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doi:10.1246/cl.2012.972

A Facile Chromatographic Method for Purification of Pinacol Boronic Esters

Shunpei Hitosugi, Daiki Tanimoto, Waka Nakanishi, and Hiroyuki Isobe*
Department of Chemistry, Tohoku University, Aoba-ku, Sendai, Miyagi 980-8578

(Received July 11, 2012; CL-120737; E-mail: isobe@m.tohoku.ac.jp)

A facile chromatographic method for purification of pinacol boronic esters has been developed. Impregnation of silica gel with boric acid was effective both for thin layer chromatography (TLC) and for flash column chromatography. Purification of a series of pinacol boronic esters was successful by suppressing loss of the compounds due to over-adsorption.

Separation and isolation of organic compounds is seemingly a routine technique in organic synthesis. Among various separation methods, chromatographic separation methods using silica gel hold a prominent position, which ideally enables the separation of any compounds in a rapid and facile manner.[1] However, especially for a new class of compounds, the chromatographic separation sometimes becomes a formidable obstacle and requires an innovative development of a reproducible and reliable method.[2–5] We recently faced such a problem during chromatographic isolation of pinacol arylboronic esters[6] and realized that a similar issue often accompanies boron-containing compounds which are important and ubiquitous substrates for organic synthesis mainly owing to the ever-increasing importance of Suzuki–Miyaura coupling reactions.[7] We herein report a facile chromatographic method for purification of pinacol boronic ester derivatives. We found that impregnation of silica gel with boric acid is effective to suppress the undesired over-adsorption of the compounds and hence reduces the loss of materials upon chromatographic separation.

We found that the shortage in silica gel chromatography for pinacol arylboronic esters originated from an over-adsorption of the substrates. One of the most frequent issues associated with the separation of arylboronic esters is the low recovery efficiency through chromatography, which can also be found as an immobile or tailing spot on TLC plates. As shown in Figure 1a, when we developed 2,7-diborylnaphthalene **1**[8] as a model substrate on a TLC plate (Merck, silica gel 60F$_{254}$; eluent: 10% AcOEt/hexane), two spots were observed: one at the eluted position of $R_f = 0.4$ and the other near the spotted origin ($R_f \approx 0$) through the visualization by UV irradiation and staining with *p*-anisaldehyde–H_2SO_4 reagent.[9] The analysis of both spots by TLC DART MS (direct analysis in real time mass spectrometry) before the staining showed the presence of **1** in both spots.[10] Thus, we detected identical ionized species of **1** (m/z 381 and 398) from both spots, and the ions were assigned as a proton-adduct and an ammonium-adduct, respectively (Figures 1b and S1[18]). The results showed that the arylboronic ester **1** remained partly at the spotted origin without any apparent degradation and hence indicates that the insufficient recovery of arylboronic esters from the chromatography does not originate from decomposition but from uneven over-adsorption that results in residual bands or spots upon chromatography.[11]

We hypothesized that the undesired over-adsorption around the spotted origin may be due to interactions of the vacant orbital on boron with nucleophilic moieties in silica gel[12] and envisioned that such nuisance interactions may be avoided by preadsorption of appropriate capping agents on silica. We thus examined a boric acid impregnation method, a classic method established for lipid isolation,[13] and succeeded in suppressing the over-adsorption. Thus, when we developed **1** (40 nmol) on a boric acid-impregnated TLC (hereafter denoted as B-TLC) plate,[14] we observed a clearer spot of **1** at $R_f = 0.4$ (eluent: 10% AcOEt/hexane) together with a faint spot at the origin by visualization with *p*-anisaldehyde–H_2SO_4 stain (Figure 1c). An image analysis of the integrated optical densities (IOD) of both spots showed the relative IOD of 72 ± 0.7% and 28 ± 0.7% for the spots at $R_f = 0.4$ and 0, respectively (Table 1). When we analyzed the results on an untreated TLC plate, the relative IOD was 56 ± 0.7% and 44 ± 0.7% for the spots at $R_f = 0.4$ and 0, respectively.[15,16] The results demonstrated the viability of the B-TLC method for the chromatographic purification of boronic esters.

The applicability of B-TLC was examined with a series of representative boron-containing compounds. As shown in Table 1, the B-TLC method was effective particularly for pinacol boronic esters **2**–**4** to reduce the amount of over-adsorbed compound at low R_f (Table 1).[15] However, we also noted a few exceptions: B-TLC was not necessary or applicable to pyridine (**5**), dimethylpropanediol ester (**6**), and boronic acid (**7** and **8**) derivatives. These compounds eluted effectively on the naked silica, whereas the boric acid impregnation could sometimes cause the over-adsorption due to distracting interactions of the substrates with boric acid.

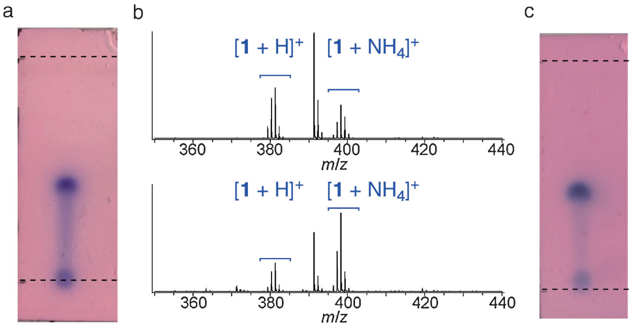
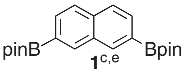
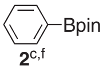
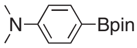
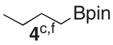
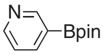
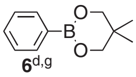
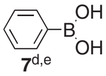
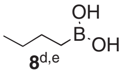
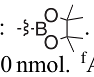


Figure 1. Chromatography of **1** and TLC DART MS analysis. (a) An image of the untreated TLC plate after anisaldehyde–H_2SO_4 staining. (b) DART MS of samples on the untreated TLC plate at $R_f = 0.4$ (top) and 0 (bottom). The middle peaks at m/z 391 correspond to dioctyl phthalate that is contained in the plates. (c) An image of the B-TLC plate after anisaldehyde–H_2SO_4 staining. See Table 1 for the result of image analysis. For a and c, the dotted lines show the positions of sample origin and solvent front.

