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A Mild Deprotection Strategy for Allyl-Protecting Groups and Its Implications in Sequence Specific Dendrimer Synthesis

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Abstract: A mild deprotection strategy for allyl ethers under basic conditions in the presence of a palladium catalyst is described. Under these conditions, aryl allyl ethers can be cleaved selectively in the presence of alkyl allyl ethers. These conditions are also effective in the deprotection of allyloxycarbonyl groups. The utility of the current methodology in sequence specific dendrimer synthesis is demonstrated.

Protection and deprotection components of organic synthesis have been compared to death and taxes in organic synthesis: they are not desirable; however, they are unavoidable.[1a] Although some of the most elegant syntheses in the literature involve strategies that avoid the use of protecting groups, protection−deprotection strategies are ubiquitous in synthesis in general. The inherent nature of the usage of protection and deprotection strategies dictates that these reactions must be performed in the presence of a variety of other functional groups. This is especially true for the deprotection step, since it is performed later in the synthesis. Therefore, it is desirable to develop methodologies that afford high yielding deprotections under mild reaction conditions. The allyl group has been frequently used in organic synthesis as a protecting group for alcohols and amines due to its stability under basic and acidic conditions.[1] In this paper, we outline a mild deprotection strategy for allyl ethers. We also show the following: (i) this methodology can be used to deprotect aryl allyl ethers in the presence of alkyl allyl ethers. (ii) Allyl ethers are cleaved exclusively in the presence of benzyl ethers. (iii) Allyloxycarbonyl groups can also be cleaved in high yields under these reaction conditions. (iv) This methodology is useful in the sequence specific incorporation of functionalities in dendrimer synthesis.

The removal of an allyl protecting group in classical syntheses typically involves a two-step sequence, in which isomerization of the double bond to the corresponding prop-1-enyl ether is followed by either H^+- or Hg^{2+}-catalyzed hydrolysis or oxidative cleavage.[2] Isomerization of the allyl to prop-1-enyl group has been achieved with strong bases such as KO^{t}Bu-DMSO[3] or transition metal catalysts such as the Wilkinson's catalyst.[4] More recently, several other reagents have been utilized for the direct deprotection of allyl ethers. These include NBS,[5] Cp_2Zr,[6] $SmCl_3$,[7] $TiCl_3$,[8] DDQ,[9] $NaBH_4/I_2$,[10] and $CeCl_3 \cdot 7H_2O-NaI$.[11] Several methodologies demonstrate that the cleavage of allyl groups can be performed under palladium-catalyzed reaction conditions.[12] All these palladium-catalyzed methodologies are carried out either under acidic conditions or in the presence of a reducing agent such as sodium borohydride. We have been interested in the deprotection of allyl groups under mildly basic conditions, since we have utilized this protecting group for sequence specific incorporation of monomers in dendrimer synthesis.[13] It is also noteworthy that others have used allyl-protecting groups for functionalized dendrimer synthesis as well.[14]

During our dendrimer synthesis based on biaryl functionalities,[15a] we noticed that allyl ethers can be cleaved under Suzuki coupling conditions ($Pd(PPh_3)_4$, K_3PO_4, DME, reflux).[15b] However, this reaction was not clean enough to be an effective methodology. Therefore, we optimized the reaction conditions and found that allyl ethers can be cleaved smoothly using $Pd(PPh_3)_4$ (0.05−1.00 mol %) and K_2CO_3 (3−6 equiv) in methanol (Table 1). The reagent can be considered as a general deallylating agent useful for aryl as well as alkyl allyl ethers, and the yields range from 82 to 97% as outlined in Table 1.

At first, we examined the deprotection of **1** with 1 mol % of $Pd(PPh_3)_4$ and 3 equiv of K_2CO_3 in methanol. After the mixture was stirred at room temperature for 2 h,

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(12) For methodologies involving $Pd(PPh_3)_4-NaBH_4$ or $LiBH_4$, see: (a) Beugelmans, R.; Bourdet, S.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 4349. (b) Beugelmans, R.; Neuville, L.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 3129. (c) Bois-Choussy, M.; Neuville, L.; Beugelmans, R.; Zhu, J. *J. Org. Chem.* **1996**, *61*, 9309. Using $Pd(PPh_3)_4-PhSiH_3$: (d) Dessolin, M.; Guillerez, M.-G.; Thieriet, N.; Guibé, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *36*, 5741. For palladium-catalyzed allyl cleavage under acidic conditions, see: (e) Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092. (f) Nakayama, K.; Uoto, K.; Higashi, K.; Soga, T.; Kusama, T. *Chem. Pharm. Bull.* **1992**, *40*, 1718. (g) In our methodology, we presume that carbonate anion acts as the nucleophile to react with the Pd−π−allyl species. However, note that this claim is unsubstantiated at this time.

