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Benchtop Monitoring of Reaction Progress via Visual Recognition with a Handheld UV Lamp: In Situ Monitoring of Boronic Acids in the Suzuki–Miyaura Reaction

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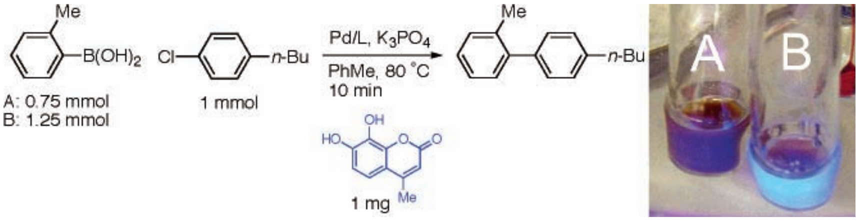
ABSTRACT



Although boronic acids are widely used in metal-catalyzed reactions, it is difficult to assay their consumption. As such, we developed a reversible fluorescent sensor that is activated upon binding a boronic acid. The sensor can be used to monitor consumption of a boronic acid in Suzuki–Miyaura reactions. Importantly, only a standard handheld long-wave UV lamp (365 nm) is required and fluorescence is easily detectable with the naked eye without disturbing the reaction mixture.

Boronic acids have become increasingly important in the field of organic synthesis over the past 20 years.[1] Three major metal-catalyzed reactions utilize these mild air- and water-stable nucleophiles, including the Pd-catalyzed Suzuki−Miyaura coupling reaction,[2] the Rh-catalyzed asymmetric conjugate addition to α,β-unsaturated carbonyl compounds,[3] and the Cu-mediated N-arylation of amines.[4] Although boronic acids are common reagents, one major drawback to their use is the difficulty in assessing them in a given reaction. This is not readily accomplished by common and rapid techniques available to the practicing organic chemist, e.g., TLC and GC. As such, this difficulty prompts chemists to perform reactions with an excess of boronic acid, even though it is often the most expensive component of the reaction. Boronate esters can be assayed much more easily and therefore can serve as alternatives, but reactions that employ these reagents are often slower than when the corresponding boronic acid is used. Moreover, many fewer boronate esters are commercially available. Because of these reasons, we queried whether it would be possible to develop a fluorescent sensor for boronic acids that would allow for their simple in situ sensing under reaction conditions often employed for the Suzuki−Miyaura reaction. Herein, we report our initial findings.

We felt the minimum requirements for a practical and functional sensor to assay boronic acids in the above-mentioned context are that the sensor must: (1) be nonfluorescent (in the presence of base in an organic solvent) in the absence of boronic acid, (2) reversibly bind to the boronic

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(1) Hall, D. G., Ed. *Boronic Acids*; Wiley-VCH: Weinheim, 2005.

(2) (a) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419−2440.

(3) (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. (b) Yoshida, K.; Hayashi, T. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; pp 171−201.

(4) Chan, D. M. T.; Lam, P. Y. S. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; pp 205−238.

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acid or when bound allow the boronic acid to participate in the coupling reaction, (3) bind the boronic acid to form a complex that absorbs light to allow the detection of the binding event using common laboratory equipment, and (4) not interfere with the reaction in which it is used.

A common method to prepare boronate esters is by the condensation of a boronic acid and a 1,2-diol. Common diols for this transformation are pinacol and catechol as they form stable boronate esters. We envisioned a sensor based upon a catechol derivative that upon binding to the boronic acid would fluoresce but remain nonfluorescent when unbound. Numerous aromatic 1,2-diols were examined; however, they did not meet requirement 1 because they were fluorescent in a basic organic medium in the absence of boronic acid. Investigating more specialized catechol derivatives led us to discover Alizarin (2,3-dihydroxy-1,8-anthraquinone), its derivatives, and dihydroxycoumarins, all of which have been reported to bind boronic acids.[5] The possibility of using Alizarin, although its use as a fluorescent sensor for boronic acids has previously been reported,[5b,d,e] was quickly discounted as the excitation wavelength (~550 nm) is difficult to access using equipment commonly found in organic chemistry laboratories. Therefore, we focused on the dihydroxycoumarins, which possess UV absorption maxima near that of a handheld long-wave UV lamp (365 nm).[6]

The first dihydroxycoumarin tested was 6,7-dihydroxy-4-methylcoumarin, **1**. This compound is essentially nonfluorescent in toluene (a solvent used in many Suzuki−Miyaura reactions[7]). Upon addition of *o*-tolyl boronic acid, little change in fluorescence (by visual detection) was observed while irradiating the sample at 365 nm (from a handheld long-wave UV lamp). However, after addition of K_3PO_4 (a common base for Suzuki−Miyaura reactions) and stirring the mixture for 5 min, the fluorescence intensity greatly increased. With 7,8-dihydroxy-4-methylcoumarin, **2**, similar results were obtained: a solution of **2** in toluene was nonfluorescent under irradiation at 365 nm. However, addition of K_3PO_4 to **2** and *o*-tolyl boronic acid led to a dramatic increase in fluorescence intensity (Figure 1).

