For more information on purification steps using Silia*Bond* Organic Scavengers, please see p. 141



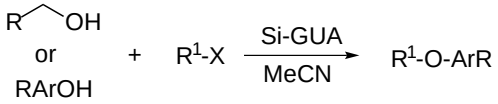
General Procedure

Acylation: The crude amino alcohols, cyano-fluorobenzoic acid 4-o or 4-p (*0.14 mmol; 1.0 equiv*), Silia*Bond* DCC (*0.19 mmol; 1.4 equiv*) and DIEA (*0.09 mmol; 0.7 equiv*) were combined in 2 % dimethylformamide (*DMF / DCM 3.0 mL*), and stirred at room temperature overnight. In cases where acylation was slow, additional Silia*Bond* DCC (*0.19 mmol; 1.4 equiv*) and a solution of HOBt (*0.04 mmol; 0.3 equiv*) in DMF / DCM (*1.0 mL*) and DIEA base (*0.03 mmol; 0.2 equiv*) were added. After acylation was deemed complete, reactions were scavenged with Silia*Bond* CO_3 (*0.18 mmol; 1.4 equiv*) and Silia*Bond* WCX (*0.18 mmol; 1.4 equiv*) for 30 min and then filtered and evaporated for 4 h.

Alkylation & Etherification Reactions

General Williamson Ether Synthesis (*Si-GUA*)

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.



General Procedure

The alcohol (*0.15 mmol; 1.0 equiv*) was added to acetonitrile (*4 mL*) and Silia*Bond* Guanidine (*0.05 mmol; 0.3 equiv*). The solution was stirred for 1 h at room temperature. Next, the alkyl halide (*0.12 mmol; 0.8 equiv*) was transferred to the reaction mixture, which was again stirred for 16 h at 60°C. Finally, the mixture was filtered, washed with 2 mL of acetonitrile and crude product was obtained after evaporation of solvents. Conversion was measured by GC-MS.

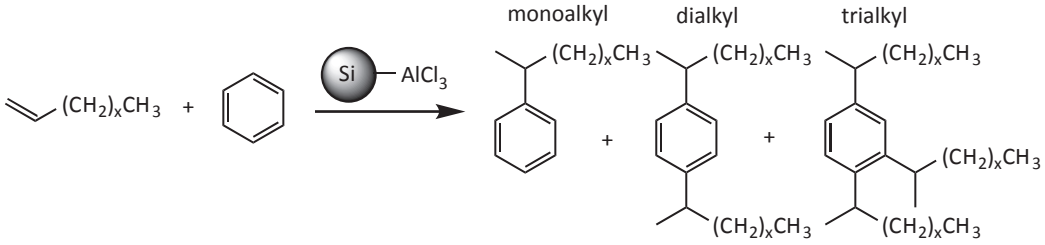
When using 1-iodopentane, yields ranging from 79 to 89 % were acheived with various alcohols, and from 75 to 94 % when using benzylbromide.

Friedel-Crafts Alkylation of Benzene (*Si-AlCl$_3$*): Comparative Study with Homogeneous AlCl$_3$

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. However, the use of these catalysts presents severe problems. For example, aluminum chloride is difficult to separate after reaction and produces a large amount of waste effluent.

General Procedure

Silia*Bond* AlCl$_3$ (0.04 mmol; *0.03 equiv*) was stirred into anhydrous benzene (*typical reaction solvent volume: 5 mL/g of Silia*Bond* AlCl$_3$*). The alkene (*1.18 mmol; 1.0 equiv*) was slowly added (*a small exothermic reaction could be observed*). After the addition was completed, the catalyst was removed by filtration and washed 3 times with anhydrous benzene.



Friedel-Crafts Alkylation Results

Alkene	Catalyst	Alkene Conversion[a] (*in %*)	Selectivity Towards Alkylbenzene (*in %*)		
			Mono	Di	Tri
1-Hexene	AlCl$_3$	100	59	31	10
	Si-AlCl$_3$	100	**71**	28	1
1-Decene	AlCl$_3$	100	69	23	9
	Si-AlCl$_3$	100	**80**	20	0

[a] Conversion determined by GC-MS

As seen in the above table, althought all reactions could be run to completion, selectivity toward the mono-alkylbenzene was much improved when using Si-AlCl$_3$, compared to homogeneous AlCl$_3$.

