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Chromatography-free Pd-catalyzed deprotection of allyl ethers using PS-DEAM as a scavenger of boronic acids and Pd catalyst

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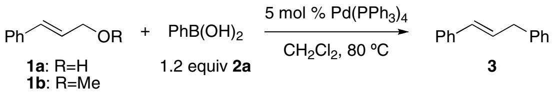
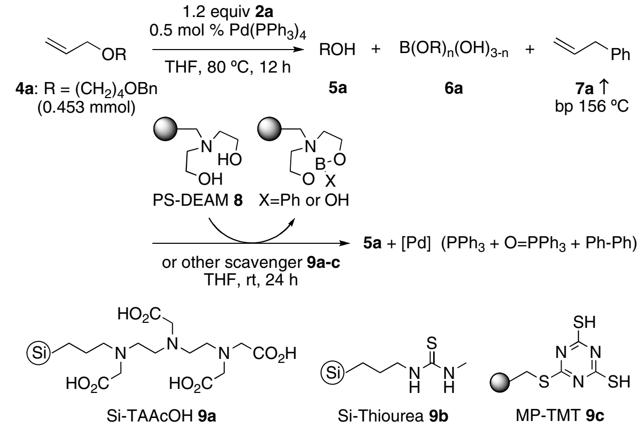
Abstract—Polystyrene-bound diethanolamine (PS-DEAM) work-up for a newly developed $Pd(PPh_3)_4$-catalyzed cleavage of allylic alkyl ethers using phenylboronic acid can effectively release Pd-free parent alcohols. Furthermore, chromatography-free deallylation can be conducted by using vinylboronic anhydride pyridine complex as an allyl scavenger with a catalytic amount of $Pd(OAc)_2$ and 4-(diphenylphosphino)benzoic acid instead of $Pd(PPh_3)_4$ to yield the desired products in high purities and yields after removal of volatile byproducts and the phosphine-derived contaminants by evaporation and sequestration through acid–base interaction with PS-DEAM, respectively.

Allyl group is one of the most useful protecting groups for alcohols due to its stability towards both acidic and basic conditions.[1] Although its palladium-catalyzed removal had been a problem owing to poor leaving ability of the ether group, it was nearly solved by recent developed deallylation methods using *p*-toluenesulfinic acid,[2a,b] polymethylhydrosiloxane–$ZnCl_2$,[2c] 1,3-dimethylbarbituric acid (DMBA),[2d,e] and anilines[2f] as allyl scavengers. Our original deallylation using DMBA as a soft carbonucleophile has advantages of commercial availability of reagents, compatibility with a wide variety of functional groups, high yields, and simple operation over other ones.[2a–c,f,3] However, they require more than a few mol % palladium catalyst loadings and purification of the deallylated product with column chromatography to remove the palladium catalyst as well as the allylated scavengers.[4] Therefore, there is still a need to develop an alternative method, which can remove the palladium catalyst and byproducts without the use of column chromatography.[5]

Previously, we reported the Pd^0-catalyzed direct cross-coupling reaction of allyl alcohols with phenylboronic acid (PBA, **2a**) as a hard carbonucleophile.[6] Boronic acid moiety in **2a** would work as Lewis acid to improve poor leaving ability of the hydroxyl group. We also confirmed that allyl ether **1b** as well as allyl alcohol **1a** could be coupled with PBA under the palladium catalysis (Scheme 1). This result encouraged us to utilize **2a** as the allyl scavenger for the cleavage of alkyl allyl ethers, because the allylated scavenger, that is, allylbenzene, is volatile.



Scheme 1. $Pd(PPh_3)_4$-catalyzed cross-coupling of **1a**–**b** with **2a**.



Scheme 2. $Pd(PPh_3)_4$-catalyzed deallylation of **4a** with **2a** followed by scavenging.

