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Palladium-catalyzed hydrodehalogenation of aryl halides using paraformaldehyde as the hydride source: high-throughput screening by paper-based colorimetric iodide sensor

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ABSTRACT

Paraformaldehyde was employed as a hydride source in the palladium-catalyzed hydrodehalogenation of aryl iodides and bromides. High throughput screening using a paper-based colorimetric iodide sensor (PBCIS) showed that $Pd(OAc)_2$ and Cs_2CO_3 were the best catalyst and base, respectively. Aryl iodides and bromides were hydrodehalogenated to produce the reduced arenes using $Pd(OAc)_2$ and $Pd(PPh_3)_4$ catalyst. This catalytic system showed good functional group tolerance. In addition, it was found that paraformaldehyde is the hydride source and the reducing agent for the formation of palladium nanoparticles.

High-throughput screening assays have been widely employed for the development of the efficient catalytic system even though they were originally developed in the pharmaceutical industry to accelerate the discovery process.[1] A number of HTS assays by using fluorescence spectroscopy have been developed in the transition metal-catalyzed coupling reaction.[2] However, most of them have drawbacks that require the preparation of the corresponding sensing substrate for the screening of the target coupling reaction.[3] To overcome the problem of the lack of universality, we recently developed the colorimetric gold nanoparticle and the paper-based colorimetric iodide sensor for the HTS.[4] These two assays showed reliable conversions in the palladium-catalyzed coupling reactions of aryl iodides. However, in the point of simplicity and convenience, PBCIS showed better than the colorimetric gold nanoparticle. To expand and evaluate the PBCIS, we have paid attention to find new catalytic system by using PBCIS.

Aryl halides are some of the most widely used substrates in the transition-metal-catalyzed coupling reactions, and are also important structure units of solvents, pharmaceuticals, perfumes, and insect repellents.[5] Although aryl halides are important structure units in organic synthesis, they are classified as pollutants due to their persistent toxic effect.[6] It is known that the activity of the carbon-halogen bond in aryl halide is lower than that in alkyl halide, because the bond dissociation energies of C–X (X = I, Br, Cl, F) in aryl halides are higher than those in alkyl halides. As a result, aryl halides are hard to degrade once they are emitted into. Therefore, a number of methods to transform aryl halides into less harmful chemicals have been developed.[7] Among them, transition-metal-catalyzed hydrodehalogenations have received attention, and palladium,[8] iron,[9] rhodium,[10] and nickel[11] have been employed as catalysts in these transformations. The palladium catalyst has been most widely and intensively used in the hydrodehalogenation of aryl halide due to the fact that palladium has shown good activity in numerous aryl halide transformations. They are usually performed with hydride sources such as H_2,[12] alcohol,[13] metal hydride,[14] formic acid,[15] DMF,[16] silane,[17] and hydrazine.[18] In our continuing studies on the development of hydrodehalogenation, we have focused on paraformaldehyde as a hydrogen source. Although a number of studies on acyl C–H activation have been reported,[19] there has been no report on hydrodehalogenation using paraformaldehyde to the best of our knowledge. Paraformaldehyde has several advantages as a hydride source, because it is stable, easy to handle and store, and inexpensive.

Here, we report the PBCIS assay for the development of transition metal-catalyzed hydrodehalogenation using paraformaldehyde (Scheme 1).

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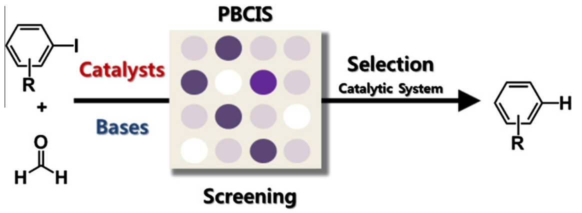
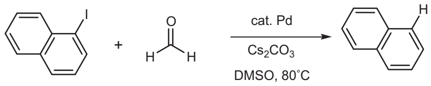


Scheme 1. Optimization of hydrodehalogenations by using PBCIS.

Table 1
Pd-catalyzed hydrodehalogenation[a]



Entry	Pd (mol %)	Mol %	Conversion (%)	Yield[b] (%)
1	$Pd_2(dba)_3$	1.0	100	93
2	$Pd(PPh_3)_4$	1.0	100	96
3	$PdCl_2$	1.0	100	99
4	$Pd(OAc)_2$	1.0	100	99
5	$PdCl_2$	0.1	75	73
6	$Pd(OAc)_2$	0.01	100	99
7	$Pd(OAc)_2$	0.005	100	95
8	$Pd(OAc)_2$	0.001	35	32

[a] Reaction condtions: 1-iodonaphthalene (0.3 mmol), paraformaldehyde (0.3 mmol), and Cs_2CO_3 (0.45 mmol) were reacted in DMSO at 80 °C for 12 h.