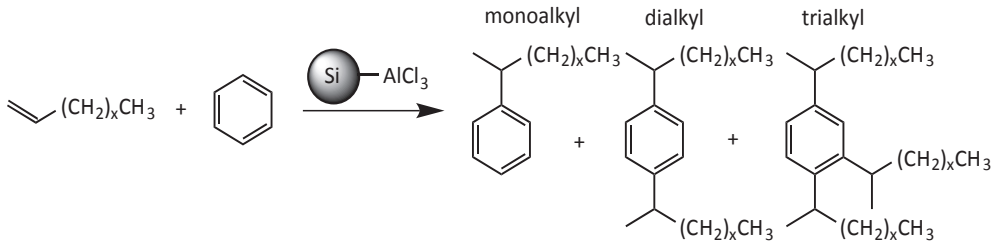
Comparative Study of Alkylation in Flow Chemistry

General Procedure (*conventional - batch*)

1-decene (*1.00 mmol; 1.0 equiv*) was added slowly (*over 30 min*) to a mixture of anhydrous benzene (*20 mmol; 20 equiv*) and Silia*Bond* $AlCl_3$ (*0.20; 0.2 equiv*). After the addition, the catalyst was removed by filtration and the crude product was analyzed by GC-MS.

General Procedure (*flow*)

A mixture of 1-decene (*1.00 mmol; 1.0 equiv*) and anhydrous benzene (*20 mmol; 20 equiv*) was pumped in a reactor charged Silia*Bond* $AlCl_3$ (*0.2 mmol; 0.2 equiv*). After completion of the reaction the mixture was analyzed by GC-MS.



Friedel-Crafts Alkylation Results

Ratio 1-Decene vs Benzene	Catalyst (*equiv*)	Time (*min*)	Flow Conditions			Conversion & Selectivity (%)			
			Flow (*µL/min*)	Vol. Reactor (*mL*)	Res. Time (*min*)	Conv.	Mono	Di	Tri
1:20	0.2	30	Conventional (*Batch*)			100	85	15	0
		20	250	0.76	3	100	89	11	0

Albeit both methodologies gave complete conversion, better selectivity could be reach using the microwave.

Deprotection Reactions

Deprotection of Methoxymethyl Groups (*Si-SCX*)

MOM groups are used as a protecting group for alcohols. The group can be removed using an acid. In this application Silia*Bond* Tosic Acid (*SCX*) has been used to deprotect alcohols previously protected by chloromethyl methyl ether.

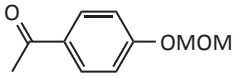
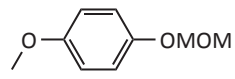
General Procedure (*conventional - batch*)

A mixture of 1-(4-(MOM)phenyl)ethanone (*2.50 mmol; 1.0 equiv)* and Silia*Bond* Tosic Acid (*0.13 mmol; 0.05 equiv)* in 10 mL of toluene / H_2O (*10:0.5*) was stirred at 65°C for 4 h. The reaction mixture was filtered and the solvent was evaporated. The crude product obtained was analyzed by GC-MS.

General Procedure (*flow*)

The reactor was filled with the desired amount of Silia*Bond* Tosic Acid and stirred at r.t. or heated at 65°C using toluene as solvent. A solution of 12.5 mmol of 1-(4-(MOM)phenyl)ethanone in 50 mL of toluene was introduced in a glass bottle connected directly to a pump. A second glass bottle, connected to another pump, was filled with solvent. The flow for the two pumps was different: 100 µL/min for the first pump and 20 µL/min for the second pump. Upon completion of the reaction, the mixture was evaporated and the crude product was analyzed by GC-MS.

Deprotection of Methoxymethyl (*MOM*) Group using Silia*Bond* SCX Results

Substrate	Catalyst (*equiv*)	Time (*h*)	Solvent	Flow Conditions: Flow (*µL/min*)	Flow Conditions: Vol. Reactor (*mL*)	Conversion (*%*) (*Yield %*)
	0.5	2	Toluene / MeOH (*0.25M*)	Conventional (*Batch*)		100 (*90*)
	0.05	4				93 (*83*)
	0.44	2	Toluene / MeOH (*0.25M*)	100	2.4	100 (*100*)
	0.1	9		120		100 (*99*)
	0.5	3	CH_2Cl_2 (*0.1 M*)[a]	50		98 (*91*)
	0.5	2		100		97 (*90*)
	0.35	2	Toluene / MeOH (*0.25M*)	100	2.4	99 (*88*)

[a] at room temperature

At equivalent conditions, better yields could be obtained using flow chemistry. Even when using a fifth of the catalyst mol %, better yields were achieved, albeit needing higher reaction times.

