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Paper-Based Colorimetric Sensor System for High-Throughput Screening of C-H Borylation

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Dedication ((optional))

Abstract: A paper-based colorimetric sensor system (PBCSS) was developed to detect the amount of bis(pinacolato)diboron (B₂Pin₂) and applied as a high-throughput screening protocol in Ir-catalyzed C-H borylation. First, 96 ligands were screened for the borylation of benzene, and then 12 of them were selected and tested for five substrates. These reaction mixtures were spotted in the PBCSS, showing a blue-violet color. The value of the gray scale of each reaction was obtained from these colored spots and converted to the extent of conversion of B₂Pin₂. The extents of conversion of B₂Pin₂ obtained from the PBCSS showed good correlation with those obtained from gas chromatography analysis. In addition, the modified conversion using blank data showed good correlation with the yield of products.

Direct introduction of new functional groups or coupling reactions through C-H activation are efficient, environmentally friendly, and inexpensive in the synthetic chemistry field, because they do not need a prefunctionalization step for the active species.^[1] Many C-H activation methodologies have been developed in the last decades and used in the pharmaceutical and materials industry.^[2] Among them, C-H borylation is one of the most useful reaction methods, because the products such as aryl or alkyl borates are not only easily transformed to other functional groups, but also react with the coupling partners.^[3] The most general method is the reaction of a substrate with bis(pinacolato)diboron (B2Pin2) or pinacolborane (HBpin) in the presence of an Ir catalyst.^[4] The regioselectivity of C-H borylation is controlled by the steric or electronic property of the substrate. The efficiency of an Ir-catalyzed C-H borylation depends on the Ir source, ligand, solvent, and temperature. To determine the suitable parameters for a substrate, considering large numbers of combination of parameters, it is important to use an efficient high-throughput screening (HTS) assay that can rapidly identify the outcome.^[5] Recently, Smith and co-workers reported the optimization of Ir-catalyzed C-H borylation by HTS using an automated HPLC.^[6] Automated analysis instruments such as NMR,^[7] HPLC,^[8] GC,^[9] MS,^[10] and GCMS^[11] have been commonly used as HTS tools in metal-catalyzed transformations. However, they have several drawbacks such as they are

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expensive instruments and need at least several minutes to analyze one sample. Although UV-visible and fluorescence spectroscopy provide quick analysis results, and colorimetric assays are simple and inexpensive, they are limited to specific substrates and the latter does not give precise information.^[12] To address these issues, we developed a simple and general HTS assay for C-H borylation. To the best of our knowledge, an efficient HTS assay for C-H borylation has not been reported.

Recently, we developed a colorimetric assay for the HTS of the transition-metal-catalyzed coupling reaction of aryl or alkyl iodides using gold nanoparticles^[13] or a paper-based colorimetric iodide sensor (PBCIS).^[14] The PBCIS is a simple and easy handling protocol for monitoring the transformation of aryl and alkyl iodides. We also reported a general HTS protocol for the coupling reactions of aryl halides.^[15] Although these protocols have several advantages such as being simple, fast, and easily accessible and not being limited by the structure of the substrates, they might produce false-positive hits due to the decomposition or unwanted coupling reactions of starting materials. To address this drawback and to meet the requirement of simple HTS protocol for C-H borylation, herein, we report the development of a paper-based colorimetric sensor system (PBCSS) for C-H borylation.

To develop a general HTS tool for C-H borylation, we focused on a paper-type sensor that is readily accessible and simple. The PBCSS is made by soaking a filter paper in a buffer solution containing l_2O_5 and starch, followed by drying the paper. The l_2O_5 present in PBCSS is converted to l_2 when it reacts with a reducing reagent such a carbon monoxide.^[16] The residual B_2Pin_2 in an Ir-catalyzed C-H borylation reaction mixture can react with the l_2O_5 present in the PBCSS because B_2Pin_2 is a reducing agent, resulting in the formation of l_2 .^[17] This l_2 forms a complex with the starch present on the PBCSS, inducing a blueviolet color as shown in Scheme 1.^[18]



Scheme 1. Preparation of PBCSS and method for determining the concentration of $\mathsf{B}_2\mathsf{Pin}_2.$

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1 mol% [lr(cod)(OMe)]

