

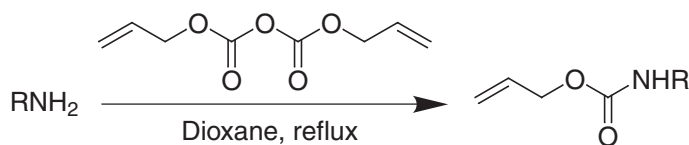
Expedient Deprotection of N-Alloc Groups Using PS-PPh₃-Pd, a Polymer-Supported Palladium Catalyst in Conjunction with MP-Borohydride, a Polymer-Supported Borohydride

INTRODUCTION

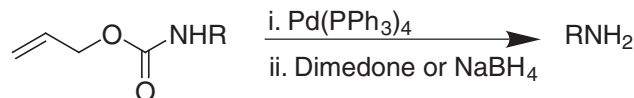
The selective protection and deprotection of functional groups is paramount in organic synthesis. Orthogonal protection and deprotection of primary and secondary amines is particularly important from the perspective of drug discovery, as amines and their derivatives are the most prevalent structural moieties found in the comprehensive medicinal chemistry database.¹ A large number of amine protecting groups have been reported in the literature.² Among them, a variety of carbamate protecting groups such as Boc, Fmoc, Cbz and Alloc have found many important applications due to their mild and selective reaction conditions.²

The allyloxycarbonyl group (Alloc) has long been reported for the protection of amines.³ However, this protecting group did not find many useful applications until recently, mainly due to the lack of mild, selective deprotection protocols. The harsh reaction conditions required for deprotection are not generally compatible with synthetic intermediates containing multiple functional groups. The N-Alloc group may be introduced using allyl chloroformate or diallyldicarbonate.⁴ Deblocking of Alloc groups may be conveniently performed under mild reaction conditions using a palladium catalyst such as Pd(PPh₃)₄ in the presence of a variety of allyl acceptors such as dimedone, sodium malonate, ammonium formate and sodium borohydride.⁵⁻⁹

N-Alloc Protection:



N-Alloc Deprotection:

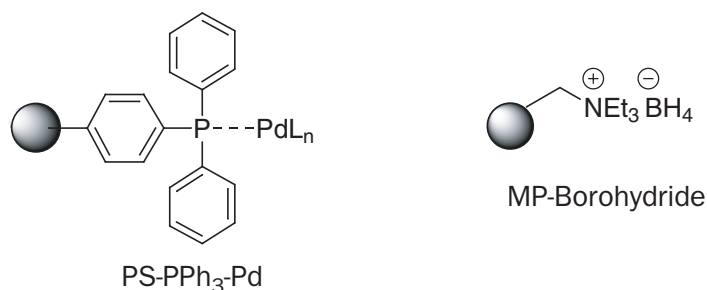


Typical reaction conditions for N-Alloc group protection and deprotection

The mild protection and deprotection conditions of the N-Alloc group are orthogonal to other carbamate protecting groups such as Boc and Cbz, and have therefore found notable applications in peptide, nucleoside and amino-sugar chemistry.⁵⁻⁸ However, the reported protocols for N-Alloc protection and deprotection are not without limitations. The major shortcomings include sluggish formation of N-Alloc with many amines, the formation of N-allylated side products on deprotection, and high palladium levels in the products after deprotection. Moreover, the isolation process typically involves aqueous workup, liquid-liquid extraction and chromatographic separation.

The use of polymer-supported reagents and scavengers is a powerful technique for expedited synthesis and purification.¹⁰ By using polymer-supported reagents and scavengers, excess reagents and byproducts can be selectively removed by simple filtration rather than liquid-liquid extraction and chromatographic purification. In addition, polymer-supported reagents offer further advantages that include reaction of active intermediates by "catch-and-release", selectivity and immobilization of toxic intermediates.

It is within this context we sought to develop novel, expedient protocols for both N-Alloc protection and deprotection using polymer-supported reagents and catalysts. We reasoned that the use of a polymer-supported triphenylphosphine Pd(0) catalyst would offer improved convenience for handling, product isolation and removal of palladium compared to the small molecule catalyst tetrakis(triphenylphosphine)palladium (0). Moreover, a supported Pd(0) catalyst may allow higher chemoselectivity with less or no side reactions. The formation of N-Alloc amines was performed using diallyldicarbonate and MP-Borohydride,¹¹ a polymer-supported borohydride. The deprotection of N-Alloc amines utilized PS-PPh₃-Pd,¹² a polymer-supported palladium catalyst in conjunction with MP-Borohydride.¹¹

