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Synergic effect of hydride and proton donors in the Pd(0)-mediated deprotection of N^{α}-Aloc proline derivatives

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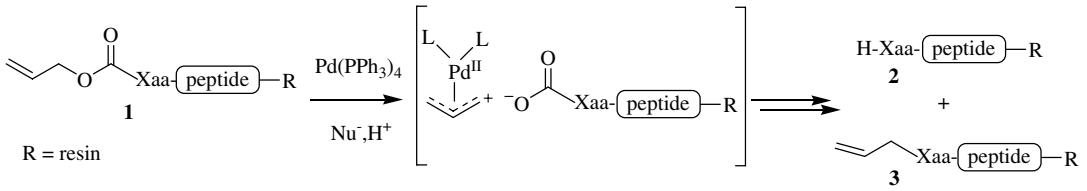
Abstract—In this study, the challenging Pd(0)-catalyzed N^{α}-Aloc removal from a proline residue using $Me_2NH{\cdot}BH_3$ or $PhSiH_3$ as allyl scavengers has been investigated. Standard conditions led to a large amount of an allylamine byproduct. A careful study of the reactions allowed us to design the optimal conditions for the quick and quantitative formation of the desired product, while taking advantage of a synergic effect between hydride and proton donors.

The solid phase technique has revolutionized peptide synthesis. Ever since the pioneering work of Merrifield, polymer supports,[1] protecting groups[2] and coupling reagents[3] have become the subject of considerable interest as they enable the routine synthesis of peptides.[4] The Fmoc strategy[5] is now widely used thanks to a large variety of piperidine-stable, acid-labile side-chain protecting groups[2] and to the convenient trifluoroacetic acid (TFA) treatment to release the deprotected peptide from the resin. Use of allylic protecting groups[6] is a popular strategy to induce a third dimension in the protection scheme, which allows the synthesis of branched or cyclic peptides and glycopeptides. Allyloxycarbonyl (Aloc) derivatives of amines, and to a lesser extent alcohols, and allyl (All) esters, aryl ethers and glycosides are the most classic examples. The deprotection step usually involves a Tsuji–Trost reaction using a combination of a soluble Pd(0) catalyst with a nucleophile or hydride donor acting as a scavenger.[6] The choice of an appropriate allyl scavenger is clearly a key factor in establishing reliable procedures. The hydride donor $PhSiH_3$[7] is reportedly an excellent and user-friendly scavenger when used in conjunction with $Pd(PPh_3)_4$ for the removal of allyl ester and allyl carbamate groups, and has become very popular, especially in peptide chemistry.[8]

Formation of an allylamine such as **3** (Scheme 1) is one of the most troublesome side reactions occurring during *N*-Aloc removal,[6] in particular when the carbamate is installed on secondary amines.[9] Allylamines have themselves been reported to be deallylated by $Pd(PPh_3)_4$ in the presence of a pronucleophilic acidic species such as



Scheme 1.

Keywords: Aloc; Alloc; Allylamine; Proline protection; Solid phase peptide synthesis.
Abbreviations: Aloc, allyloxycarbonyl; PAM, phenylacetamidomethyl; PEGA, polyethylglycol polyacrylamide; Pbf, 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl; TFA, trifluoroacetic acid.
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Kunz's *N*,*N*′ dimethylbarbituric acid (NDMBA)[10] and Genêt's thiosalicylic acid (TSA).[11] It is believed that the allylamine needs to be protonated to generate a π-allyl palladium complex necessary for an effective deprotection.[10b,11b] NDMBA and TSA have also been shown to smoothly deprotect *N*-Aloc acyclic secondary amines,[12] probably through concomitant formation of both allylamine **3** and secondary amine **2** and conversion of the former species to the latter one. However, though TSA worked well in the removal of N^{α}-Aloc from cyclic secondary amine in solution,[11a] NDMBA was shown to be ineffective in removing N^{α}-Aloc from solid-supported ones.[13] Moreover, one drawback in the reactions involving the pronucleophilic species is their slow kinetics compared to reactions involving tin, boron or silicon hydrides.[12] We considered the possibility of designing fast and clean deprotection conditions using standard hydride donors such as $PhSiH_3$.[7] To address this question, we chose a challenging case in which an Aloc was installed on a supported cyclic secondary amine, which is more nucleophilic than an acyclic one, hence more prone to form allylamine. To explore the Aloc removal from a terminal N^{α}-Aloc-proline peptide resin, the model sequence **A**[14] was chosen, grafted on a polystyrene resin. All the deprotection experiments were conducted using a catalytic amount (20 mol %) of $Pd(PPh_3)_4$ as a source of Pd(0). Ratios of the different products were determined by cleavage of the peptide from the resin under appropriate conditions followed by HPLC analysis of the crude mixture.

