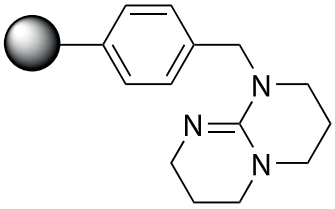
Biotage® PS-TBD

Polymer-Supported Base



Key Facts

Stoichometric

Shelf Life

Capacity (mmol/g)

BSE/TSE

Scalable

Particle Size (µm)

Thermally & Mechanically Stable

Good Laboratory Practice

Bulk Density (g/L)

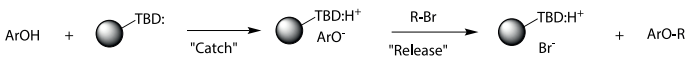
Specifications

Chemical Name:	1,5,7-triazabicyclo[4.4.0]dec-5-ene polystyrene
Resin Type:	1% Cross-linked poly(styrene-co-divinylbenzene)
Application:	Alkylation of phenols and amines; esterification of carboxylic acids using alkyl halides; alkylation of activated methylene compounds; dehalogenation of organic halides; high throughput synthesis of aryl triflates and aryl nonaflates; Williamson ether synthesis
Typical Application Conditions:	2–3 equiv. relative to limiting reagent
Compatible Solvents:	Dichloromethane (DCM), Acetonitrile (MeCN), Acetone, Ethyl Acetate (EtOAc), N,N-Dimethylformamide (DMF), Dimethylsulfoxide (DMSO)

Biotage® PS-TBD is a polymer-supported base, which consists of a bicyclic guanidine moiety (1,5,7-triazabicyclo[4.4.0]dec-5-ene) anchored on polystyrene. Published applications of PS-TBD include alkylation of phenols[1] and amines;[2] esterification of carboxylic acids using alkyl halides; alkylation of activated methylene compounds; de-halogenation of organic halides;[3] high throughput synthesis of aryl triflates and aryl nonaflates,[4] and the regioselective synthesis of lysophospholipids.[5]

In alkylation reactions, the resin may be used in a “catch and release” protocol, whereby an acidic species is caught on the PS-TBD resin as a solid-supported nucleophile (e.g. phenol forming a bound phenolate). On reaction with an electrophile, the product is released into solution. By using the electrophile as the limiting reagent, full conversion to product can be achieved, while the excess nucleophile remains bound to the resin. Filtration and solvent evaporation affords the desired product in high purity.

The Williamson[6] ether synthesis was discovered in the mid 19th Century and to date it remains one of the best ways to synthesize unsymmetrical ethers. The original conditions were harsh and required prolonged heating in basic environments. Recent modifications for reactions below 100 °C, involve addition of alkyl derivatives of Brönsted acids, such as alkyl sulfates[7]. Not only is the removal of salt following the reaction involve an additional step, which may be problematic, but these are often carcinogenic and pose health and safety issues at scale.



Scheme 1. Mode of action of PS-TBD resin

PS-TBD resin can facilitate Williamson ether synthesis at room temperature using very mild conditions, as it is effective at deprotonating moderately acidic hydrogen (up to pKa ca 13). The resin may also be used for the N-alkylation of aryl halides, esterification of carboxylic acids, and alkylation of acidic methylenes.[8]

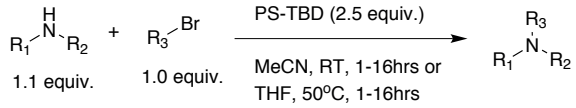
PS-TBD is stable under bench conditions and can be dispensed using standard laboratory tools (spatulas, Biotage Argoscoop). The resin may be stored at room temperature for extended periods.

Biotage®

Representative Procedures

Synthesis of Tertiary Amines by Reaction of Secondary Amines with Activated Alkyl Bromides

A series of tertiary amines was synthesized by reaction of secondary amines with activated alkyl bromides in the presence of PS-TBD (Scheme 2). The amine was used in slight excess (1.1 equiv.) of the alkyl bromide and best results were obtained with 2.5 equivalents of PS-TBD. The choice of solvent and temperature of the reaction was found to be important, with optimal conditions provided by THF at 50 °C or MeCN at room temperature. Complete conversion of the alkyl bromide occurred in 16 h to afford a mixture of the desired tertiary amine and residual secondary amine (ca. 0.1 equiv.)



Scheme 2. Synthesis of tertiary amines by reaction of secondary amines with activated alkyl bromides.