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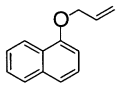
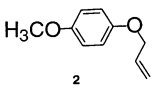
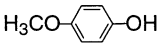
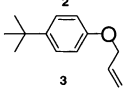
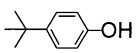
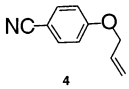
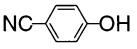
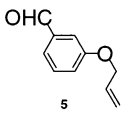
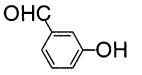
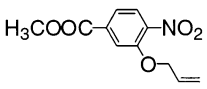
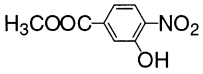
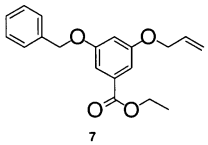
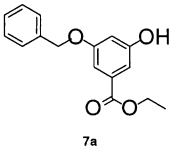
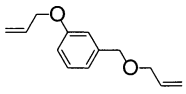
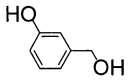
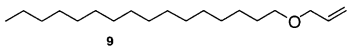
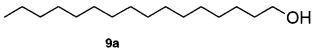
TABLE 1. Deprotection of Allyl Ethers[a]

Entry	Substrate	Product	Time (hrs)	Yield (%)[b]
1	 1	 1a	2	97
2	 2	 2a	12	96
3	 3	 3a	12	85
4	 4	 4a	6	92
5	 5	 5a	6	82
6	 6	 6a	6	95
7[c]	 7	 7a	2	85
8[d]	 8	 8a	12	90
9[e]	 9	 9a	12	84

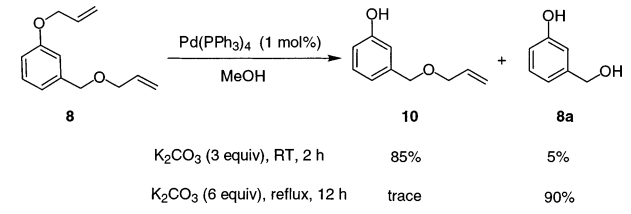
[a] General reaction condition: 1.0 equiv of substrate, 1 mol % of $Pd(PPh_3)_4$, K_2CO_3 (3 equiv), methanol. [b] Yields refer to isolated product. [c] Ethanol was used as solvent. [d] K_2CO_3 (6 equiv), 12 h, reflux.

1-naphthol (**1a**) was obtained in 97% yield. It should be noted that **1a** was obtained in 98% yield even with 0.05 mol % catalyst loading. This method was effective for aryl allyl ether substrates containing both electron-donating groups (entries 2−3) and electron-withdrawing groups (entries 4−6). It was also observed that aryl allyl ethers containing electron-withdrawing groups required shorter reaction times compared to the ones with electron-donating groups. This result is consistent with the proposal that the first step in $Pd(PPh_3)_4/NaBH_4$-catalyzed deprotection involves an oxidative addition of palladium to insert between the C−O bond.[12a−c,g] We show here that a range of reducible functionalities such as cyano, aldehyde, nitro, and ester is unaffected under these reaction conditions (entries 4−7). We have also noticed that the reaction of **7** with $Pd(0)/K_2CO_3$ in methanol afforded the compound **7a** along with the corresponding transesterified methyl ester **7b** after 2 h. We were able to obtain the compound **7a** in its pure form when the reaction was performed in ethanol under the same reaction conditions (entry 7). At ambient temperature, the reaction was too slow for the deprotection of allyl groups in alkyl allyl ethers. In refluxing methanol, we found that this reaction can be accelerated (entries 8−9). Also, we note that no deprotection product was observed when the reaction was carried out in the absence of the Pd(0) catalyst. When the reaction was carried out in MeOH in the presence of Pd(0) catalyst, but without the base, the reaction proceeded very slowly. A small amount of product was observed in TLC after nearly 48 h of reaction in methanol at ambient temperature.