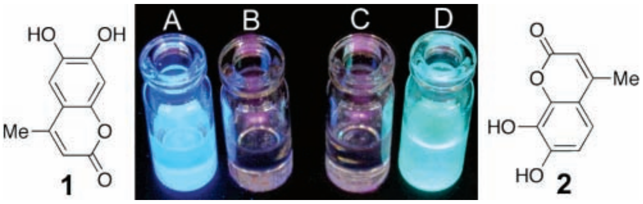

Figure 1. Photograph of four vials, each containing ~5 mg of *o*-tolyl boronic acid and ~5 mg of K_3PO_4 in toluene irradiated by a handheld UV lamp (365 nm). Vial A contains ~1 mg of **1** and vial D contains ~1 mg of **2**. The purple hue from vials B and C is from the reflection of light from the UV lamp.

With these results in hand, we attempted to utilize **1** and **2** in the study of Suzuki−Miyaura coupling processes. The example studied was that of *o*-tolyl boronic acid[8] with 4-*n*-butylchloro-benzene using K_3PO_4 as base, with 1 mol % of $Pd(OAc)_2$ and 2 mol % of SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) in toluene at 80 °C. Two reaction protocols were employed that differed in which coupling partner was the limiting reagent. In the first reaction, 0.75 equiv of *o*-tolyl boronic acid was used, and in the second reaction, 1.25 equiv of *o*-tolyl boronic acid was employed (both relative to 4-*n*-butylchloro-benzene). Additionally, 1 mg of **1** was added to both reaction mixtures. Figure 2 shows these two reaction mixtures in separate reaction vessels after 10 min (enough time for the completion of each reaction). Clearly, the fluorescence intensity of the reaction mixture with excess boronic acid (reaction B) was much greater than that of the reaction with excess aryl chloride (reaction A), in which no *o*-tolyl boronic acid remains. Furthermore, it was determined by GC analysis that the presence of **1** did not interfere with the cross-coupling reaction; 0.75 mmol of the aryl halide was consumed in reaction A, and full consumption of aryl halide was observed in reaction B.[9] Additionally, we were concerned that boron-containing species (likely boric acid) that are formed after transmetalation of the boronic acid would bind to **1** or **2** and cause fluorescence. However, two Suzuki−Miyaura reactions were conducted that contained $B(OH)_3$ instead of *o*-tolyl boronic

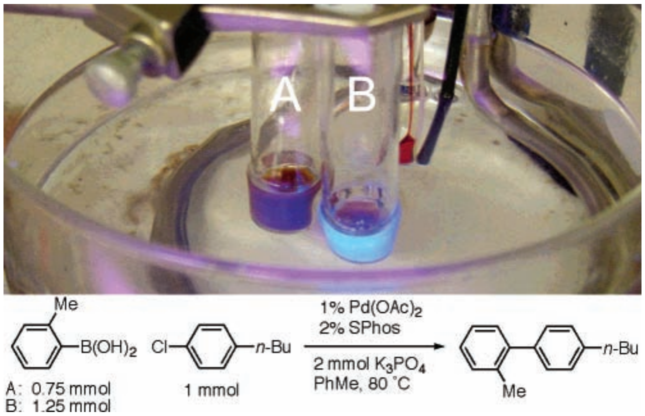

Figure 2. Photograph of two Suzuki−Miyaura reactions with 1 mg of **1** after 10 min, irradiated with 365 nm of light. Reaction A has 0.75 equiv of boronic acid, and B has 1.25 equiv of boronic acid.

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(5) (a) Rudakova, I. S. *Uch. Zap. Inst. Farmakol. Khimioter A. M. N. SSSR* **1963**, *3*, 316−335. (b) Szebellady, L.; Tomay, S. *Z. Anal. Chem.* **1936**, *107*, 26−30. (c) Springsteen, G.; Wang, B. *Tetrahedron* **2002**, *58*, 5291−5300. (d) Campaña, A. M. G.; Barrero, F. A.; Ceba, M. R. *Analyst* **1992**, *117*, 1189−1191. (e) Chimpalee, N.; Chimpalee, D.; Boonyanitchayakul, B.; Burns, D. T. *Anal. Chim. Acta* **1993**, *282*, 643−646.

(6) 6,7-Dihydroxycoumarin, λ_{max} = 354 nm. 7,8-Dihydroxycoumarin, λ_{max} = 335 nm. *CRC Atlas of Spectral Data and Physical Constants for Organic Compounds*; Grasselli, J. G., Ed.; CRC Press: Cleveland, 1973.

(7) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876.

(8) If the boroxine is used, fluorescence is still visible; it is likely the boroxine is converted to **3** under the reaction conditions.

(9) The only other peak observed from the GC analysis was that of the product.

acid using **1** and **2**; no fluorescence was visible from these mixtures upon irradiation at 365 nm (see the Supporting Information).

