

SiliaBond®

Compatibility With
New Technologies



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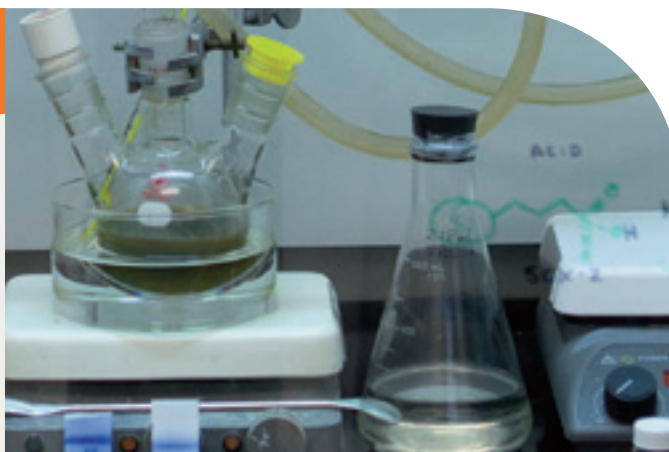
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Flow Chemistry Applications

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

- Increase in R&D and manufacturing productivity
- Separation of the catalyst from the products does not require any filtration (*or further handling*)
- Flow-through processes are more reliable and safer than in batch
- SiliaBond, SiliaCat and SiliaMetS can be used without degradation



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 a short time. 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 stabilities and ease of scalability. SiliCycle has developed innovative silica-based catalysts (SiliaCat), reagents (SiliaBond) and metal scavengers (SiliaMetS) that can be used in flow chemistry.

Acylation Reactions Using SiliaBond DMAP

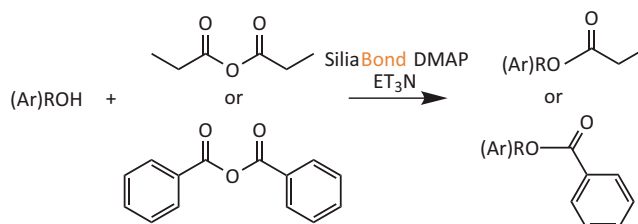
Acylation reactions can generate esters using activated carboxylic acids (*acids chlorides*) and alcohols, even hindered tertiary alcohols.

General Procedure (*conventional - batch*)

Typical reaction: acetylation of 1-phenyl-1-propanol. A mixture of 6 mmol of substrate, 1.5 eq. of acetic anhydride, 1.5 eq. of triethylamine and 5 mol % SiliaBond DMAP 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.

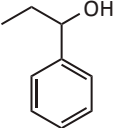
General Procedure (*flow*)

Typical reaction: acetylation of 1-phenyl-1-propanol. A mixture of 4 mmol of substrate, 1.5 eq. of acetic anhydride, 1.5 eq. of triethylamine in 10 mL of CH_2Cl_2 was stirred at room temperature for 5 minutes. Two fractions of 5 mL solution were introduced into the reactor charged with the 9 mol % SiliaBond DMAP (0.45 g). Upon completion of the reaction, the mixture was analyzed by GC-MS to determine the conversion.





Acylation Reactions Using SiliaBond DMAP (con't)

Acylation Reaction Results								
Substrate	Reagent	Catalyst (eq.)	Time (h)	Flow Conditions			Conversion (%) (Yield %)	
				Flow ($\mu\text{L}/\text{min}$)	Vol. Reactor (mL)	Res. Time (min)		
2-Octanol	Ac ₂ O	5	2	Conventional (Batch)			98 (99)	
		9	1.67 0.93	100.0 200.0	0.7	7.0 3.5	100 (99) 98 (99)	
	Bz ₂ O	10	24	Conventional (Batch)			91	
		9	6.67 13.3	25.0 12.5	0.7	28 56	93 (95) 95 (97)	
		Ac ₂ O	5	1.5	Conventional (Batch)			98 (99)
			9	3.30 1.67 0.83	50.0 100.0 200.0	0.7	14.0 7.0 3.5	97 (99) 97 (99) 97 (99)
Bz ₂ O			5	24	Conventional (Batch)			88
		9	1.67 3.38 6.67	100.0 50.0 25.0	2.38	24 48 96	88 (98) 94 (99) 97 (99)	
		Ac ₂ O	6	24	Conventional (Batch)			67
9			3.33 6.67 16.67	50.0 25.0 10.0	2.38	48 96 239	27 (97) 40 (97) 61 (95)	