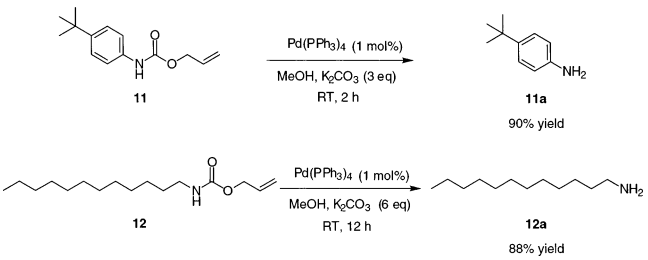
Since we observed that the alkyl allyl ethers are cleaved very slowly at ambient temperature, we were interested in investigating whether aryl allyl ethers can be cleaved selectively in the presence of alkyl allyl ethers. Therefore, we performed the deprotection of **8** under our standard reaction conditions at ambient temperature for 2 h. The product mixture contained 85% of the aryl deprotected product **10**, while the di-deprotected product **8a** was obtained in only 5% yield as shown in Scheme 1. This reaction also demonstrates that benzyl ethers are not cleaved under these reaction conditions.

Allyloxycarbonyl (Alloc) is an excellent protecting group for the hydroxyl groups in carbohydrates and amine and imide moieties of nucleoside bases and peptides. The palladium-catalyzed deprotection of allyl carbamate usually passes through the π-allyl Pd complex which could then be intercepted by either carbon nucleophiles (dimedone,[16a] *N*,*N*′-dimethyl barbituric acid[16b]) or heteronucleophiles (potassium 2-ethylhexanoate,[17] amines,[18,19]

SCHEME 1. Selective Deprotection of Aryl Allyl Ether in the Presence of Alkyl Allyl Ether



SCHEME 2. Deprotection of the Allyloxycarbonyl Group



thiols[19]). However, allylamine or allyl ether was frequently observed as a byproduct in the latter case.[20] A notable exception is the procedure developed by Guibe and co-workers using a reagent combination Pd(0)−Bu_3-SnH-acid,[21] which has been applied in the solid-phase peptide synthesis[22] and in complex natural products synthesis.[23] We noticed that our methodology can be used for deprotection of *N*-allyloxycarbonyl derivatives of aryl and alkylamines under mildly basic conditions. Reaction of **11** and **12** with $Pd(PPh_3)_4/K_2CO_3$ in methanol afforded the corresponding amines **11a** and **12a** in 90% and 88% yields, respectively (Scheme 2).

Recently, we developed a methodology for synthesizing dendrons with a variety of functionalities on the periphery, which involved the allyl-protecting group.[13] One of our goals has been to utilize an efficient deprotection strategy to achieve the sequence specific incorporation of monomers with minimal effort. Therefore, to demonstrate the utility of the current methodology, we attempted the synthesis of the 3-mer dendron **17** with two different peripheral groups using a reaction sequence that does not need any purification in the intermediate steps. The reaction sequence is shown in Scheme 3. Accordingly, the monomer **13** was refluxed with 4-*tert*-butylbenzyl bromide, K_2CO_3, and 18-crown-6 in acetone to afford **14**. After the acetone was evaporated, the crude product **14** was treated with $Pd(PPh_3)_4$ and K_2CO_3 in methanol to afford a 1:1 mixture of **15a** and **15b**.[24] The mixture of products was confirmed by ^{1}H NMR. After the solvent was evaporated, the reaction mixture was passed through a plug of silica gel. The reaction mixture of **15a** and **15b** was treated with 3-methylbenzyl bromide in the presence of K_2CO_3 in acetone to afford the product mixture containing **16a** and **16b**. After the evaporation of the solvent, the ester group of the crude reaction mixture containing **16a** and **16b** was reduced with $BH_3 \cdot Me_2S$ to afford the product **17** in 85% overall yield. We were also able to prepare the compound **17** from monomer **18** in 70% overall yield, as shown in Scheme 4. Although the latter sequence involves one step less, the overall yield of this reaction sequence is lower. This result can be attributed to the slower deprotection of allyl groups in the presence of the relatively electron-donating hydroxymethyl group. We have not yet optimized this procedure to obtain higher yields.