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To determine the optimal conditions of PBCSS for B₂Pin₂ quantification, the PBCSS was prepared using various conditions of the PBCSS components. Various concentrations of I_2O_5 and pH levels were tested, and the concentration of starch was fixed at 10 g/L according to previous studies.^[14] (see Supporting Information) The optimal condition of a solution for preparing the PBCSS involves a citrate buffer solution (pH 4, 250 mM) containing starch (10 g/L) and I₂O₅ (5 mM). To quantify B₂Pin₂, the PBCSS was spotted with various concentrations of B₂Pin₂ and scanned using a flat-bed scanner, and the scanned image was converted to a grayscale. The grayscale intensities of the spots were analyzed using a Photoshop program, and the B₂Pin₂ concentrations were calculated from the grayscale intensities. The grayscale intensities in the scanned image of the PBCSS exhibited a high correlation with the B₂Pin₂ concentrations (Figures 1(a) and 1(b)). Moreover, the PBCSS showed a high selectivity for B₂Pin₂ over other potential borate species including HBpin generated in the Ir-catalyzed C-H borylation reaction (Figures 1(c) and 1(d)).



Figure 1. (a) Grayscale image of the PBCSS for B_2Pin_2 titration. (b) Calibration curve of the PBCSS for B_2Pin_2 . (c) Grayscale image of the PBCSS for borate species. (a : phenylboronic acid pinacol ester, b : phenylboronic acid, c : boronic acid, d : HBpin). (d) Response of PBCSS to borate species.

With this PBCSS in hand, first 96 ligands used in Ir-catalyzed C-H borylation were screened. The reaction of benzene (1) with B_2Pin_2 and $[Ir(COD)(OMe)]_2$ was selected as the standard reaction.

Seven types of ligands – phenanthroline, monopyridine, bipyridine, aliphatic amine, 1,3-diketone, heterocyclic compounds bearing nitrogen (imidazole, pyrazole), and bisphosphine – were selected and applied to 96 ligands (**L1~96**) in the standard reaction. After completing the reaction, the reaction mixture was diluted to 25 mM. Then, 2 μ L of the diluted reaction mixture was dropped on the PBCSS. These 96 samples showed different color from blue-violet to white in a few minutes (see Supporting Information).

The paper was scanned as shown in Figure 2(b), and the image was converted to a grayscale. Based on these data and the equation of the standard curve, the extent of conversion of B_2Pin_2 was obtained. However, the conversions did not always match with the yields of the products, because B_2Pin_2 is decomposed or converted to unwanted compounds. To address this issue, blank reactions were run using the 96 ligands,



Figure 2. (a) Scheme of Ir-catalyzed C-H borylation. (b) Grayscale image of the PBCSS for 96 reaction samples. (c) Grayscale image of the PBCSS for 96 blank reaction samples. (d) Correlation graph between the modified extents of conversion from the PBCSS and yields obtained from GC analysis.

40

— Conversion (%)

60

20

LOS

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 $[Ir(COD)(OMe)]_2$, and B_2Pin_2 without the substrate. All the reaction samples were spotted in the PBCSS, and the scanned image is shown in Figure 2(c). Thus, the conversions of B_2Pin_2 in the absence of substrate, the blank data, were obtained from the PBCSS. Considering of these blank data, the modified extents of conversion of B_2Pin_2 were recalculated.

As shown in Figure 2(d), the modified conversions correlate with the yields of the product obtained from the GC analysis in most of the cases. We found that the modified conversions did not provide the wrong information which might be caused by the false-positive hits. These data, provided information about the activity of the ligands in the Ir-catalyzed C-H borylation. Phenanthroline and bipyridine derivatives were good ligands, other ligands were not suitable for this reaction. However, in some cases, the yield of the product was higher than the conversion of B_2Pin_2 . This false-negative hit, indicates that some ligands exhibited good activity for HBpin which was formed from B_2Pin_2 in the reaction. In addition, the blank reaction data provided information about the decomposition of B_2Pin_2 .