The excess secondary amine was selectively scavenged from the mixture by the addition of MP-Isocyanate (a macroporous scavenger for amines) and subsequent stirring at room temperature. MP-Isocyanate was used because of its high reactivity in MeCN. Filtration and concentration afforded the desired tertiary amines as homogeneous products in good-to-excellent yields (Table 1). While the conditions for the synthesis of the amines may be generalized for certain substructures, the effect of the substrates needs to be considered. For example, the reaction of dibutylamine with both ethyl α-bromoacetate and 4´-bromobenzyl bromide afforded higher yields in MeCN at room temperature than in THF at elevated temperatures (71% vs. 30% and 70% vs. 60%, respectively). The low yield and high purity in THF may be due to loss of the volatile amine at elevated temperatures in conjunction with reaction of the resultant excess alkyl bromide with the resin to form a bound quaternary salt. In contrast, the reaction of indole-3-carboxaldehyde with 4-bromobenzyl bromide afforded higher yields in THF at 50 °C than in MeCN (90% vs. 33%).

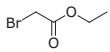
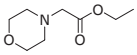
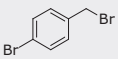
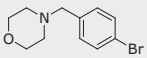
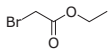
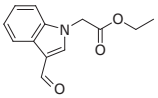
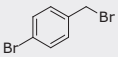
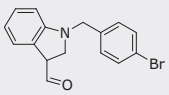
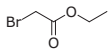
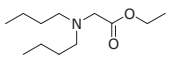
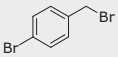
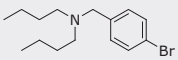
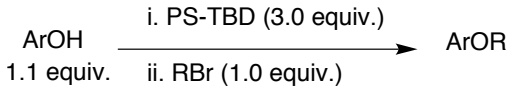
Amine	Electrophile	Product	MeCN RT, 16 h		THF 50 °C, 16 h	
			% Yield	% Purity	% Yield	% Purity
			84	100	64	100
			83	100	87	100
			68	100	79	100
			33	100	90	100
			71	100	30	100
			70	100	60	100

Table 1. Results of amine alkylation using PS-TBD resin.



Scheme 3. The use of PS-TBD resin in the Williamson ether synthesis.

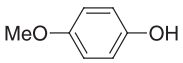
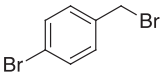
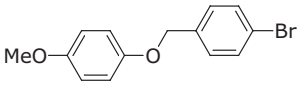
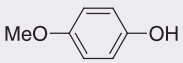
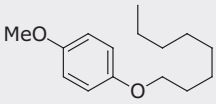
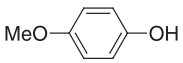
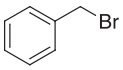
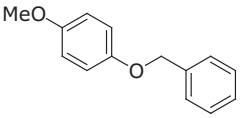
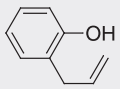
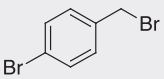
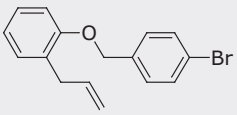
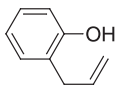
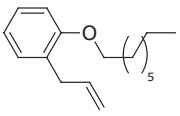
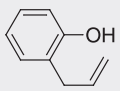
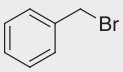
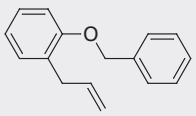
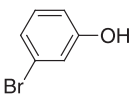
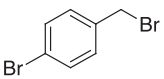
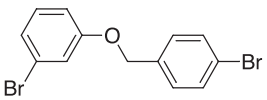
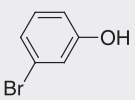
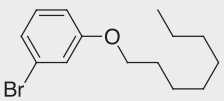
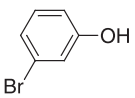
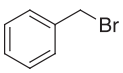
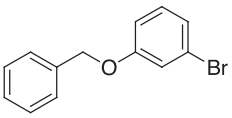
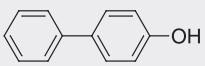
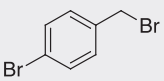
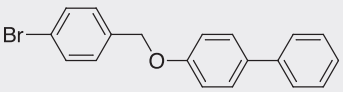
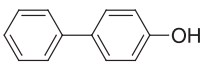
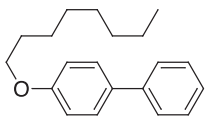
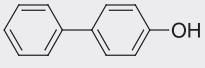
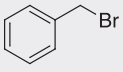
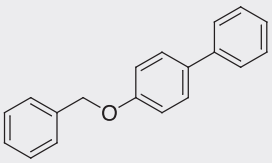
Phenol	Electrophile	Product	MeCN 55 °C 16 h		THF RT 16 h	
			% Yield	% Purity	% Yield	% Purity
			89	100	87	100
			97	100	63	45
			91	100	90	100
			95	100	38	89
			94	100	88	100
			96	100	89	100
			90	100	45	17
			92	100	66	42
			91	100	77	100
			90	100	77	100
			85	100	91	100
			88	100	90	100

Table 2. Results of Williamson Ether Synthesis using PS-TBD.