An initial set of experiments was carried out under the most classic conditions using a large excess of $PhSiH_3$ as the allyl scavenger and CH_2Cl_2 as the solvent[15] (Table 1, entries 1–3). Conversion of the Aloc protected proline **1** was complete after 120 min but was accompanied by the side-formation of a noticeable amount of allylamine **3**, as expected in this challenging case. Surprisingly, the latter was smoothly transformed into amine **1** over another 180 min (Table 1, entry 3). We postulated that the source of proton necessary for this deallylation process could be the small amount of HCl dissolved into CH_2Cl_2.[16] In trying to address this point, a second set of experiments was carried out in NMP (Table 1, entries 4–7). The initial reaction profiles were similar to those of experiments conducted in CH_2Cl_2. However, the allylamine was not converted into amine, even after a prolonged reaction time (Table 1, entries 6 and 7), whereas the target amine **2** was obtained quickly and quantitatively by simply adding dilute anhydrous HCl to the reaction mixture (Table 1, entry 9). Aloc removal was somewhat slower in NMP (Table 1, entry 6) than in CH_2Cl_2 (Table 1, entry 2), probably due to either poorer solvation of the protected peptide resin **A** in NMP, or slower kinetics in the Pd(0) catalytic cycle.

This study was extended using the hydride donor dimethylamine borane[12] as the allyl scavenger, previously described as the one best-suited from scavenger screenings within the context of difficult *N*-Aloc removals.[13,17] The reaction was carried out in NMP to avoid the presence of any adventitious source of proton. To enable good solvation of the reagents during the reaction, we chose the unprotected peptide resin **B**,[18] the sole protecting group being Aloc installed on the terminal N^{α}-Pro.[20] Under these conditions,[23] quantitative conversion of the N^{α}-Aloc peptide resin **B** was observed after 30 min but accompanied by the formation of a considerable amount (68%) of allylamine **3** (Table 2, entry 1). This

Table 1. On solid support *N*-Aloc deprotection using $PhSiH_3$ as an allyl scavenger[a]

	Solvent	*t* (min)	Added time (HCl)[b]	Yield[c] (%)		
				N-Aloc **1**	NH **2**	*N*-Allyl **3**
1	CH_2Cl_2	90		24	57	19
2	CH_2Cl_2	120		0	65	35
3	CH_2Cl_2	300		0	100	0
4	NMP	90		65	30	5
5	NMP	300		14	58	28
6	NMP	600		0	55	45
7	NMP	1200		0	53	47
8	NMP	300	+300	10	70	20
9	NMP	600	+600	0	100	0

[a] Conditions: $Pd(PPh_3)_4$: 0.2 equiv; $PhSiH_3$: 50 equiv; temperature: 20 °C; peptide resin **A**: Aloc-Pro-Gly-Arg(Pbf)-Ala-Wang resin.
[b] In the presence of 2 equiv of HCl.
[c] Estimated by integration of the HPLC peaks at 214 nm.

