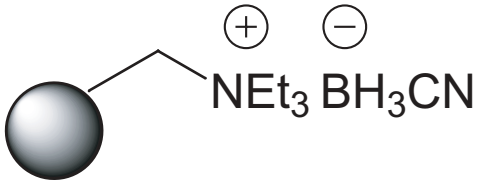
Technical Note 507

MP-Cyanoborohydride

Reducing Agent



Chemical Name: Macroporous triethylammonium methylpolystyrene cyanoborohydride (0.5% inorganic antistatic agent)

Resin Type: Macroporous(styrene-*co*-divinylbenzene)

Loading: 2.0–3.0 mmol/g (based on acid/base titration)

Bead Size: 350–1250 micons, 18–52 mesh (95% within)

Application: Reductive amination; reductive methylation of primary and secondary amines, reduction of imines; reduction of conjugated enones to unsaturated alchols.

Typical Conditions for Reductive Amination : 1.2 mmol of carbonyl compound, 1.0 mmol of primary or secondary amine in THF, 1.0 mL of HOAc and 2.5 mmol of MP-Cyanoborohydride stirred overnight at room temperature. Product isolated by filtration to remove the resin.

Compatible Solvents: THF (2.9 mL/g), DCM (3.0 mL/g) DMF (2.9 mL/g), MeOH (2.9 mL/g)

MP-Cyanoborohydride is a macroporous polystyrene-bound cyanoborohydride,[1] which is a resin-bound equivalent of tetraalkylammonium cyanoborohydride. The bound cyanoborohydride can be utilized as a versatile reducing agent[2,3] for the reductive amination of carbonyl compounds and reduction of imines. Resin-bound cyanoborohydride can also be utilized for a number of other important reductive applications.[1] A few examples include reduction of α,β-unsaturated carbonyl compounds to the corresponding unsaturated alcohols, conversion of pyridinium ions to tetrahydropyridine derivatives and dehalogenation reactions. The reaction work-up protocol is greatly simplified by using the resin-bound reagent. Specifically, compared with the small molecule sodium cyanoborohydride, it is reported[1] that toxic cyanide is not released on reaction work-up and therefore does not either contaminate the product nor pose a danger towards the user.

The general protocol for the use of MP-Cyanoborohydride for reductive amination is summarized in **Table 1.** Reactions are performed with 2.5 equivs of MP-Cyanoborohydride relative to the limiting reagent. The carbonyl compound is used as the limiting reagent in the synthesis of secondary amines to suppress overalkylation. For tertiary amine synthesis, the carbonyl compound is used in excess to allow the use of "catch and release" purification with MP-TsOH columns[4] or commercially available SCX cartridges.[5] The reactions are carried out with at least 5 equiv of acetic acid to facilitate imine or iminium ion formation, which undergo reduction with MP-Cyanoborohydride. Tetrahydrofuran (THF) is preferred to dichloroethane due to its greater stability in the presence of reactive amines.

After reduction is complete, the crude reaction mixture is comprised of the product amine as an acetate salt and excess amine or carbonyl compound depending on the stoichiometry employed. At this point, there are several options for final purification (**Figure 1**). These options are described in more detail in the following sections.