To further evaluate this PBCSS, five substrates such as 1,2dimethylbenzene (3), 1,3-dimethoxybenzene (4), 1.3dichlorobenzene (5), 1-bromo-3-methylbenzene and (6). benzo[b]furan (7) were reacted with 12 ligands, which showed good activity in the C-H borylation of benzene. These 60 reactions were conducted in THF. After the completion of the reactions, all the samples were treated with similar methods and the reaction mixtures were spotted on the PBCSS. As shown in Figure 3, all the spots from substrates 5 and 6 showed very dark color, indicating that THF is not a suitable solvent. Therefore, heptane and methyl tert-butyl ether (MTBE) were selected for substrates 5 and 6, respectively. These additional 24 reactions were conducted, and the reaction mixtures were spotted on the PBCSS. A total of 84 spots were scanned and transformed to grayscale image.



Figure 3. Grayscale image of the PBCSS for 84 reaction samples.

Based on these values, the extent of conversion of B_2Pin_2 in each sample was calculated. Finally, the modified conversions that removed the false-positive hits caused by the decomposition of B_2Pin_2 were obtained. These values were obtained by excluding the conversions from the blank data of

each ligand. [Modified conversion of B_2Pin_2 = conversion of B_2Pin_2 in the presence of substrate - conversion of B_2Pin_2 in the absence of substrate].

Based on these data obtained from the PBCSS, the best condition for each substrate was selected. As shown in Table 1, the yields of the products are consistent with the extents of modified conversion of B_2Pin_2 . In addition, the isolated yields are consistent when the reaction were conducted using the best condition.

Table 1. Ir-catalyzed C-H borylation of five substrates^[a]

19

THF



^[a]Reaction condition : substrate (15 mmol), B₂Pin₂ (3 mmol), [Ir(COD)(OMe)]₂ (0.015 mmol), ligand (0.03 mmol). ^[b]Determined by GC analysis.^[c]Isolated vield.

100

12

88

83

In summary, a HTS protocol was developed for C-H borylation using a PBCSS for the first time. This system was prepared by soaking a filter paper in a buffer solution containing l_2O_5 and starch. The PBCSS generated blue-violet color in the presence of residual B_2Pin_2 in an Ir-catalyzed reaction library. The color change exhibited a high correlation with the B_2Pin_2 concentration and efficiency of Ir-catalyst. This PBCSS has several advantages : 1) The preparation method is very simple and inexpensive, 2) It is readily accessible because only a paper and scanner are needed, 3) It provides fast and accurate extent of conversion of B_2Pin_2 by qualitative analysis using visual color change and quantitative conversions using a grayscale image, 4 The use of blank data removes the wrong information caused by the false-positive hits.

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Experimental Section

Preparation of sample solutions of reaction mixtures for HTS : The reaction mixture (2 µL aliquot) was dropped onto the prepared PBCSS. For reproducible results, the following essential procedures were used. The first procedure is the removal of the organic solvent in the PBCSS. Because of the presence of residual B₂Pin₂ in the organic phase after the completion of the reaction, the reaction mixture (0.2 mL) was extracted with ethyl acetate (1.3 mL) and water (5 mL) in a 10mL vial. After the extraction, 3 M brine (1 mL) containing sodium chloride (17.5 g) and water (100 mL) was added to break the emulsion. Then, 1 M HCl (1 mL) diluted with water (5 mL) was added. Then, the diluted solution was dropped on the PBCSS. However, the starch-iodine complex is unstable in the presence of an organic solvent. Therefore, after the spotting, the PBCSS was dried in air for 10 min to remove the organic solvent. The second procedure is the water supply required to accelerate the redox reaction of I_2O_5 and starch-iodine complex formation. If water is added directly, the colored complex is eluted into the solution and low reproducible results are obtained. To solve this problem, after the drying of organic solvent, the PBCSS was incubated for 30 min in a closed box filled with water vapor for uniform water supply at room temperature. After the incubation, optical images were recorded using an optical flatbed scanner (Epson Perfection V33) with a resolution of 300 dpi (dots per inch). The data were analyzed with an 8-bit grayscale histogram in a Photoshop program (Adobe Systems Inc.).

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Paper-based colorimetric sensor for the detection of bis(pinacolato)diboron (B₂pin₂) was developed and used as the High-Throughput Screening (HTS) protocol in the Ir-catalyzed C-H borylation. It was proved to be an efficient tool in the screening of the C-H borylation.



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