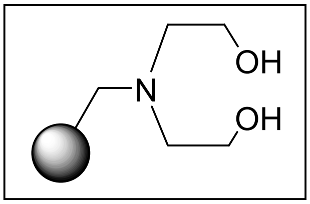


Polymer-Bound Diethanolamine

PS-DEAM

Application:	Scavenging oxophilic metal complexes, including boronic acids, titanium(IV) chloride, titanium(IV) isopropoxide, and tin (IV) chloride.
Typical Boronic Acid Scavenging Conditions:	2 – 3 equivalents of PS-DEAM relative to boronic acid at room temperature for 4 h.
Typical Titanium(IV) Chloride Scavenging Conditions:	4.5 equivalents of PS-DEAM and PS-DIEA relative to $TiCl_4$ at room temperature for 4 h.
Typical Titanium(IV) Isopropoxide Scavenging Conditions:	2 equivalents of PS-DEAM relative to $Ti(O^iPr)_4$ at room temperature for 16 h.
Compatible Solvents:	THF (7.5 mL/g), DCM (4.0 mL/g), MeOH (3.0 mL/g), DMF (6.7 m/g). PS-DEAM can also be used in THF-EtOH, THF-MeOH mixtures.
Storage:	Storage in closed container at room temperature is recommended. Drying resin in a vacuum desiccator is recommended before use in titanium scavenging applications.

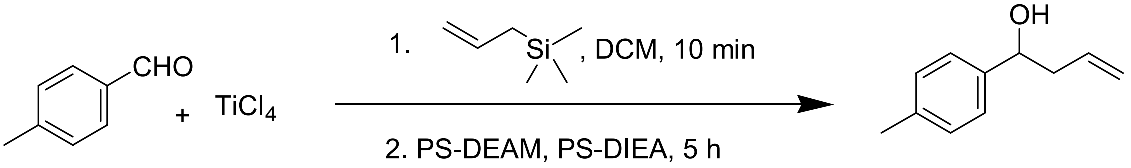
PS-DEAM is a polystyrene-bound diethanolamine, which is a resin-bound equivalent of the tridentate (N, O, O) N-alkyldiethanolamine ligand. PS-DEAM is an effective scavenger for a variety of oxophilic organometallic and inorganic complexes. The resin can be used to quench reactions and remove metallic reagents, catalysts or byproducts, allowing the purified product to be isolated by filtration. Boronic acids are scavenged by PS-DEAM. This has been exploited in the purification of Suzuki reactions through the removal of excess boronic acid and coupling byproducts.[i, ii]

PS-DEAM is also effective at removing common Lewis acids, including Ti(IV) and Sn(IV) complexes. PS-DEAM has been found to scavenge titanium(IV) chloride from Sakurai[iii] and related reactions. Titanium(IV) chloride and its alkoxide derivatives are widely used as Lewis acid catalysts in a number of important organic reactions. Particularly noteworthy are 1,2 and 1,4 additions of allylsilanes to carbonyl and enone compounds (Sakurai reaction, **Scheme 1**), the Mukaiyama aldol reaction and the Knoevenagel condensation. These reactions require an

PS-DEAM

		PART NUMBER	QUANTITY
Resin Type:	1% crosslinked polystyrene		
Capacity:	1.5 – 2.2 mmol/g diethanolamine (based on nitrogen analysis)	800430	10 g
Bead Size:	75 – 150 µm, 100 – 200 mesh (95% within)	800431	25 g
		800432	100 g
		800433	1000 g

aqueous work-up and filtration of TiO_2 precipitate. This can be problematic. We have found that a cocktail of PS-DEAM (4.5 equiv) and polymer-bound diisopropylethylamine, PS-DIEA (4.5 equiv) effectively quenches and removes titanium tetrachloride from Sakurai reactions, thereby eliminating the aqueous work-up step (**Table 1)**. Thus purification by resin scavenging overcomes the problem of separating the gelatinous titanium hydroxide and oxide salts that are formed when aqueous workup is employed. By analogy, tin(IV) tetrachloride can also be removed from organic solutions by the PS-DEAM/PS-DIEA mixture. PS-DIEA should be used in conjunction with PS-DEAM in cases where coordination of diethanolamine with the metal results in the release of hydrogen halides or other acidic species.