PART NUMBER	QUANTITY
800405	10 g
800406	25 g
800407	100 g
800408	1000 g

Biotage

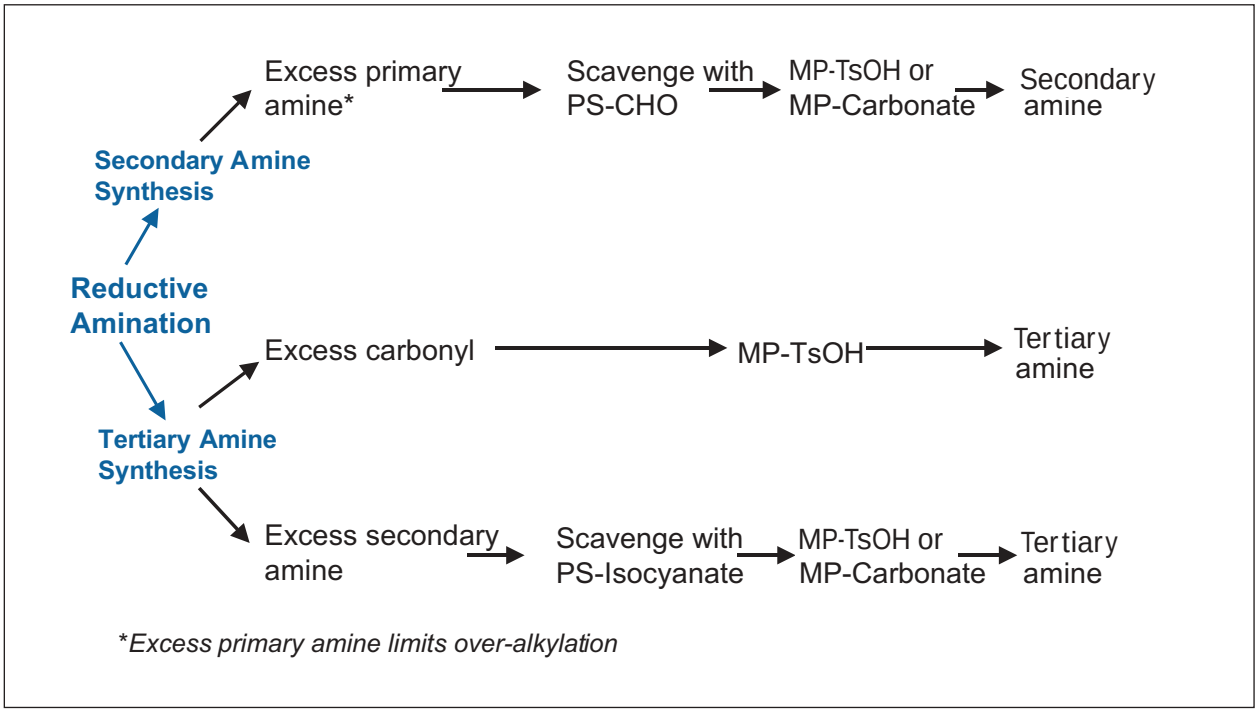


Figure 1: Strategies for the Synthesis of Secondary and Tertiary Amines via Reductive Amination Using MP-Cyanoborohydride

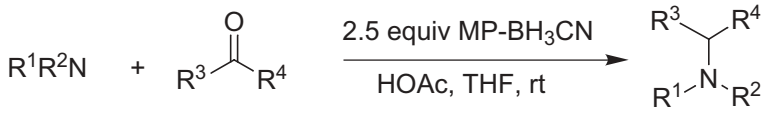


Table 1: Stoichiometry, Scavenging and Purification Options

Amine	Carbonyl	Amine:Carbonyl Stoichiometry	% HOAc	Scavenger Resin	Final Purification
1°	Aldehyde	1.2:1	25	PS-Benzaldehyde	MP-TsOH or MP-Carbonate
1°	Ketone	1.2:1	25	PS-Benzaldehyde	MP-TsOH or MP-Carbonate
2°	Aldehyde	0.8:1	5	None	MP-TsOH
2°	Ketone	0.8:1	5	None	MP-TsOH

SECONDARY AMINE SYNTHESIS

Minimization of overalkylation is a key consideration for reductive alkylation of primary aliphatic amines. The amine was used in 20% excess in order to favor selectivity towards monoalkylation. Reductive amination reactions proceeded overnight at room temperature in a 25% acetic acid/THF solvent mixture. The product mixture was treated with PS-Benzaldehyde to selectively scavenge excess primary amine. In these reactions, 25% acetic acid/THF was used to assure complete scavenging of amines. Since only five equivalents of acetic acid are required for the reductive amination step, the additional acetic acid to bring the concentration to 25 vol % can be introduced with the scavenging resin. After filtration and evaporation, the residue is dissolved in dichloromethane (DCM) and neutralized with MP-Carbonate or by "catch and release" purification with MP-TsOH or SCX columns to afford the product amine as a free base in good to excellent yield and purity.

This protocol was demonstrated in the reductive alkylation of an exemplary set of primary amines (**Entries 1-3, Table 2**). High purity and yield were obtained in the reductive alkylation of cyclopentanone. Reaction of N-(3-aminopropyl)morpholine with cyclohexanecarboxaldehyde afforded approximately 30% overalkylated product. In the case of 3-aminopyridine, it was advantageous to carry out the reductive amination in 25% acetic acid to facilitate imine formation of this less reactive heterocyclic amine. A cocktail of PS-Benzaldehyde and PS-$TsNHNH_2$ was used to scavenge both amine and carbonyl compound to afford the desired amine in high yield and purity. MP-Carbonate was used to neutralize the secondary amine in all three examples presented in **Table 2.**