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Table 1. Scavenger effect on the removal of Pd

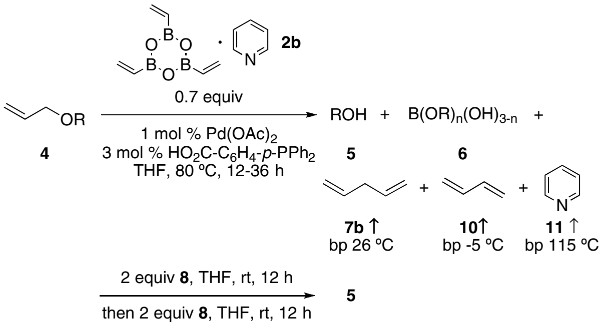
Entry	Scavenger	Loading (mmol/g)	Weight	Residual Pd (ppm)[a]	Reduction in Pd (%)
1	**8**	1.7	0.53 g[b]	15.63	99.4
2	Polystyrene	—	0.53 g	1424	49.5
3	**9a**	0.7	13.0 mg[c]	1157	60.6
4	**9b**	1.1	8.3 mg[c]	50.32	98.3
5	**9c**	1.0	9.1 mg[c]	82.36	97.1

[a] The initial concentration was around 2800 ppm. The residual Pd concentration was determined by ICP-ES.

[b] 2 equiv of **8** to **4a** was used.

[c] 4 equiv of **9a–c** to Pd(PPh$_3$)$_4$ was used.

Fortunately, further optimization of the reaction conditions revealed that the deallylation of **4a** proceeded and completed in the presence of less than 1 mol % of catalyst in THF instead of dichloromethane (Scheme 2).[7]



Scheme 3. Pd-catalyzed deallylation of **4** with **2b** followed by PS-DEAM scavenging.

In addition, we noticed that the use of readily prepared[8] or commercially available[9] polystyrene-bound dietha-