In summary, we have developed a mild deprotection strategy for allyl ethers under basic conditions. Aryl allyl ethers can be selectively cleaved in the presence of alkyl allyl ethers; allyloxycarbonyl groups can also be cleaved under these reaction conditions. We have demonstrated the utility of this methodology in the sequence specific incorporation of functionalities in dendrimers, by synthesizing a 3-mer dendron. The current methodology offers very attractive features such as compatibility of functional groups, mild reaction conditions, and selective deprotection. Therefore, this method holds the promise of finding extensive applications in organic synthesis.

Experimental Details

General Procedure for Deprotection of Allyl or Allyloxycarbonyl Group. To a stirred solution of appropriate allyl or allyloxycarbonyl protected compound (1.0 mmol) in MeOH (10 mL) was added catalytic amounts of $Pd(PPh_3)_4$ (0.05−1.00 mol %) under a nitrogen atmosphere. The slightly yellow solution was stirred for 5 min, and K_2CO_3 (3.0−6.0 mmol) was added. The reaction was monitored by TLC. All reactions were complete within 2−12 h. The reaction mixture was concentrated in vacuo, and the residue was treated with 2 N HCl. The aqueous solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes/EtOAc). In the case of amines, the crude product was treated with water after evaporation of the solvent. The reaction mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purified by neutral alumina column chromatography.

Synthesis of 3-(4-*tert*-Butylbenzyloxy)-5-(3-methylbenzyloxy)-benzyl Alcohol (17) from 13. To a solution of **13** (0.220 g, 1 mmol) and 4-*tert*-butylbenzylbromide (0.227 g, 1 mmol) in acetone (10 mL) was added K_2CO_3 (0.276 g, 2 mmol) and 18-crown-6 (0.0132 g, 0.05 mmol). The reaction mixture was refluxed for 12 h. The solvent was evaporated, and the residue was dried under vacuum. The crude compound **14** was dissolved in methanol (15 mL), and $Pd(PPh_3)_4$ (0.011 g, 0.01 mmol, 1 mol %) was added under a nitrogen atmosphere. The slightly yellow solution was stirred for 5 min, and K_2CO_3 (0.138 g, 1 mmol) was added. After 1 h, the starting material was completely consumed, but two product spots were observed in TLC. Methanol was evaporated, and the crude product was passed through a plug of silica gel and evaporated. The mixture corresponded to **15a** and **15b** in approximately 1:1 ratio as confirmed by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.17 (m, 12H), 6.71−6.69

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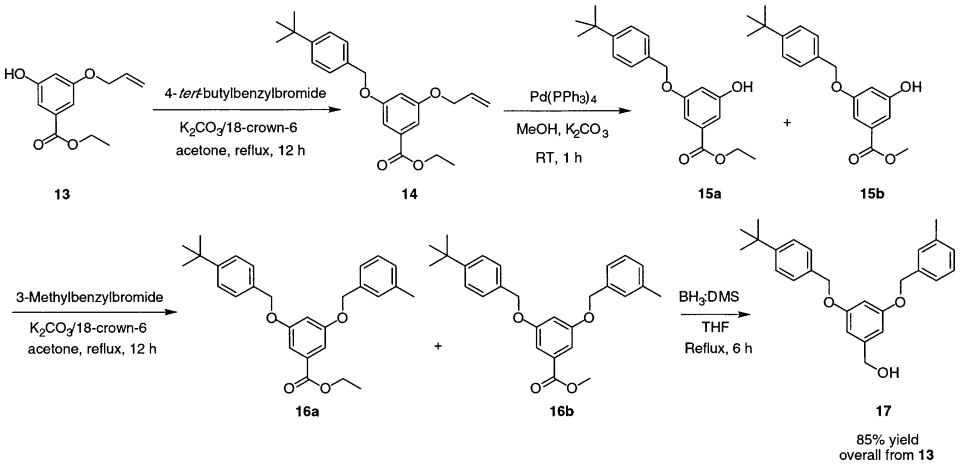
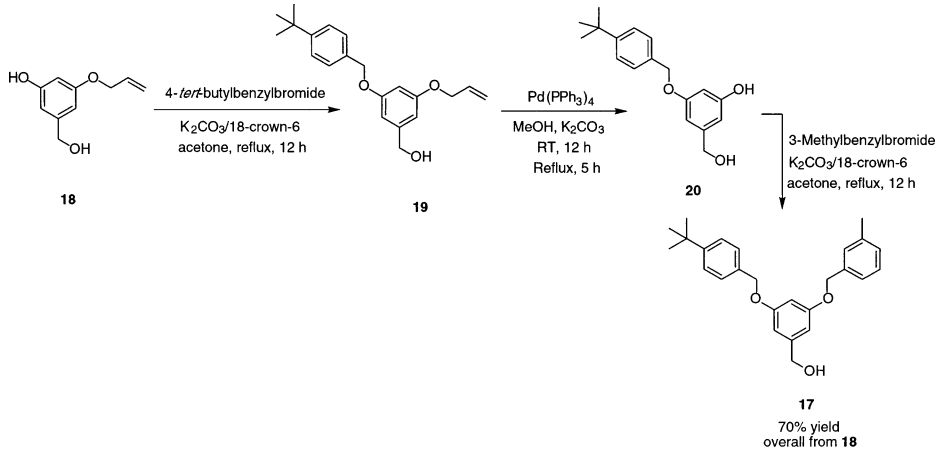
(24) When this reaction was carried out in ethanol, the corresponding deprotected ethyl ester was obtained as the only product. See also Table 1, entry 7.