Table 2. On solid support *N*-Aloc deprotection using $Me_2NH{\cdot}BH_3$ as an allyl scavenger in NMP[a]

	t (min)	Added time $[B(OH)_3]$[b]	Yield[c] (%)		
			N-Aloc **1**	NH **2**	*N*-Allyl **3**
1	30		0	32	68
2	90		0	47	53
3	330		0	100	0
4	30	+60	0	100	0

[a] Conditions: $Pd(PPh_3)_4$: 0.2 equiv; $Me_2NH{\cdot}BH_3$: 6 equiv; temperature: 20 °C; peptide resin **B**: *Aloc*-PPAHGVTSAPDTRPAPGSTA-*PAM-PEGA resin* (PAM: phenylacetamidomethyl; PEGA: polyethylglycol polyacrylamide).
[b] In the presence of 6 equiv of $B(OH)_3$.
[c] Estimated by integration of the HPLC peaks at 214 nm.

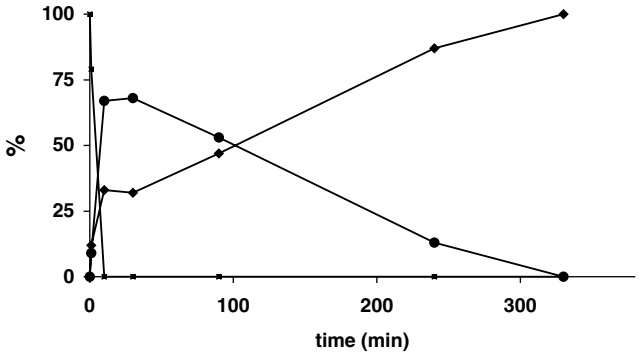
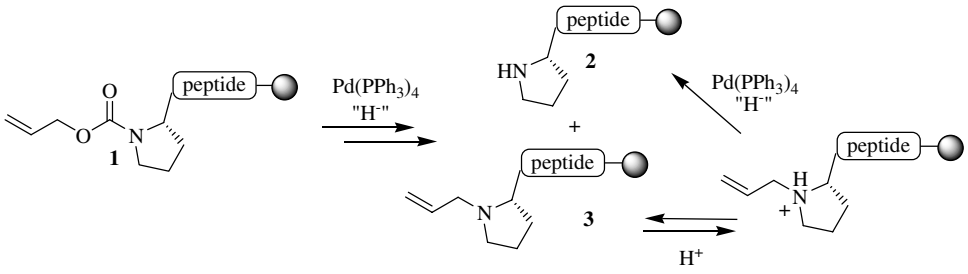


Figure 1. Kinetics of *N*-Aloc deprotection from peptide resin **B**. The reaction was performed in NMP in the presence of 6 equiv $Me_2NH{\cdot}BH_3$ at room temperature. The percentage of each product was estimated by integration of the HPLC peaks at 214 nm after final deprotection of the peptide resin using NaOH. (square) *N*-Aloc **1**; (diamond) α-amine **2**; (circle) *N*-allylamine **3**.



Scheme 2.

confirmed, once again, that the removal of N^{α}-Aloc from supported proline residues is a challenging task.[24] Rather surprisingly, increasing the reaction time up to 330 min led to the quantitative formation of the target amine **2** (Table 2, entry 3).[25] The kinetics of this reaction was studied in more details by HPLC (Fig. 1). At the very beginning of the reaction, the *N*-Aloc derivative **1** was quickly converted into a mixture of the desired product **2** and allylamine **3**. After a plateau, a second reaction, slower than the first, afforded the amine while allylamine **3** was being consumed. We suspected this time again an adventitious source of protons to be responsible for this unusual reaction profile. $Me_2NH{\cdot}BH_3$ is known to be slowly hydrolyzed into boric acid and volatile dimethylamine,[12] and we wondered if the presence of boric acid could be responsible for the efficiency of the deallylation process. To evaluate this hypothesis, $B(OH)_3$ was added to the reaction mixture after 30 min (Table 2, entry 4). After a total time of only 90 min, quantitative deallylation of the *N*-allyl proline was observed, whereas the same reaction carried out without any additive, still led to 53% of allylamine **3** (Table 2, entry 2). These data strongly support that the known high efficiency of $Me_2NH{\cdot}BH_3$ in the *N*-Aloc deprotection system depends not only on the trapping of the π-allyl palladium complex by the hydride but also on the conversion of the allylamine byproduct into an amine after its protonation by hydrolysis products according to Scheme 2.