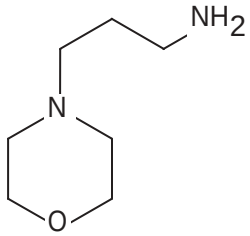
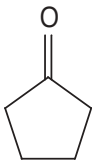
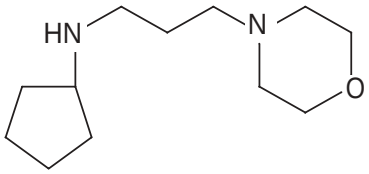
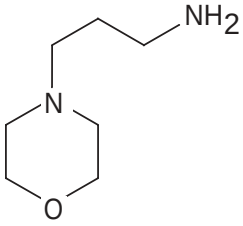
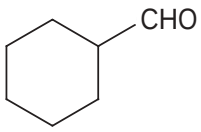
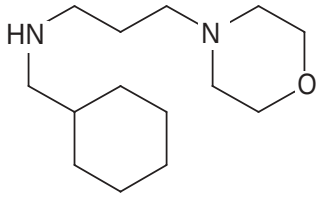
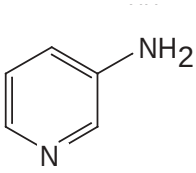
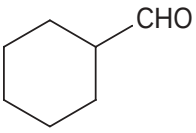
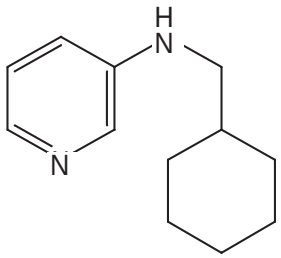
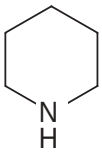
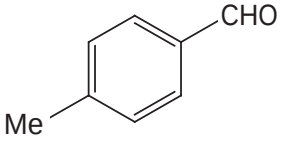
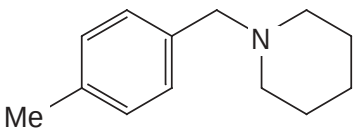
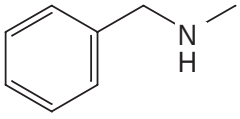
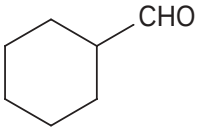
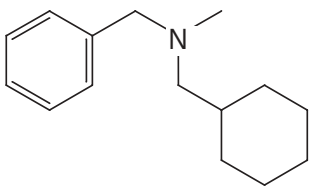
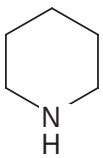
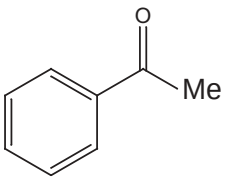
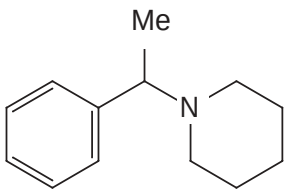
TERTIARY AMINE SYNTHESIS

Reductive amination using secondary amines with aldehydes and ketones was carried out with amine as the limiting reagent with 5 equiv of acetic acid. The product amines were purified from non-basic impurities by "catch and release" using MP-TsOH columns. Upon completion of the reaction, the solution was filtered from the spent resin and the filtrate was passed through an MP-TsOH column, followed by washing with DCM to remove nonbasic impurities. The product tertiary amine was eluted from MP-TsOH with a solution of 2 M ammonia in methanol and isolated as a free base by concentration to dryness.

Application of the general procedure was demonstrated in the reductive alkylation of piperidine with *p*-tolualdehyde to afford the desired tertiary amine in high yield and purity (**Entry 4, Table 2**). Alicyclic secondary amines, *e.g.* N-benzylmethylamine, are effective as substrates as demonstrated by the reductive amination of cyclohexanecarboxaldehyde (**Entry 5, Table 2**). Although the procedure is generally effective for ketones, less reactive ketones require more forcing conditions. Reductive amination of acetophenone with piperidine was successful with 5 equivalents of acetic acid in ethanol at 65 °C (**Entry 6, Table 2**).[6]

If the carbonyl compound contains a basic moiety, "catch and release" purification will not selectively bind the product, and it is recommended to use excess secondary amine in the reductive amination and purify with PS-Isocyanate. It is important to limit the acetic acid to 5 equivalents, since higher levels can lead to acetamide formation in the scavenging step. Isolation of the free amine is achieved by neutralization with MP-Carbonate or "catch and release" purification after scavenging.

Table 2: Reductive Alkylation of Amines

Entry	Starting Amine	Carbonyl Compound	Product Amine	% Yield (isolated)	% Purity
1				97	99
2				88	71[a]
3				85	100
4				81	97
5				87	97
6[b]				74	98

a) Dialkylated product present as the major impurity. (b) The conditions required for acetophenone are 5 equivalents acetic acid, ethanol, 65 °C.

