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Single-Pass Reaction Column System with Super Brønsted Acid-loaded Resin

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Abstract: Various acid-promoted reactions gave the desired products in high yields by passing a solution of reactants through a reaction column packed with polystyrene-bound super Brønsted acid (1) just once. Polar and nonpolar organic solvent-swellable 1 is much superior to Nafion[®] SAC-13 (2) as a Brønsted acid-loaded resin packed in the column.

Key words: Brønsted acid, reaction column, flow system, resin, catalyst

Resin-bound catalysts offer several advantages in preparative procedures. Simplification of product workup, separation, and isolation as well as reuse of the catalyst could lead to an economical automation system. Although the use of immobilized homogeneous catalysts is of interest, there are few known examples of polymer-bound super Brønsted acids.^{1,2} Recently, we succeeded in preparing polystyrene-bound super Brønsted acid (1).¹ It has been ascertained that 1 is effectively swollen by both polar and nonpolar organic solvents, and its catalytic activity for various organic reactions is superior to that of Nafion®-H/ silica nanocomposite [Nafion® SAC-13 (2)],³ which has a 10⁴-fold higher surface area than Nafion[®]-H beads (Nafion[®] NR50) (Scheme).¹ However, as **1** is repeatedly reused in a batch system, it becomes more difficult to recover 1 by filtration, since vigorous agitation degrades the resin beads. To avoid physical degradation of the resin beads, we applied **1** to a flow reaction system.^{4,5} In this Letter, we demonstrate that various acid-promoted reactions proceed to afford the desired products in high yields by passing a solution of reactants through a reaction column packed with 1 just one time ('single-pass reaction column system').





Figure shows the column catalysis assembly we designed for this purpose. A 2-mL syringe attached to a syringe fil-

Synlett 2002, No. 8, Print: 30 07 2002. Art Id.1437-2096,E;2002,0,08,1296,1298,ftx,en;G12602ST.pdf. © Georg Thieme Verlag Stuttgart · New York ISSN 0936-5214 ter was used as a reaction column. A mixture of **1** [1.05 mmol H⁺/g resin: polystyrene, 2% cross-linked with divinylbenzene cross-linker, 38-75 μ m (200-400 mesh)] and Celite[®] 545 (17 μ m) was packed in a 2 mL syringe, and a solution of reactants was passed through the reaction column. Super Brønsted acid-loaded resin **1** could be easily isolated from a mixture of **1** and Celite[®] based on the difference in their specific gravity: while **1** floats on water, Celite[®] sinks.



Figure Single-pass reaction column assembly.

We tested the reaction column packed with 9.5 mg of 1 (0.01 mmol) and 500 mg of Celite[®] 545 in acetylation reaction (1 mmol-scale) of alcohols with acetic anhydride (Table 1).⁶ First, the column was flushed with 2 mL of acetonitrile under air. An ambient-temperature solution of Lmenthol (1 mmol) and acetic anhydride (1.5 mmol) in acetonitrile (2 mL) was added to the column. The reaction was initiated by allowing the reactant mixture to percolate through the reaction column. Additional acetonitrile (10 mL) was added to allow complete elution of the column contents. After passing through the reaction column over 1 h (flow rate, 0.2 mL/min), the eluted reaction mixture was concentrated to afford L-menthyl acetate in quantitative yield. 2,4,6-Trimethylphenyl acetate was also obtained in quantitative yield in a similar manner. Acetylation of 2,6-di-tert-butyl-4-methylphenol was relatively slow, but the corresponding ester was obtained in 73% yield by allowing the eluents to flow under gravity without pressurization (0.8 mL/h). It was noted that 1 was much more effective than 2.4

The reaction column with 1 was effective for the esterification of carboxylic acids with methanol.⁷ For instance, methyl 3-phenylpropionate was obtained in 53% yield by

Table 1	Acetylation	of Alcohols	with Acetic	Anhydride
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ROH + AcoO	[1 (9.5 mg, 1 mol%)+Celite [®] (500 mg)] → ROAc			
1 mmol 1.5 mmol	MeCN, rt, flow			
ROH	Flow rate	Yield (%) ^a		
OH 	0.2 mL/min	99 [6]		
-C-R ¹ OH	0.1 mL/min 0.8 mL/h	>99 [12] 73 [<5]		
$R^{1} = Me$ $R^{1} = t - Bu$				

^a Yield in using 2 (9.5 mg) in place of 1 is indicated in brackets.

passing through 1 (5 mol%) just once. On the other hand, 2 was much less effective for this esterification (Equation 1).



Equation 1

Acetalization with trialkyl orthoformates also proceeded very well by passing through **1**.⁸ In particular, trimethyl-orthoformate is very reactive, and 2,2-dimethoxy-4-phen-ylbutane was obtained quantitatively by passing through **1** (1 mol%) just once (Equation 2).



Equation 2

The single-pass reaction column system was used for an in situ acetal exchange reaction of benzylacetone or 3-phenylpropionaldehyde with diols in the presence of trimethylorthoformate (Table 2).⁸ Most cyclic acetals were obtained in good yield by passing through **1** (1 mol%). Acetonitrile was useful as a solvent to dissolve diols.

To demonstrate the usefulness and effectiveness of the single-pass reaction column system, its catalytic activities in several other important synthetic reactions were com-





^a Yield in using 2 (9.5 mg) in place of 1 is indicated in brackets.

pared with those of Nafion[®] SAC-13 (Equations 3–6). The reaction column containing **1** was highly active and reusable for all of the reactions examined: the Mukaiyama aldol reaction (Equation 3), the Sakurai–Hosomi allylation reaction (Equation 4), the Mukaiyama–Michael addition reaction (Equation 5), and the Mukaiyama aldol-type reaction of benzaldehyde dimethylacetal (Equation 6). The catalytic activity of **1** in the flow system as well as in the batch system¹ was superior to that of **2**, which may be the strongest Brønsted acid among the known solid acids. Hydrolysis of trimethylsilyl ethers obtained in Equations 3–5 was also carried out by passing a solution of crude products in H₂O–THF [1:5 (v/v)] through the same reaction column containing **1**.















Equation 6

In conclusion, a single-pass reaction column system was realized based on the extremely high catalytic activity of 1.¹ Although the present system can be applied to a continuous-flow reaction system, in most cases products can be obtained in high yield by passing through the reaction column with 1 just once. The use of the reaction column greatly simplifies the purification of the crude reaction mixture, allowing for shorter production times and thus lower costs under certain circumstances. In particular, a single-pass reaction column system at ambient tempera-

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