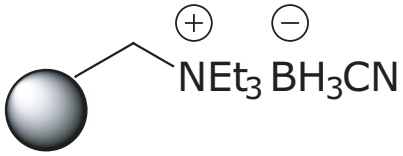
Biotage® MP-Cyanoborohydride

Reducing Agent



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:	Macroporous triethylammonium methylpolystyrene cyanoborohydride (0.5% inorganic antistatic agent)
Resin Type:	Macroporous poly(styrene-co-divinylbenzene)
Application:	Reductive amination; reductive methylation of primary and secondary amines, reduction of imines; reduction of conjugated enones to unsaturated alcohols.
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).
Storage:	Cool, dry location

Biotage® MP-Cyanoborohydride is a macroporous polymer-supported cyanoborohydride,[1] which is a solid-supported 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. Solid-supported cyanoborohydride can also be utilized for a number of other important reductive applications.[1] Examples include reduction of a,b-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 solid-supported reagent. Specifically, compared with the small molecule sodium cyanoborohydride, it is reported[1] that toxic cyanide is not released on reaction workup and therefore does not contaminate the product or 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 equivalents 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 over alkylation. For tertiary amine synthesis, the carbonyl compound is used in excess to allow the use of catch-and-release purification with MP-TsOH cartridges[4] or SCX cartridges.[5] The reactions are carried out with at least 5 equivalents of HOAc to facilitate formation of imine or iminium ions, which undergo reduction with MP-Cyanoborohydride. Tetrahydrofuran (THF) is preferred to dichloroethane as solvent due to its greater stability in the presence of reactive amines.

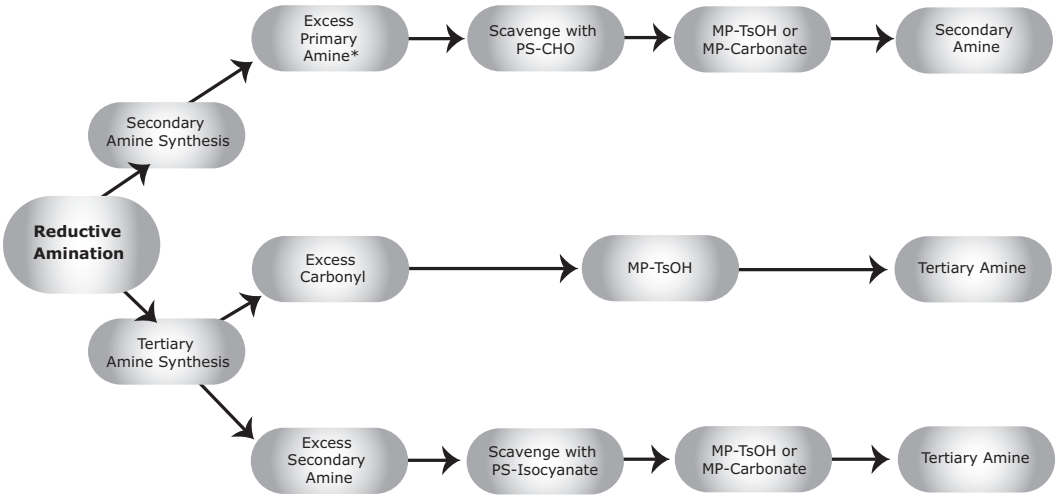


Figure 1. Stoichiometry, scavenging, and purification options.
*Excess primary amine limits over-alkylation

Amine	Carbonyl	Amine:Carbonyl Stoichiometry	% HOAc in Solvent	Scavenger Resin	Final Purification
1°	Aldehyde	1.2:1	25	PS-Benzaldehyde or MP-TsOH	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

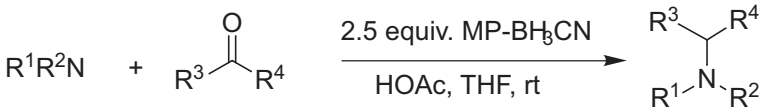


Table 1. Stoichiometry, scavenging, and purification options.

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.