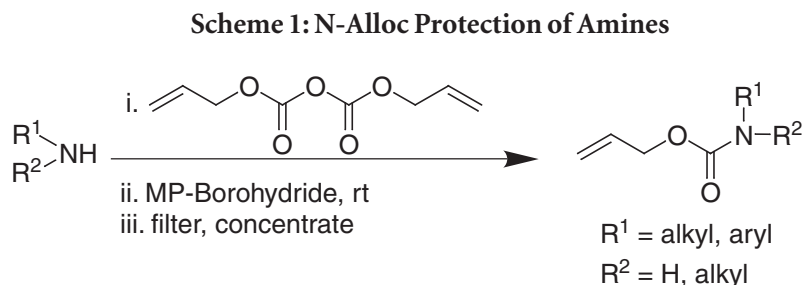


Structures of polymer-supported palladium catalyst PS-PPh₃-Pd and polymer-supported reagent MP-Borohydride

RESULTS AND DISCUSSION

N-Alloc Protection

N-Alloc protected amines were prepared from the corresponding primary and secondary amines using diallyldicarbonate (**Scheme 1**). Typical reaction conditions required 1.2 equiv. of diallyldicarbonate relative to the starting amine. The reactions were performed in THF and proceeded to completion in 2 hours at room temperature under air; no inert conditions were required. After the reaction was complete, MP-Borohydride (1.2 equiv.) was added to the reaction mixture to scavenge the allylcarbonyl byproduct. The N-Alloc protected amines were isolated in high yield and purity by filtration of the resin and evaporation of the solvent.



For reactions using an amine hydrochloride salt, the same reaction conditions were followed except that MP-Carbonate,¹³ a polymer-supported carbonate base, was added to neutralize the amine salt (**Scheme 2**). The scope of N-Alloc protection was evaluated using a variety of primary and secondary amines, and the results are summarized in **Table 1**. The products were characterized by GC and NMR analysis. As shown in **Table 1**, the reaction conditions were found to be effective for both aliphatic and aromatic amines. Orthogonal N-Alloc protection of mono-N-Boc protected diamines and hydroxyamines was possible under these reaction conditions, as exemplified in entries 2, 3 and 8 (**Table 1**).

Scheme 2: N-Alloc Protection using Amine Hydrochlorides

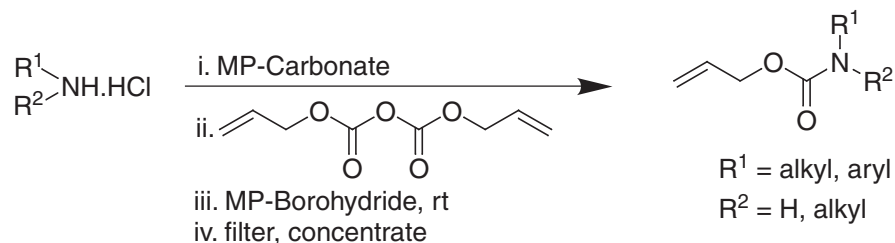
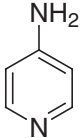
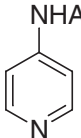
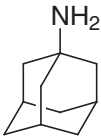
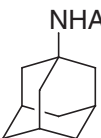
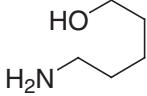
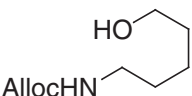


Table 1: N-Alloc Protection Scope Studies

Entry	Starting Amine	Product	% Yield	% Purity
1			90	98
2			88	97
3	BocHN-CH ₂ -CH ₂ -CH ₂ -NH ₂	BocHN-CH ₂ -CH ₂ -CH ₂ -NHAlloc	85	97
4			92	96
5			85	98

Entry	Starting Amine	Product	% Yield	% Purity
6			82	97
7			90	99
8			84	95

N-Alloc Deprotection

Palladium catalyzed deprotection of N-Alloc groups to the corresponding amines was conveniently performed using a polymer-supported palladium catalyst, PS-PPh₃-Pd¹² in conjunction with MP-Borohydride¹¹ as the allyl acceptor (**Scheme 3**). The results are summarized in **Table 2**. Typical reaction conditions required 2 mol % of PS-PPh₃-Pd catalyst and 3.0 equiv. of MP-Borohydride. A number of solvent mixtures were evaluated for optimum performance and best results were obtained by using a 5:4:1, v/v mixture of DCM:MeOH:H₂O. In general, no allylated side product was obtained under these reaction conditions. The reactions proceeded to completion in 2 hours at room temperature under air; no inert conditions were required. The product amines were isolated in high yield and purity by simple filtration of the reaction mixture through an ISOLUTE[®] sodium sulfate drying cartridge¹⁴ followed by evaporation of the solvent. The deprotection conditions were found to be orthogonal to the N-Boc group (entries 2 and 3, **Table 2**). The deprotected amine products typically contained low levels of palladium (< 100 ppm).