In conclusion, this study revisited the challenging N^{α}-Aloc removal from secondary amines using $Me_2NH{\cdot}BH_3$ and $PhSiH_3$ as allyl scavengers. Our data suggest that the efficacy of these hydride donors arises not only from their nucleophilic properties but also from an adventitious source of proton due to the decomposition of the solvent (CH_2Cl_2) or the hydrolysis of the allyl scavenger itself ($Me_2NH{\cdot}BH_3$). A careful study of the reaction allowed us to design optimized conditions leading to the quantitative formation of the desired unprotected product, taking advantage of the synergic effect between hydride and proton donors.

Acknowledgements

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15. *Typical procedure for palladium-catalyzed N-Aloc removal in the presence of $PhSiH_3$.* To peptide-resin **A** (10 mg; 3 μmol) solvated in the appropriate solvent (1 ml), $PhSiH_3$ (50 equiv) was added under agitation, and, a few min later, followed by $Pd(PPh_3)_4$ (0.7 mg; 0.2 equiv) under an argon atmosphere. After the reaction time specified in the table, the resin was washed with the solvent used for the reaction (3×) and CH_2Cl_2 (3×). Then, the peptide resin was treated with TFA/*i*Pr_3SiH/H_2O, 95/2.5/2.5 (0.5 ml) for 2 h. After draining the resin, the peptide was precipitated by addition of cold Et_2O and centrifuged. The crude product dissolved

in H_2O (2 mg/ml) was analyzed by HPLC and mass spectrometry.
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20. To synthesize peptide resins **B** and **C**, we followed a procedure optimized in our laboratory.[21] In brief, the phenylacetamidomethyl (PAM) linker was installed on the PEGA resin by using the commercially available Boc-Ala-4-(oxymethyl)phenylacetic acid linker.[19a] After Boc removal by TFA treatment and DIEA neutralization, the elongation was carried out following the Fmoc/*t*Bu strategy.[5] The *N*-terminal amino acids, Ala and Pro, were introduced as N^{α}-Aloc-protected amino acids.[22] Subsequent cleavage of the acid-labile side-chain protecting groups with TFA/iPr$_3$SiH/H_2O, 95/2.5/2.5 afforded peptide resins **B** and **C**.
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23. *Typical procedure for palladium-catalyzed N-Aloc removal in the presence of* $Me_2NH{\cdot}BH_3$. Peptide resin (10 mg; 1.81 μmol) was solvated in NMP (1 ml) under an argon atmosphere. $Me_2NH{\cdot}BH_3$ was added in an appropriate concentration under agitation, followed by $Pd(PPh_3)_4$ (0.42 mg; 0.2 equiv). After the reaction time specified in the table, the peptide resin was washed with NMP (3×), NMP containing 0.5% sodium diethyldithiocarbamate trihydrate (3×) and DMF (3×). The peptide was released from the solid support through saponification with 0.1 N NaOH (0.5 ml) in DMF (0.5 ml) for 20 min. An aliquot of the solution was neutralized with HCl and analyzed by HPLC and mass spectrometry.
24. The Pd(0)/$Me_2NH{\cdot}BH_3$ system afforded the quantitative release of Aloc from peptide resin **C** (where Aloc was installed on a primary amine) over 30 min without any formation of the allylamine.
25. This same observation was already reported when Aloc, installed on the supported piperidine secondary amines, was being removed.[13]