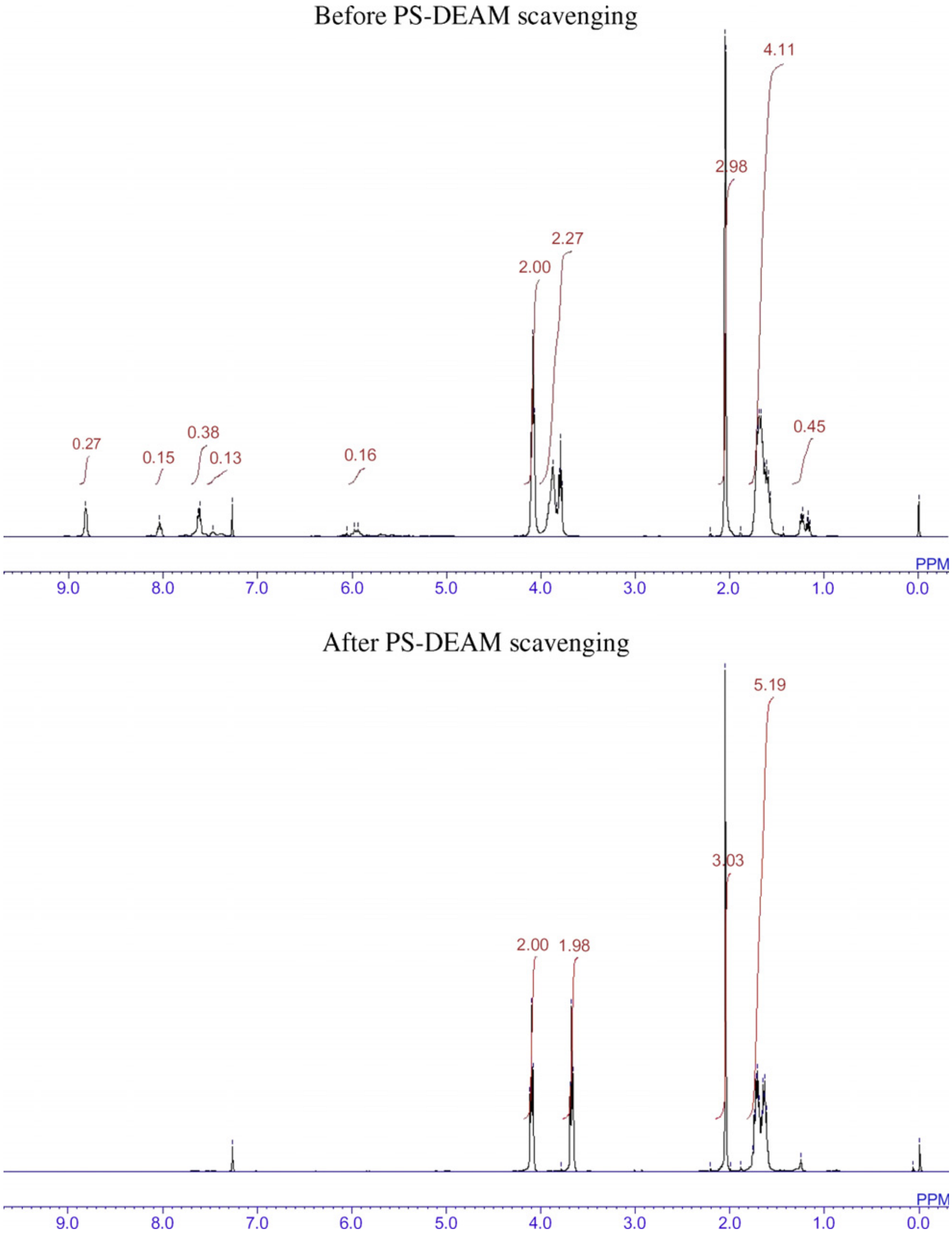


Figure 1. ^{1}H NMR spectra of **5d**.

nolamine (PS-DEAM, **8**) for removal of an excess of **2a** and trans-esterification of a partially formed borate **6a** led to release of the parent alcohols **5a** with decolorization. Since the decolorization would be due to the decrease in palladium contamination, residual Pd levels in the crude material were determined by inductively coupled plasma-emission spectroscopy (ICP-ES) (Table 1).[10] To our surprise, treatment with PS-DEAM scavenged 99.4% of the used palladium catalyst (entry 1). The diethanolamine moiety in **8** should be essential for the removal because non-functionalized cross-linked polystyrene itself hardly scavenged the catalyst (entries 1 vs 2). The work-up with PS-DEAM could reduce the residual Pd more than that with 4 equiv of commercially available Pd^0 scavengers **9a–c**[9,11] to the Pd catalyst (entries 1 vs 3–5). Use of a stoichiometric amount of PS-DEAM to **4a**, namely an excess amount to the $Pd(PPh_3)_4$ catalyst, is necessary for the removal of boronic acid **2a** and ester **6a**, would make up for its weaker affinity for the Pd and could effectively scavenge the Pd strongly ligated with triphenylphosphine. To the best of our knowledge, PS-DEAM has never been employed for the Pd scavenger.

Although PS-DEAM could scavenge not only the boronic acids but also the palladium metal, the crude product contained a small amount of phosphine, phosphine oxide, and biphenyl as an oxidative homocoupling product of **2a**,[12] besides. In order to remove all of these byproducts without the use of column chromatography,[13] vinylboronic anhydride pyridine complex (**2b**)[14] was employed as the allyl scavenger instead of **2a** in the presence of 1 mol % $Pd(OAc)_2$ and 3 mol % 4-(diphenylphosphino)benzoic acid[14] (Scheme 3). The boron reagent **2b** would be transformed into more volatile byproducts, that is, 1,4-pentadiene, 1,3-butadiene, and pyridine, during the deallylation. Furthermore, the basic PS-DEAM would be expected to scavenge the acidic phosphine and its oxide via acid–base interaction. In fact, this new protocol can also cleave allyl ethers in **4a–g** completely to give deallylated products **5a–g**[15] in high purities and yields after PS-DEAM treatment (Fig. 1, Table 2).[16,17] ^1H NMR spectra of **5d** before and after PS-DEAM scavenging are shown in Figure 1, which indicate that PS-DEAM converts partially formed boronic esters to the free alcohol **5d** and removes impurities derived from **2b** and the triarylphophine.