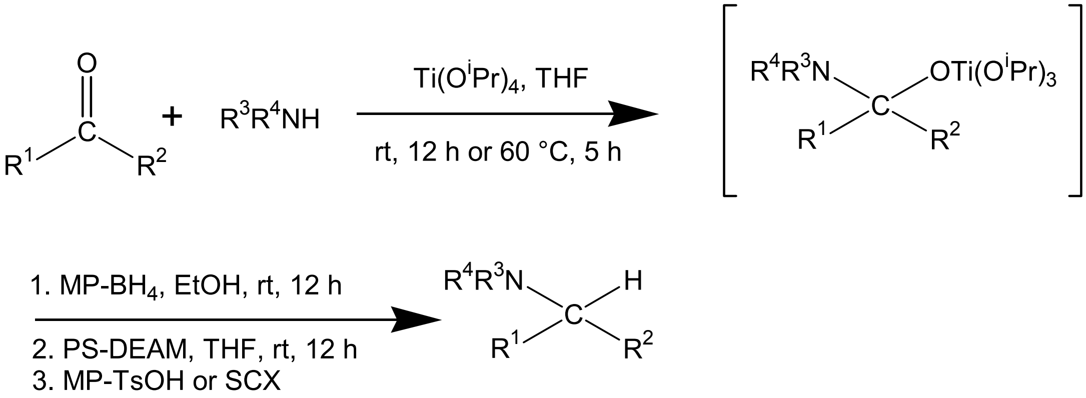
Scheme 1: Scavenging of $TiCl_4$ from 1,2 Addition of Allylsilane

The purification of titanium(IV) isopropoxide-mediated reductive amination reactions forms another important new application of PS-DEAM.[iv] This methodology enables controlled reductive alkylation of primary amines to secondary amines and reductive amination of enolizable carbonyl compounds, acetophenones and sterically hindered carbonyl substrates. Moreover, the neutral reaction conditions are applicable to substrates containing acid-sensitive motifs.

The reaction work-up for titanium isopropoxide-mediated reductive amination typically uses aqueous quenching to precipitate titanium as the gelatinous hydroxide and oxide solid, followed by filtration and liquid-liquid extraction. Purification of these reactions is simplified by using a polymer-supported reducing agent, MP-Borohydride[v], in conjunction with PS-DEAM to scavenge titanium(IV) isopropoxide (**Scheme 2**).

This improved process was demonstrated for a series of reductive aminations using carbonyl compounds with a wide reactivity profile (**Table 2**). A 1:1 ratio of amine:carbonyl was used and the products were purified using PS-DEAM, followed by catch and release using MP-TsOH columns[vi] or commercially available SCX cartridges[vii]. The procedure afforded the desired secondary and tertiary amines in high purity and very good yield. In contrast to our results with MP-Cyanoborohydride, over-alkylation was suppressed when primary amines were reacted with the very reactive cyclohexane carboxaldehyde (**Table 2**, entries 1 and 2). Notably, sterically hindered adamantyl methyl ketone was reactive with primary amines under these conditions (**Table 2**, entries 6 and 7). A secondary amine, 1-methylpiperazine, underwent reductive amination with cyclohexane carboxaldehyde and cyclopentanone (**Table 2**, entries 3 and 5), however, was not reactive with adamantyl methyl ketone. Reactions with 4-(3-aminopropyl)morpholine did not proceed to complete conversion, and scavenging traces of unreacted 4-(3-aminopropyl)morpholine with PS-Benzaldehyde was required (**Table 2**, entries 2, 4, 7). Product amines had titanium levels that were less than the detection limit of 10 ppm and boron levels were ≤ 20 ppm as measured by elemental analysis.

PS-DEAM is hygroscopic, and absorbed water present in the resin can cause precipitation of titanium(IV) oxide when used for scavenging titanium(IV) complexes. It is recommended that the resin be dried under vacuum or in a drying oven (to constant weight) before use in these applications. Once dried, the resin can be stored in a closed bottle.



Scheme 2: Scavenging of $Ti(O^iPr)_4$ with PS-DEAM in Reductive Amination Reactions

Capacity and stability: The capacity of the “diethanolamine” moiety of the resin was calculated from nitrogen elemental analysis. The resin is stable indefinitely at room temperature in a closed container.