Scheme 3: N-Alloc Deprotection

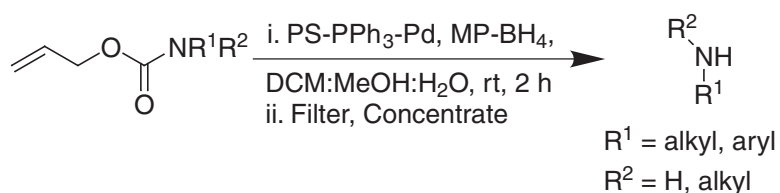
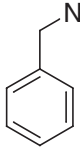
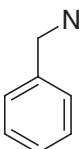
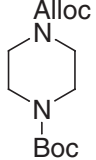
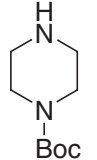
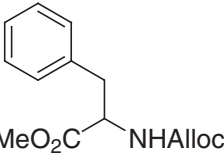
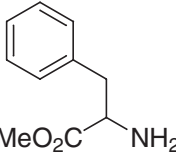
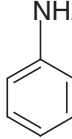
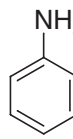
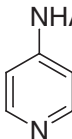
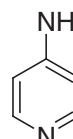
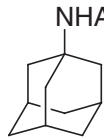
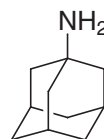


Table 2: Reductive Deprotection of N-Alloc

Entry	Substrate	Product Amine	% Yield	% Purity
1			85	98
2			82	97

Entry	Substrate	Product Amine	% Yield	% Purity
3	BocHN-CH ₂ -CH ₂ -NHAlloc	BocHN-CH ₂ -CH ₂ -NH ₂	79	97
4	 MeO ₂ C-CH(NHAlloc)-CH ₂ -Ph	 MeO ₂ C-CH(NH ₂)-CH ₂ -Ph	90	99
5	 NHAlloc-Ph	 NH ₂ -Ph	90	97
6	 NHAlloc-Pyridine	 NH ₂ -Pyridine	88	96
7	HO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NHAlloc	HO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NH ₂	83	95
8	 NHAlloc-Bicyclic	 NH ₂ -Bicyclic	93	99

SUMMARY

In summary, we have described clean, expedient formation of N-Alloc protected amines using MP-Borohydride and diallyldicarbonate in high yield and purity. Highly efficient deprotection conditions for N-Alloc amines were developed using PS-PPh₃-Pd(0) catalyst in conjunction with MP-Borohydride. Both the protection and deprotection reactions were performed at ambient temperature. Pure products were isolated by simple filtration, in high yield, and no liquid-liquid extraction or column chromatography was required. The deprotected amine products typically contained low levels of palladium (< 100 ppm).

EXPERIMENTAL

N-Alloc Protection of Primary and Secondary Amines:

A mixture of the amine (1.0 mmol), diallyldicarbonate (0.2 mL) and THF (3.0 mL) was stirred at room temperature for 2 hours. MP-Borohydride (3.0 mmol/g, 0.4 g, 1.2 mmol)¹¹ was then added and the mixture was agitated for 30 minutes. The solution was filtered and the resin was washed with THF. The combined solution was concentrated to afford the N-Alloc protected amine. The isolated N-Alloc amines were analyzed by GC and NMR. With reactions involving amine hydrochlorides, the same reaction conditions were followed except that MP-Carbonate (2.8 mmol/g, 0.7 g, 2.0 mmol)¹³ was added to the reaction mixture.

N-Alloc Deprotection of Primary and Secondary Amines:

A mixture of the N-Alloc protected amine (0.5 mmol), PS-PPh₃-Pd (0.1 mmol/g, 0.1 g, 0.01 mmol),¹² MP-Borohydride (2.85 mmol/g, 0.52 g, 1.5 mmol)¹¹ in 3 mL of DCM:MeOH:H₂O (5:4:1, v/v) was stirred at room temperature for 1 hour. The solution was filtered through an ISOLUTE sodium sulfate drying cartridge¹⁴ and the resin was washed with THF. The combined solution was concentrated to afford the free amine. The isolated amines were analyzed by GC and NMR.

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