Applications

Secondary Amine Synthesis

Minimization of over alkylation is a key consideration for reductive alkylation of primary aliphatic amines. The amine was used in 20% excess in order to favor selectivity towards mono alkylation. Reductive amination reactions proceeded overnight at room temperature in a 25% HOAc/THF solvent mixture. The product mixture was treated with PS-Benzaldehyde to selectively scavenge excess primary amine. In these reactions, 25% HOAc/THF was used to assure complete scavenging of amines. Since only 5 equivalents of HOAc are required for the reductive amination step, the additional HOAc to bring the concentration to 25 vol % can be introduced with the scavenging resin. After filtration and evaporation, the residue is dissolved in DCM and neutralized with MP-Carbonate or by catch-and-release purification with MP-TsOH (ISOLUTE® SCX-2)[5] 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 a set of primary amines (Table 2, entries 1–3). High purity and yield were obtained in the reductive alkylation of cyclopentanone. Reaction of N-(3-aminopropyl)morpholine with

cyclohexanecarboxaldehyde afforded approximately 30% over alkylated product. In the case of 3-aminopyridine, it was advantageous to carry out the reductive amination in 25% HOAc to facilitate imine formation of this less reactive heterocyclic amine. A cocktail of PS-Benzaldehyde and PS-$TsNHNH_2$ was used to scavenge both primary 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.

Tertiary Amine Synthesis

Reductive amination using secondary amines with aldehydes and ketones was carried out with amine as the limiting reagent and 5 equivalents of HOAc. The product amines were purified from non-basic impurities by catch-and-release using MP-TsOH cartridges. Upon completion of the reaction, the spent resin was filtered from the solution and the filtrate was passed through an MP-TsOH cartridge followed by washing with DCM to remove non-basic impurities. The product tertiary amine was eluted from MP-TsOH with a solution of 2 M ammonia in MeOH 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 (Table 2, entry 4). Alicyclic secondary amines, (e.g., N-benzylmethylamine), are effective as substrates as demonstrated by the reductive amination of cyclohexanecarboxaldehyde (Table 2, entry 5). 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 HOAc in EtOH at 65 °C (Table 2, entry 6).[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 HOAc 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.

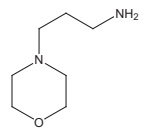
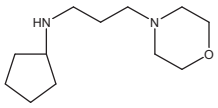
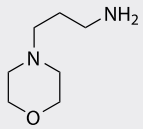
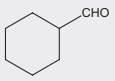
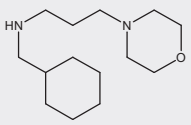
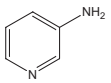
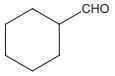
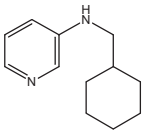
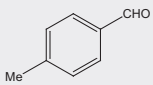
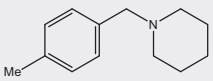
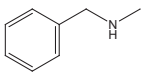
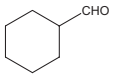
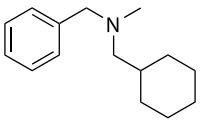
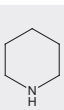
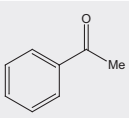
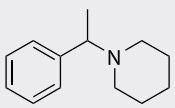
Entry	Starting Amine	Carbonyl Compound	Product Amine	% Yield (isolated)	% Purity
1				97	99
2				88	71[a]
3				85	100
4				81	97
5				87	97
6[b]				74	98

Table 2. Reductive alkylation of amines.
[a]Dialkylated product present as the major impurity.
[b]The conditions required for acetophenone are 5 equivalents HOAc, EtOH, 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-andrelease 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.

Reductive Alkylation of Secondary Amines (Table 2, Entry 4)

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 ptolualdehyde (0.6 mmol), 0.14 mL HOAc (5 equivalent), and 0.75 mL THF. MP-Cyanoborohydride resin (0.5 g, 2.5 mmol/g, 1.25 mmol, 2.5 equivalents) was added and the reaction agitated at room temperature for 16 h. The reaction was filtered and the filtrate was passed through a preconditioned (DCM) MP-TsOH column (1 g). 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.

Ordering Information

Part Number	Quantity
800511	3 g
800405	10 g
800406	25 g
800407	100 g
800408	1000 g

Representative Procedures

Reductive Alkylation of Primary Amines (Table 2, Entry 1)

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 HOAc, and 1.0 mL THF. MP-Cyanoborohydride resin (0.5 g, 2.5 mmol/g, 1.25 mmol, 2.5 equivalents) was added and the reaction agitated at room temperature for 16 h. To the reaction mixture was added PS-Benzaldehyde (0.5 mmol) and the scavenging reaction mixture was stirred at room temperature for 16 h. The solution was filtered and the filtrate was concentrated to dryness. The crude product was dissolved in 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.

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).
5. ISOLUTE® SCX-2 (Part Number 532-0050-C). 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.

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