Table 1. Chromatography of a series of boron-containing compounds on untreated TLC and B-TLC[a]

Compound[b]	Untreated TLC		B-TLC	
	high R_f	low R_f	high R_f	low R_f
 **1**[c,e]	56 ± 0.7%	44 ± 0.7%	72 ± 0.7%	28 ± 0.7%
 **2**[c,f]	87 ± 3%	13 ± 3%	93 ± 1%	7 ± 1%
 **3**[c,g]	94 ± 1%	6 ± 1%	101 ± 2%	−1 ± 2%
 **4**[c,f]	90 ± 0.4%	10 ± 0.4%	97 ± 4%	3 ± 4%
 **5**[c,h]	99 ± 0.6%	1 ± 0.6%	98 ± 0.6%	2 ± 0.6%
 **6**[d,g]	98 ± 6%	2 ± 6%	88 ± 2%	12 ± 2%
 **7**[d,e]	91 ± 5%	9 ± 5%	86 ± 4%	14 ± 4%
 **8**[d,e]	95 ± 6%	5 ± 6%	92 ± 4%	8 ± 4%

[a]The relative values are obtained as the average values from the multiple plates (5–6).[15] [b]Bpin: . [c]Stain: anisaldehyde. [d]Stain: $KMnO_4$. [e]Analyte: 40 nmol. [f]Analyte: 60 nmol. [g]Analyte: 120 nmol. [h]Analyte: 80 nmol.

Finally, we examined the boric acid impregnation of silica gel for separation of pinacol arylboronic ester with flash column chromatography.[1,17] As a typical example, we used **1** (201 mg) as a substrate for the purification. The recovery of **1** through the column of boric acid impregnated silica was 98% (197 mg; eluent: 90% $CHCl_3$/hexane, $R_f = 0.25$) and was superior to that from untreated silica (89%, 178 mg). In a separate set of experiments, we also confirmed that the method was also applicable to the crude materials from a reaction mixture to result in an improved isolated yield.

In summary, we have developed a chromatographic method for separation of pinacol boronic esters. By employing boric acid to cap the nucleophilic sites of silica gel, we succeeded in suppressing the over-adsorption of the compounds both on TLC and column chromatography to assure efficient recovery. The method of boric acid impregnation is concise enough to be implemented in any organic laboratory with readily available materials and may be applied to various borylated compounds bearing nuisance vacant orbital for chromatographic separation.

This study is partly supported by KAKENHI (Nos. 24241036, 20108015, and 22550094) and NEDO. Generous trial use of the TLC DART MS instrument from JEOL is gratefully acknowledged. We also thank Dr. K. Endo (Kanazawa Univ.) for helpful discussion and Y. Nakamura for preliminary investigations.

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11 As shown in Figure S1,[18] we could not detect MS peaks assignable to the hydrolyzed compounds from the spotted origin.

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14 We prepared the B-TLC plates from commercially available plates (Merck, silica gel $60F_{254}$) through immersion in 5% w/v $B(OH)_3$/ethanol for 20 min and subsequent desiccation in vacuo over 1 h at ambient temperature. The time-length of the immersion process was screened from 1 min to 12 h, and the 20-min immersion resulted in the best result. We also noted that the TLC should be developed shortly (<1 min) after the spotting of the compound to ensure the reproducibility. Alternatively, commercially available plates for B-TLC (Analtech, Delaware, U.S.A.) could be used.

15 The image analysis was carried out by deriving the integrated optical densities (IOD) from the scanned plates with ImageJ (W. S. Rasband, U. S. National Institutes of Health, Bethesda, Maryland, USA, http://imagej.nih.gov/ij/, 1997–2012). See also: H. Isobe, N. Tomita, J. W. Lee, H.-J. Kim, K. Kim, E. Nakamura, *Angew. Chem., Int. Ed.* **2000**, *39*, 4257; H. Isobe, S. Sugiyama, K.-i. Fukui, Y. Iwasawa, E. Nakamura, *Angew. Chem., Int. Ed.* **2001**, *40*, 3364. The background IOD was subtracted with the IOD at a vacant place as the reference. This subtraction resulted in the negative values in some cases where the spots are too faint to be detected.

16 We initially attempted to quantify the compound on the TLC plate in absolute values by TLC DART MS or image analysis (ref. 3 and J. I. Ruiz, B. Ochoa, *J. Lipid Res.* **1997**, *38*, 1482.). However, we found that the errors were unacceptably large, probably due to the inconsistent blurring of the spots.

17 The procedure for the impregnation of silica gel with boric acid is as follows: Silica gel (150 g, Kanto, 60N) was immersed in ethanol containing 5% w/v boric acid (550 mL) for 1 h with gentle shaking. After removal of solvent by filtration, the gel was washed with ethanol (600 mL), dried in vacuo over 1.5 h at 60 °C and used in column chromatography.

18 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.