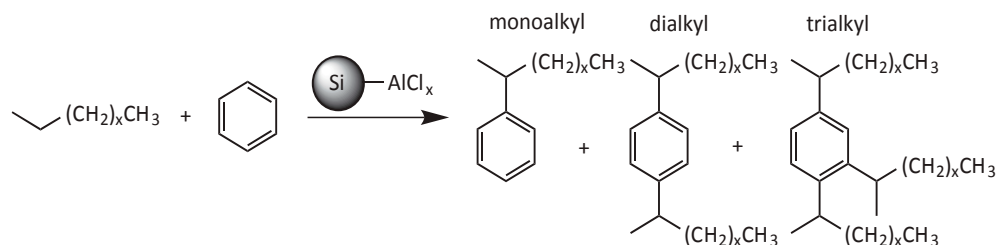
Friedel-Craft Alkylations Using SiliaBond Aluminum Chloride

General Procedure (conventional - batch)

1 eq. of 1-decene was added slowly (over 30 min) to a mixture of anhydrous benzene (20 eq.) and 0.02 eq. of SiliaBond Aluminum Chloride (1.67 mmol/g). 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 eq. of 1-decene and 20 eq. of anhydrous benzene was pumped in a reactor charged with 0.2 eq. of SiliaBond Aluminum Chloride. After completion of the reaction the mixture was analyzed by GC/MS.



Friedel-Craft Alkylation Results									
Ratio 1-Decene vs Benzene	Catalyst (eq.)	Time (min)	Flow Conditions			Conversion & Selectivity (%)			
			Flow ($\mu\text{L}/\text{min}$)	Vol. Reactor (mL)	Res. Time (min)	Conv.	Mono	Di	Tri
1:20	0.2	30	Conventional (Batch)			100	85	15	0
	0.2	20	250	0.76	3	100	89	11	0

Knoevenagel Condensations using SiliaBond Piperidine

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 2 mmol of benzaldehyde, 1.5 eq. of ethylcyanoacetate and 10 mol % of SiliaBond Piperidine 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 10 mol % of SiliaBond Piperidine (7.36 g) and heated at 110°C using toluene as solvent. A mixture of 15 mmol of benzaldehyde, 1.5 eq. of ethylcyanoacetate in 110 mL of toluene was stirred at room temperature for 5 minutes. The mixture was then introduced in a glass bottle directly connected to the pump. Upon completion of the reaction, the reaction mixture was evaporated 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)			80 (98)
2	55	1.67	50	0.7	14	82 (99)
3	4	25	50	0.7	14	75 (99)
4	10	19	100	2.4	24	90 (100)





Deprotection of Methoxymethyl Groups using SiliaBond SCX

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

General Procedure (conventional - batch)

A mixture of 2.5 mmol of 1-(4-(MOM)phenyl)ethanone and 0.05 eq. of SiliaBond Tosic Acid (0.8 mmol/g) in 10 mL of toluene/H₂O (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 SiliaBond Tosic Acid and heated at room temperature or 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 SiliaBond SCX Results

Substrate	Catalyst (eq.)	Time (h)	Solvent	Flow Conditions			Conversion (%) (Yield %)
				Flow (µL/min)	Vol. Reactor (mL)	Res. Time (min)	
	0.5	2	Toluene/MeOH (0.25M)	Conventional (Batch)			100 (90)
	0.05	4	Toluene/MeOH (0.25M)	Conventional (Batch)			83 (93)
	0.44	1.67	Toluene/MeOH (0.25M)	100	2.4	24	100 (100)
	0.1	8.34	Toluene/MeOH (0.25M)	120	2.4	17.5	99 (100)
	0.5	3.33	CH ₂ Cl ₂ (0.1 M) ^a	50	2.4	48	91 (98)
	0.5	1.67	CH ₂ Cl ₂ (0.1 M) ^a	100	2.4	24	90 (97)
	0.35	1.67	Toluene/MeOH (0.25M)	100	2.4	24	88 (99)

^aat RT.