Table 2. Pd-catalyzed deallylation of **4a–g** with **2b**

Entry	4	R	5	Yield of **5** (%)	Reduction in Pd[a] (%)
1	**4a**	$(CH_2)_4OBn$	**5a**	96	95.4
2	**4b**	$(CH_2)_4OTBS$	**5b**	81	96.3
3	**4c**	$(CH_2)_4OMOM$	**5c**	79	96.5
4	**4d**	$(CH_2)_4OAc$	**5d**	83	97.8
5	**4e**	$(CH_2)_4OBz$	**5e**	98	96.8
6[b]	**4f**	(−)-Menthyl	**5f**	92	97.8
7[b]	**4g**	1-Adamantyl	**5g**	86	95.7

[a] The reduction in Pd was calculated on the basis of the residual Pd concentration determined by ICP-ES.

[b] Reaction at 110 °C.

In summary, we have disclosed that boronic acids **2a** and **2b** could cleave alkyl allyl ethers effectively in the presence of less than 1 mol % palladium catalyst and that the following work-up with PS-DEAM could remove not only the boronic acids but also the palladium metal. The deallylation using combination of vinylboronic anhydride **2b** and a catalytic amount of $Pd(OAc)_2$ and acid-containing phosphine ligand followed by PS-DEAM scavenging allows formation of deprotected alcohols in high purities and yields without the use of column chromatography. The non-aqueous work-up is suitable for isolation of polar deprotected compounds. Further studies on development of more facile deallylation methods are underway in our laboratory.