Next, we wanted to determine if other boronic acids (e.g., hindered or electron-deficient aryl, vinyl, or alkyl) could also be detected using **1** and **2**. In these cases, **2** was employed instead of **1** as it more rapidly produced highly fluorescent complexes at room temperature. Figure 3 depicts four boronic acids (A, *n*-hexyl boronic acid; B, *trans*-octenyl boronic acid; C, 2,6-dimethylphenyl boronic acid; and D, 2,4-difluorophenyl boronic acid) in the presence of ~1 mg of **2** and K_3PO_4 in toluene. Indeed, each boronic acid/**2** combination was fluorescent under 365 nm of light, with varying emission wavelengths.

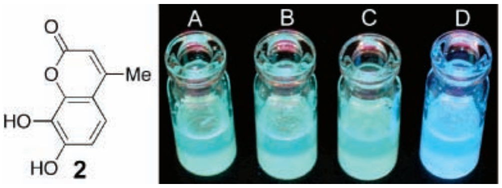

Figure 3. Four different boronic acids (~5 mg each) in the presence of ~1 mg of **2** and ~5 mg of K_3PO_4 in 1 mL of toluene irradiated by 365 nm of light. (A, *n*-hexyl boronic acid; B, *trans*-octenyl boronic acid; C, 2,6-dimethylphenyl boronic acid; and D, 2,4-difluorophenyl boronic acid).

Additionally, we wanted to see if the fluorescence sensing was reversible during the course of a reaction. This could help determine if destruction of the boronic acid is causing a Suzuki–Miyaura reaction to fail to go to completion. To test this, a reaction of 1-naphthalene boronic acid (0.75 mmol) and 4-*n*-butylchloro-benzene (1 mmol) was conducted using the same conditions as above, in the presence of 1 mg of **2**. The base, aryl boronic acid, aryl halide, and **2** were added to a test tube. After the addition of toluene, the tube was placed into a preheated oil bath at 90 °C. The reaction vessel was irradiated with 365 nm of light, and the reaction mixture was found to be highly fluorescent (Figure 4A). Next, a toluene solution of $Pd(OAc)_2$ and SPhos was added to the reaction vessel via syringe. After 10 min, the reaction vessel was exposed to 365 nm of light and only a minimal amount of fluorescence was visible (Figure 4B). Finally, a slurry of 1-naphthalene boronic acid (0.50 mmol) in toluene (1 mL) was added via syringe to the reaction vessel. After ~1 min, it was exposed to 365 nm of light and the solution was again fluorescent (Figure 4C).[10] This ability for the sensor to be turned from on to off to on again may allow circumventing the use of excess boronic acid in Suzuki–Miyaura reactions, thereby saving valuable boronic acid.

Because K_3PO_4 was required for the sensor to be turned on in the presence of the boronic acids, we examined if other bases commonly used in Suzuki–Miyaura reactions (M_2CO_3 where M = Na or K and KF) could be employed. In fact, the use of Na_2CO_3, K_2CO_3, or KF in the presence of *o*-tolyl boronic acid and **2** produced a fluorescent solution, albeit substantially weaker in fluorescence intensity than in the presence of K_3PO_4. From this observation, we believe that an anion is required to bind to the boron center in **3**, thus facilitating fluorescence (Figure 5).

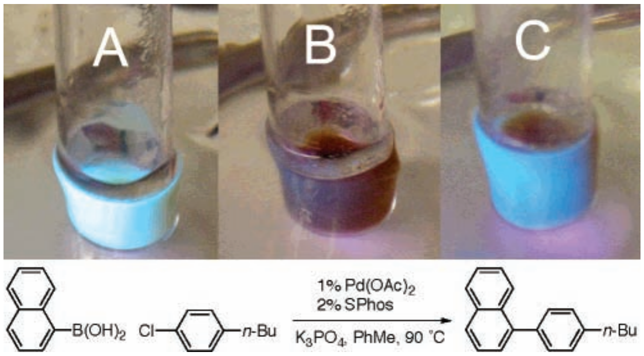

Figure 4. Photographs of the above Suzuki–Miyaura reaction: (A) before addition of the catalyst, (B) 10 min after addition of the catalyst, and (C) after addition of excess boronic acid (after ~1 min).

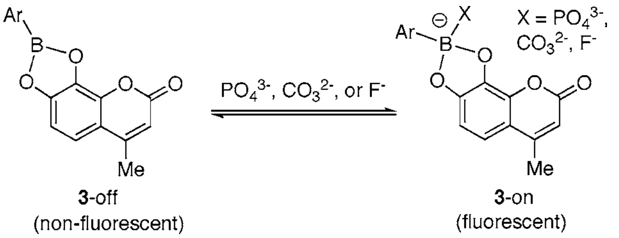

Figure 5. Hypothesis as to the necessity of phosphate, carbonate, or fluoride to produce a fluorescent complex from **3**.

In summary, we have developed a fluorescent sensor that can be utilized for the simple in situ monitoring of boronic acids in Suzuki–Miyaura coupling reactions using a common handheld UV lamp. We are currently examining other applications of **1**, **2**, and related compounds to aid in catalyst development in a variety of other cross-coupling reactions.

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Supporting Information Available: Experimental procedures and entire photographs of Figures 2 and 4 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] If less boronic acid is used, the visual fluorescence intensity decreases.