Microwave Applications

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

- Faster kinetics: only a few minutes per reaction
- Higher yields and excellent purities
- Compatibility with many solvents
- SiliaBond, SiliaCat and SiliaMetS can be used without degradation
- Wide variety of reactions and applications

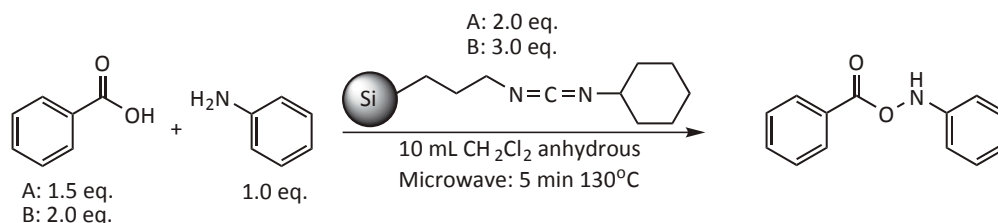


Importance of Microwave Assisted Synthesis

In recent years, microwave synthesizers have taken organic chemistry by storm. Fast kinetics, higher yields, excellent purities, wide compatibility of solvents and their applicability to a variety of reactions and applications, make them very important 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 SiliaBond Reagents as well as an electrophile and nucleophile that demonstrate the effectiveness of these reagents for microwave applications.

Amide Couplings using SiliaBond Carbodiimide



Amide Coupling Yield^a (Purity)^b in %

Method	Microwave	Bulk (RT, 24 h)
A	73.3 (88.0)	52.7 (99.5)
B	94.9 (95.0)	80.1 (98.1)

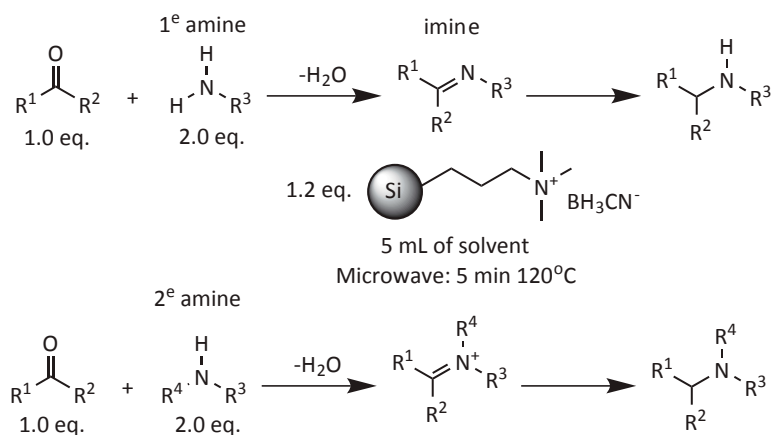
^aDetermined from GC-FID,

^bRefers to the isolated product



Reductive Aminations using SiliaBond Cyanoborohydride

General Procedure



Acylsulfonamide Synthesis Conversion (%) Results

Amine	Carbonyl	Microwave ^a	Bulk (RT, 2.5 eq. <i>Si</i> -CBH) ^a	
		5 min	1 h	24 h
Piperidine	Benzaldehyde	> 99	80	> 99
N-Benzylmethylamine	Benzaldehyde	> 99	97	> 99
3-Phenyl-1-propylamine	Cyclohexanone	> 99	88	87

^aConversion determined by GC-FID

Henry Reactions using SiliaBond Carbonate

General Procedure

1-nitropropane (1 eq.) was added to a solution containing THF (5 mL) and valeraldehyde (1 eq.). To this reaction mixture, SiliaBond Carbonate (0.1 eq.) was added and maintained at 100°C for 10 min in the microwave. The reaction mixture was 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).