Williamson Ether Synthesis

The use of PS-TBD in Williamson ether synthesis was investigated as an example of a catch-and-release protocol. A series of phenols was incubated with PS-TBD and then treated with a series of alkyl bromides as the limiting reagent (Scheme 2). The reaction was initially examined using 1.5 and 3 equivalents of PS-TBD. The phenols were incubated with PS-TBD for an hour to generate bound phenolates. The alkyl bromides were then added. Three equivalents of PS-TBD resin afforded complete conversion of bromides to aryl ethers, which after filtration and concentration were of high purity. [The same reactions carried out with 1.5 equivalent of PS-TBD resulted in phenol contamination in the majority of cases]. Since 3 equivalents of PS-TBD was more effective at sequestering the phenol from the final reaction mixture as bound phenolate, it was chosen for a more complete series of aryl ethers using both THF and MeCN as solvents (Table 2, page 3).

In contrast to PS-TBD mediated tertiary amine synthesis, the use of MeCN in the Williamson ether synthesis was demonstrated to be effective only at elevated temperature. Heating these reactions in MeCN to 55 °C for 16 h was optimal and generated the ethers in excellent purities and in high yields, in comparison with the corresponding reactions carried out in THF. Reactions in THF were effective at room temperature; however, the product yield and purity were variable. In cases where low purity products were obtained, mixtures of unidentified by-products were observed.

To demonstrate the formation of bound phenolate using PS-TBD, a 0.3 M solution of 4-methoxyphenol in MeCN was mixed with 1 equivalent of the resin. The solution was sampled and the concentration of 4-methoxyphenol was measured relative to an internal standard. After 2 h, the resin had sequestered 84% of the 4-methoxyphenol from solution. The solid-supported phenolate was then drained and washed with MeCN. Analysis showed that no. 4-methoxy-phenol was lost from the PS-TBD in this process. This indicates that the phenolate PS-TBD salt is stable to MeCN washing. In a similar set of experiments, the uptake of phenol by PS-TBD in THF was about half of that observed in MeCN.

Alkylation of Secondary Amines Using PS-TBD Resin

PS-TBD resin (0.28 mmol, 2.5 equivalents, 200 mg, 1.4 mmol/g) was incubated with a solution of amine (0.12 mmol, 1.1 equivalent, 0.49 mL, 0.25 M) in each of THF and MeCN for 1 h. (Note: shorter equilibration times are likely to be equally effective.) A solution of halide (0.11 mmol, 1.0 equivalent., 0.45 mL, 0.25 M) was added to each of the reaction vessels followed by 1 mL of either THF or MeCN to make up a total volume of 2 mL. Reactions in THF were performed at 50 °C for 16 h and reactions carried out in MeCN were performed at room temperature for 16 h. To each of the vessels was then added MP-Isocyanate scavenger (0.99 mmol, 10 equivalents, 570 mg, 1.73 mmol/g) and the reactions agitated at room temperature for a further 16 h and filtered. The filtrate was concentrated and the purities determined by GC and structures confirmed by ^{1}H NMR.

Alkylation of Phenols Using PS-TBD Resin

PS-TBD resin (0.34 mmol, 3.0 equivalents, 240 mg, 1.4 mmol/g) was incubated with a solution of phenol (0.12 mmol, 1.1 equivalent, 0.49 mL, 0.25 M) in each of THF and MeCN for 1 h. A solution of halide (0.11 mmol, 1.0 equivalent, 0.45 mL, 0.25 M) was added to each of the reaction vessels, followed by 1 mL of either THF or MeCN, to make up a total volume of 2 mL. Reactions in THF were carried out at room temperature for 16 h and reactions in MeCN were carried out at 55 °C for 16 h. The reaction solutions were filtered, the filtrate was concentrated and the purities determined by GC and structures confirmed by ^{1}H NMR.

Ordering Information

Part Number	Quantity
800513	3 g
800421	10 g
800422	25 g
800423	100 g
800424	1000 g

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