BORON IMPURITIES

Amine products were tested for the presence of boron by elemental analysis. When "catch and release" purification was used the level of boron present in the samples was less than 10 ppm. MP-Carbonate neutralization afforded products with a boron level of 200 ppm. Both of these values are well below the boron levels measured for the crude product, which was generally in the 0.2-0.4 wt. % range. It is therefore important to apply "catch and release" purification or the neutralization procedure to remove boron impurities. The crude samples were tested for free cyanide with cyanide test strips and showed levels less than 15 ppm.

EXPERIMENTAL

Representative procedure for reductive alkylation of primary amines (Entry 1, Table 2).

To a 0.5 M THF solution of N-(3-aminopropyl)morpholine (1.2 mL, 0.60 mmol) was added 1.0 mL of a 0.5 M THF solution of cyclopentanone (0.50 mmol), 1.0 mL acetic acid, and 1.0 mL THF. MP-Cyanoborohydride resin (0.5 g, 2.5 mmol/g, 1.25 mmol, 2.5 equiv) was added and the reaction agitated at room temperature for 16h. To the reaction mixture was added PS-Benzaldehyde (0.5 mmol) and the scavenging reaction was allowed to stir at room temperature for 16 h. The solution was filtered and the filtrate was concentrated to dryness. The crude product was diluted with 2 mL of THF and 0.89 g of MP-Carbonate (2.8 mmol/g, 2.5 mmol) was added. After 1.5 h the mixture was filtered and the filtrate was concentrated *in vacuo* to yield the desired secondary amine as a free base. The product secondary amine was characterized by gas chromatography and ^{1}H NMR.

Representative procedure for reductive alkylation of secondary amines (Entry 4, Table 2).

To a 0.5 M THF solution of piperidine (1.0 mL, 0.5 mmol) was added 1.2 mL of a 0.5 M THF solution of *p*-tolualdehyde (0.6 mmol), 0.14 mL acetic acid (5 equiv), and 0.75 mL THF. MP-Cyanoborohydride resin (0.5 g, 2.5 mmol/g, 1.25 mmol, 2.5 equiv) was added and the reaction agitated at room temperature for 16 h. The reaction was filtered and the solution was passed through a pre-conditioned (DCM) MP-TsOH column (1g). The flow rate was adjusted to 1 mL/min, which was maintained for all subsequent elution steps.[4] The cartridge was washed with DCM (20 mL) and the washing was discarded. The product tertiary amine was released using 2 M NH_3-MeOH (5 mL) followed by DCM (15 mL). The combined eluent was concentrated in vacuo to yield the desired tertiary amine as a free base. The product tertiary amine was characterized by gas chromatography and ^{1}H NMR.

REFERENCES:

1. Hutchins, R. O.; Natale, N. R.; Taffer, I. M. *J. Chem. Soc. Chem. Commun.* **1978**, 1088.

2. Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A-G.; Hall, B. J. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 2239.

3. Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc. Perkin Trans.* 1, **1998**, 3127.

4. "Catch and Release" purification is described in the MP-TsOH technical section. The MP-TsOH column was conveniently prepared by adding 0.7 g of resin to a 6 mL ISOLUTE® Filtration column (part number 120-1113-C) fitted with a universal PTFE stopcock (part number 121-0009). Alternatively MP-TsOH cartridges (part number 800477-C30) can be used.

5. SCX (strong cation exchanger) is a bonded-phase silica with sulfonic acid functional groups. For examples of SCX in purification of amines: Lawrence, R.M.; Biller, S.A.; Fryszman, O.M.; Poss, M.A. *Synthesis* **1997**, 553. Siegel, M.G.; Hahn, P.J.; Dressman, B.A.; Fritz, J.E.; Grunwell, J.R.; Kaldor, S.W. *Tetrahedron Lett.* **1997**, *38*, 3357.

6. An alternative method for reductive amination of sterically hindered ketones utilizes MP-Borohydride in the presence of titanium(IV) isopropoxide. The titanium is removed by PS-DEAM in a subsequent scavenging step. Details are provided in the PS-DEAM technical section.

040-702

Biotage

United Staes and Canada
T: + 1 434 979 2319
Toll-Free: +1 800 446 4752
ordermailbox@biotage.com

United Kingdom, EIRE
Biotage
T: + 44 1443 811811
eurosales@eu.biotage.com

Sweden
Biotage
T: + 46 18 56 59 00
order@eu.biotage.com

Japan
Biotage
T: + 81 422 281233
order@biotage.co.jp