Representative Procedure for Scavenging of Titanium(IV) Chloride from Sakurai Reactions (Entry 2, Table 1):

To a solution of cyclohexane carboxaldehyde (56 mg, 0.50 mmol) in DCM (2 mL) was added a solution of titanium(IV) chloride (95 mg, 0.50 mmol) in DCM (2 mL) at room temperature with magnetic stirring under an atmosphere of nitrogen. The mixture was stirred for 5 min and a solution of allyltrimethylsilane (57 mg, 0.60 mmol) in DCM (2 mL) was added. After the resulting mixture was stirred for 10 min, PS-DEAM (1.26 g, 1.75 mmol/g, 2.2 mmol), PS-DIEA (0.6 g, 3.7 mmol/g, 2.2 mmol) and DCM (12 mL) were added and agitated for 5 h to quench the reaction and scavenge titanium(IV) chloride. The solution was filtered and the resin was washed with DCM (10 mL x 2). The combined solution was passed through a short silica gel plug (0.5 g) and the filtrate was concentrated to obtain an oily residue. ^1H NMR analysis of the crude product indicated that it was an 80:20 mixture of the product homo-allylic alcohol and the starting aldehyde. A portion of the filtrate (2 mL) was treated with aqueous NaOH (1 M, 1 mL); no white precipitation was observed, indicating complete scavenging of titanium(IV) chloride.

Typical Procedure for Scavenging of Titanium(IV) Isopropoxide from Reductive Amination Reactions (Entry 3, Table 2) :

A mixture of cyclopentanone (42 mg, 0.50 mmol), titanium(IV) isopropoxide (170 mg, 0.60 mmol) and 2-(aminomethyl)pyridine (54 mg, 0.50 mmol) in dry THF (3 mL) was allowed to stir at room temperature for 16 h (alternatively at 60 °C for 5 h). $MP-BH_4$ (410 mg, 3.0 mmol/g, 1.2 mmol) and dry EtOH (3 mL) were then added and the resulting mixture was stirred at room temperature for 8 h. PS-DEAM (1.2 mmol) and THF (4 mL) were added to scavenge titanium(IV) isopropoxide, and the mixture was agitated for 12 h and passed through a pre-conditioned (DCM) 0.7 g MP-TsOH column.[vi] The flow rate was adjusted to 1 mL/min and maintained at this rate for all subsequent elution steps. The cartridge was washed with DCM (15 mL) and the eluent discarded. The product amine was released using 2 M NH_3/MeOH (4 mL) followed by DCM (15 mL). Alternatively, a 1 g ISOLUTE® SCX-3 cartridge (International Sorbent Technology, IST®) was used in place of the MP-TsOH column. Concentration of the collected solution afforded the product amine. In cases where an excess of starting amine is still present, PS-Benzaldehyde[viii] (for primary amines) or PS-Isocyanate[ix] (for secondary amines) may be used as scavengers for purification in a subsequent step.

Table 1: Scavenging of Titanium(IV) Chloride with PS-DEAM and PS-DIEA from Titanium(IV) Chloride-Mediated 1,2 Addition of Trimethylallylsilane to Carbonyl Compounds:

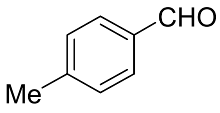
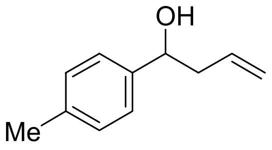
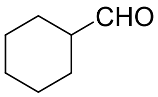
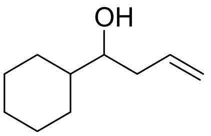
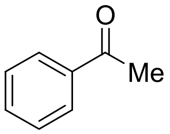
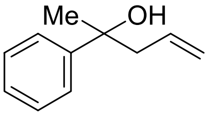
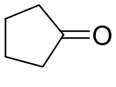
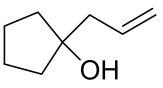
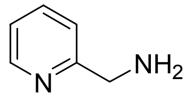
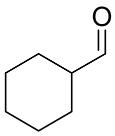
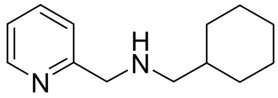
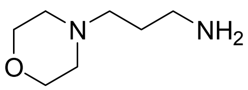
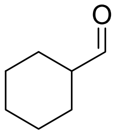
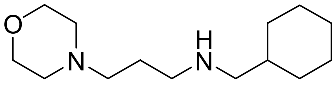
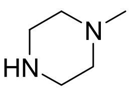
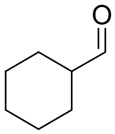
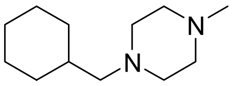
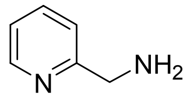
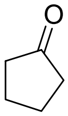
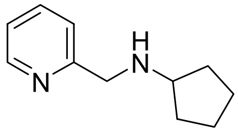
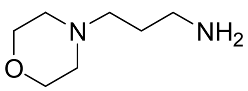
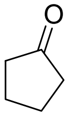
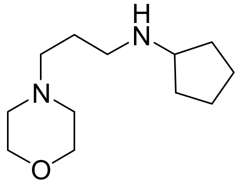
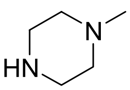
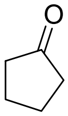
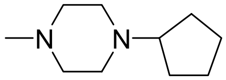
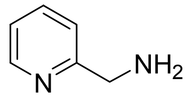
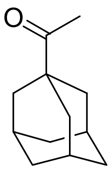
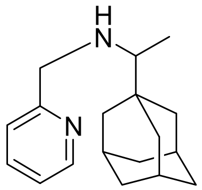
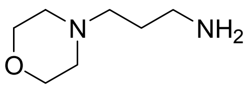
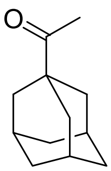
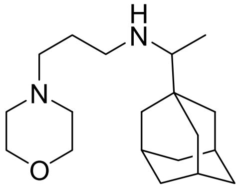
Entry	**Carbonyl Compound**	**Product Alcohol**	**$TiCl_4$ mmol**	**PS-DEAM mmol**	**PS-DIEA mmol**	**% $TiCl_4$ Scavenged**
1			**0.5**	**2.2**	**2.2**	**100**
2			**0.5**	**2.2**	**2.2**	**100**
3			**0.5**	**2.2**	**2.2**	**100**
4			**0.5**	**2.2**	**2.2**	**100**

Table 2: Reductive Amination Results using Titanium(IV) Isopropoxide and MP-borohydride in Conjunction with PS-DEAM Purification.

Entry	Starting Amine	Carbonyl Compound	Product Amine	Yield %	Purity GC (%)
1				95	93 mono 2 di-
2				90	99 mono 1 di-
3				97	100
4				89	100
5				60	100
6				95	100
7				86	94*
8				89	90*

*The only impurities present were the starting carbonyl compounds.

---

[i] Bolton, G.L.; Booth, R.J.; Cresswell, M.W.; Hodges, J.C.; Warmus, J.S.; Wilson, M.W.; Kennedy, R.M. WO 97/42230 (1997)

[ii] Hall, D. G.; Tailor, J.; Gravel, M. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3064

[iii] Sakurai, H. *Pure Appl. Chem*. **1982**, *54*, 1.

[iv] Bhattacharyya, S. *J. Org. Chem.* **1995**, 60, 4928; Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem. Soc. Perkin Trans 1*, **1998**, 2527; Bhattacharyya, S.; Fan, L.; Vo, L.; Labadie, J. *Combinatorial Chemistry and High Throughput Screening* **2000**, *3*, 117.

[v] Argonaut Part Numbers: 800401, 10 g; 800402, 25 g; 800403, 100 g

[vi] The MP-TsOH column was conveniently prepared by adding 0.7 g of resin to a 6-mL ISOLUTE Filtration column (International Sorbent Technology, Part Number 120-1113-C), fitted with a universal PTFE stopcock (International Sorbent Technology, Part Number 121-0009).

[vii] International Sorbent Technology, Part Number 533-0100-C

[viii] Argonaut Part Numbers: 800360, 10 g; 800361, 25 g; 800362, 100 g

[ix] Argonaut Part Numbers: 800260, 10 g; 800261, 25 g; 800262, 100 g