Acknowledgment

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9. PS-DEAM and MP-TMT were purchased from Argonaut technologies.
10. *General procedure for Table 1*: To a test tube containing **4a** (99.5 mg, 0.452 mmol), **2a** (66.4 mg, 0.545 mmol), and $Pd(PPh_3)_4$ (2.5 mg, 2.2 µmol) was added anhydrous THF (1.0 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 12 h. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.7 mmol/g, 0.53 g, 0.90 mmol) and THF (5.3 mL) were added to the mixture. The mixture was agitated at room temperature for 24 h. The mixture was filtered and thoroughly washed with THF. The filtrate was concentrated in vacuo and residue **5a** was dissolved in 1,4-dioxane, ultra pure water, and aqua regia (10 mL) and subjected to ICP-ES. The reduction in Pd was calculated on the basis of the residual Pd concentration determined by ICP-ES.
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13. Although commercially available polymer-bound triphenylphosphine-Pd(0) (PS-PPh_3-Pd) was used as a catalyst for this purpose, it turned out to be ineffective. Parlow et al. reported that anthracene-tagged phosphine-palladium(II) catalyst for Suzuki–Miyaura cross-coupling allowed for the easy removal of the Pd catalyst along with the dissociated phosphine ligand and phosphine oxide byproducts by sequestration through a chemoselective Diels–Alder reaction with a maleimide resin. Lan, P.; Berta, D.; Porco, J. A., Jr.; South, M. S.; Parlow, J. J. *J. Org. Chem.* **2003**, *68*, 9678.
14. Vinylboronic anhydride pyridine complex and 4-(diphenylphosphino)benzoic acid were purchased from Aldrich.
15. Characterization data for compounds **5a**–**e**. 4-Benzyloxybutan-1-ol (**5a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H), 4.53 (s, 2H), 3.66 (t, 2H, $J = 5.9$ Hz), 3.53 (t, 2H, $J = 5.8$ Hz), 2.14 (br s, 1H), 1.78–1.63 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.2, 128.5, 127.8, 127.7, 73.0, 70.3, 62.6, 30.0, 26.5; IR (neat): ν_{max} (cm^{-1}) 3392, 2939, 2863, 1094, 1057, 733, 697; EI-MS *m*/*z* (relative intensity) 180 (M)$^+$ (17), 107 (97), 91 (100); EI-HRMS calcd for $C_{11}H_{16}O_2$ (M)$^+$ 180.1150, found 180.1140. 4-*tert*-Butyldimethylsilyloxybutane-1-ol (**5b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68–3.61 (m, 4H), 2.49 (br s, 1H), 1.69–1.62 (m, 4H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 63.3, 62.7, 30.1, 29.7, 25.8, 18.2, −5.6; IR (neat): ν_{max} (cm^{-1}) 3336, 2929, 2858, 1254, 1098, 1061, 834, 774; FAB-MS *m*/*z* 205 (M+H)$^+$. 4-Methoxymethoxybutan-1-ol (**5c**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.64 (s, 2H), 3.70 (t, 2H, $J = 5.9$ Hz), 3.58 (t, 2H, $J = 5.9$ Hz), 3.37 (s, 3H), 1.73–1.66 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 96.4, 67.6, 62.4, 55.1, 29.6, 26.2; IR (neat): ν_{max} (cm^{-1}) 3404, 2935, 2873, 1148, 1109, 1038. 4-Acetyloxybutan-1-ol (**5d**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.11 (t, 2H, $J = 6.3$ Hz), 3.69 (t, 2H, $J = 6.2$ Hz), 2.06 (s, 3H), 1.79–1.59 (m, 4H), 1.38 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 171.4, 64.2, 62.2, 28.9, 24.9, 20.8; IR (neat): ν_{max} (cm^{-1}) 3408, 2944, 2875, 1735, 1237, 1044. 4-Benzoyloxybutan-1-ol (**5e**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (dd, 2H, $J = 1.4$, 8.5 Hz), 7.57 (dd, 1H, $J = 1.4$, 7.4 Hz), 7.45 (dd, 2H, $J = 7.4$, 8.5 Hz), 4.38 (t, 2H, $J = 6.5$ Hz), 3.74 (t, 2H, $J = 6.3$ Hz), 1.93–1.69 (m, 4H), 1.37 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.8, 133.0, 130.4, 129.6, 128.4, 64.7, 62.3, 29.1, 25.1; IR (neat): ν_{max} (cm^{-1}) 3421, 2946, 2873, 1715, 1270, 1113, 1069, 1027; EI-MS *m*/*z* (relative intensity) 194 (M)$^+$ (3.7), 166 (11), 123 (83), 105 (100), 77 (38); EI-HRMS calcd for $C_{11}H_{14}O_3$ (M)$^+$ 194.0943, found 194.0945.
16. For complete conversion of **4** to **5**, this catalytic system requires higher catalyst loading and longer reaction time than the former. The work-up consisting of agitation with PS-DEAM, filtration, and evaporation must be repeated twice for complete conversion of partially formed borates **6** to free alcohols **5**. PS-DEAM might capture **5** partially as its borate and decrease isolated yield of **5** slightly.
17. *General procedure for Table 2*: To a test tube containing **4a** (49.7 mg, 0.226 mmol), **2b** (36.4 mg, 0.151 mmol), and 4-diphenylphophinobenzoic acid (2.1 mg, 6.9 µmol) was added a solution of $Pd(OAc)_2$ in anhydrous THF (6.0 mM, 0.38 mL, 2.3 µmol) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 12 h. The mixture was cooled down to room temperature, and then PS-DEAM™ (1.8 mmol/g, 0.25 g, 0.45 mmol) and THF (2.5 mL) were added to the mixture. The mixture was agitated at room temperature for 12 h. The mixture was filtered and thoroughly washed with THF. The filtrate was concentrated in vacuo and the residue was subjected to the above PS-DEAM treatment again to give **5a** (39.0 mg, 0.216 mmol, 96%). The reduction in Pd was calculated on the basis of the residual Pd concentration determined by ICP-ES.