SCHEME 3. Synthesis of Dendron 17 from 13



SCHEME 4. Synthesis of Dendron 17 from 18



(m, 2H), 5.0 (s, 4H), 4.34 (q, J = 7.2 Hz, 2H), 3.89 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.32 (s, 18H). The crude mixture from above was dissolved in acetone (10 mL), and 3-methylbenzyl bromide (0.220 g, 1.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol), and 18-crown-6 (0.0132 g, 0.05 mmol) were added. The reaction mixture was refluxed for 12 h and acetone was evaporated. Water and dichloromethane were added to the crude mixture, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and evaporated. The crude mixture **16a** and **16b** was dried under vacuum and subjected to reduction using $BH_3 \cdot Me_2S$ (1 M solution in THF, 2 mL, 4 mmol) in dry THF under reflux for 6 h. The crude mixture was quenched with 2 N HCl and extracted with dichloromethane. The organic layer was evaporated, and the residue was purified by silica gel column chromatography using EtOAc/hexanes (20:80) mixture as eluent. Yield 0.34 g (85% yield).

Synthesis of 3-(4-*tert*-Butylbenzyloxy)-5-(3-methylbenzyloxy)-benzyl alcohol (17) from 18. To a solution of **18** (0.180 g, 1 mmol) and 4-*tert*-butylbenzyl bromide (0.227 g, 1 mmol) in acetone (15 mL) was added K_2CO_3 (0.276 g, 2 mmol) and 18-crown-6 (0.0132 g, 0.05 mmol). The reaction mixture was refluxed for 12 h, acetone was evaporated, and the residue was dried under vacuum. The crude compound **19** was dissolved in methanol (10 mL), and $Pd(PPh_3)_4$ (0.011 g, 0.01 mmol, 1mol %) was added under a nitrogen atmosphere. The slightly yellow solution was stirred for 5 min, and K_2CO_3 (0.820 g, 6.0 mmol) was added. The reaction mixture was stirred at room temperature for 12 h and refluxed for 5 h. Methanol was evaporated, and the crude product was passed through a plug of silica gel and evaporated. The crude mixture **20** was dissolved in acetone (10 mL), and 3-methylbenzyl bromide (0.220 g, 1.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol), and 18-crown-6 (0.0132 g, 0.05 mmol) were added. The reaction mixture was refluxed for 12 h, and acetone was evaporated. Water and dichloromethane were added to the crude mixture, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over Na_2SO_4 and evaporated. The crude residue was purified by silica gel column chromatography using EtOAc/hexanes (20:80) mixture as eluent. Yield 0.28 g (70%).

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Supporting Information Available: Experimental details and characterization data for all the new compounds are reported, and a mild deprotection strategy for allyl ethers and allyloxycarbonyl groups is described. This material is available free of charge via the Internet at http://pubs.acs.org.

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