Ordering Information for Batch Reactor Mode (*Bulk*)

All Reagents are available in the following sizes: 5 g, 10 g, 25 g, 50 g, 100 g, 250 g, 500 g, 1 kg, 5 kg, 10 kg, 25 kg, etc. Up to multi-ton scale!

All Particle Size and Pore Size are respectively 40 - 63 µm and 60 Å. Other matrices are available upon request.

SiliaBond Reagents	
Reagent Name	Reagent Product Number
SiliaBond $AlCl_3$	R74530B
SiliaBond Amine	R52030B
SiliaBond Carbodiimide	R70530B
SiliaBond Carbonate	R66030B
SiliaBond Cyanoborohydride	R66730B
SiliaBond Dichlorotriazine	R52230B
SiliaBond Dimethylamine	R45030B
SiliaBond Diphenylphosphine	R39030B
SiliaBond DMAP	R75630B
SiliaBond EDC	R70630B
SiliaBond Guanidine	R68230B
SiliaBond HOBt	R70730B
SiliaBond Maleimide	R71030B
SiliaBond Morpholine	R68030B
SiliaBond Piperazine	R60030B
SiliaBond Piperidine	R71530B
SiliaBond Tosic Acid	R60530B
SiliaBond Tosyl Chloride	R44030B

SiliaBond Oxidants	
Oxidant Name	Oxidant Product Number
SiliaBond $KMnO_4$	R23030B
SiliaBond PCC	R24030B
SiliaBond PDC	R24530B

SiliaBond Acids & Bases	
Acid / Base Name	Acid / Base Product Number
SiliaBond Carboxylic Acid	R70030B
SiliaBond Propylsulfonic Acid	R71230B
SiliaBond Tosic Acid	R60530B
SiliaBond Amine	R52030B
SiliaBond Carbonate	R66030B
SiliaBond Dimethylamine	R45030B
SiliaBond Guanidine	R68230B
SiliaBond Morpholine	R68030B
SiliaBond Piperazine	R60030B
SiliaBond Piperidine	R71530B

SiliaBond Linkers	
Linker Name	Linker Product Number
SiliaBond Allyl	R53530B
SiliaBond Bromophenyl	R55030B
SiliaBond Glycidoxy	R36030B
SiliaBond Phenylmethylchloride	R56530B
SiliaBond Propyl Bromide	R55530B
SiliaBond Propyl Chloride	R59030B

Ordering Information: Available Kits

For screening purposes, especially if you are new to this technology, we have convenient kits for testing various funtionalities and various experimental conditions, to select the ones that best fit your synthetic application.

All these kits are procurable in 5 g, 10 g, 25 g, 50 g and 100 g formats
(*custom formats are also available, contact us for more details*).

How to Order

Simply note the **Product Number** which starts with "**K**", add a dash mark and your choice of format, e.g.: **K30330B-10G** to obtain **10G** of each one of the scavenger listed in the kit.

All following kits have all been designed for definite needs:

SiliaBond Kits		
Kit Name	**Kit PN**	**Composition**
SiliaBond Base Kit	K31630B	Amine, Carbonate, Dimethylamine, Diethylamine, Morpholine, Pyridine & Guanidine
SiliaBond Oxidant Kit	K30330B	Potassium Permanganate, TEMPO, Pyridinium Chlorochromate & Pyridinium Dichromate
SiliaBond Reversed-Phase Kit	K32530B	C8 mono, C18 (*17 %*), C18 (*17 %*) Mono, C18 (*23 %*), Cyano & Phenyl
SiliaBond Acid Kit	K31330B	Carboxylic Acid, Propylsulfonic Acid, TAAcOH & Tosic Acid
SiliaBond Reagent Kit	K32230B	Carbodiimide, Cyanoborohydride, Dichlorotriazine, DMAP, EDC & HOBt
SiliaBond Ion Exchanger Kit	K31430B	WAX, WCX, SCX-2, SCX, SAX & TMA Acetate