[b] Determined by gas chromatography with an internal standard.

To find suitable catalytic system, as shown in Table 1, 1-iodonaphthalene was chosen as a model substrate and reacted with paraformaldehyde under 96 reaction conditions. The reaction of iodonaphthalene and paraformaldehyde was carried out in the presence of catalyst and base in DMSO at 80 °C for 6 h. As a catalyst, $PdCl_2$ (**a**), $Pd(OAc)_2$ (**b**), $NiCl_2$ (**c**), $Ni(OAc)_2$ (**d**), CuCl (**e**), $CuCl_2$ (**f**), $FeCl_3$ (**g**), and $CoBr_2$ (**h**) were employed. Five kinds of weak inorganic bases [Cs_2CO_3 (**A**), K_2CO_3 (**B**), Na_2CO_3 (**C**), K_3PO_4 (**D**), and K_2HPO_4 (**E**)], four kinds of organic bases [DBU (**F**), Et_3N (**G**), DBN (**H**), and TMEDA (**I**)], and three kinds of strong bases [NaH (**J**), KO^tBu (**K**), and NaO^tBu (**L**)] were tested. First, we monitored the conversion of iodonaphthalene by using PBCIS, which is simpler and easier than using gold nanoparticles, and much faster than gas chromatography. The reaction mixture was diluted and treated with 0.2 N HCl, and this solution was spotted into the PBCIS. All the reactions provide different strengths of color, as shown in Figure 1(a). The spots on the scanned PBCIS were converted to grayscale values using Adobe Photoshop. Then, they were converted to the extent of conversion using the conversion equation shown in Figure 1 (b).[20]

As shown in Figure 1, we found several things as followings: (1) PBCIS is a very useful tool to find the optimized condition for the hydrodeiodination. (2) PBCIS is a suitable assay for the transition metal catalyst such as palladium, copper, nickel, iron, and cobalt. (3) At seeing the darkness of spots, the extent of conversion was obtained quickly, and the value of that was obtained from their grayscale intensity. From the results of Figure 1, the reactions with palladium showed higher conversion extents than other catalysts. Among the palladium-catalyzed reactions, weak inorganic bases such as Cs_2CO_3, K_2CO_3, and Et_3N and strong bases such as NaH and NaO^tBu showed high conversion extents (sample numbers 1, 2, 7, 10, 12, 13, 14, 19, 22, and 24). Considering the mild reaction conditions, $PdCl_2$ and $Pd(OAc)_2$ were chosen. In addition, $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ were added as palladium sources due to their good activities in the Pd-catalyzed hydrodehalogenation of aryl bromide.[13b] They were tested for the hydrodehalogenation of iodonaphthalene in the presence of Cs_2CO_3.[21] Their conversions and product yields were monitored by gas chromatography with an internal standard.

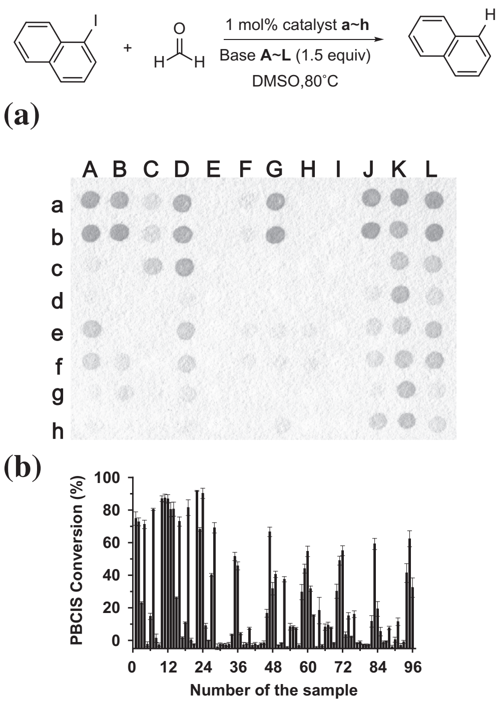


Figure 1. Screening of catalysts and bases for the hydrodehalogenation using PBCIS. Catalyst: **a**–**h**, Base: **A**–**L**. (a) Picture of the PBCIS results of the reactions. (b) The extent of conversion of 1-iodonaphthalene was determined by equation [$\text{conversion (PBCIS)}\% = (-1.0506) \times (\text{grayscale intensity} - 243.9713)$] which is obtained from linear plot of standard samples.

$Pd_2(dba)_3$ and $Pd(PPh_3)_4$ showed 100% conversion of 1-iodonaphthalene, however, the yields of products were 93% and 96%, respectively (entries 1 and 2). Both $PdCl_2$ and $Pd(OAc)_2$ showed good yields when 1.0 mol % of them was used (entries 3 and 4). These results were similar to those from PBCIS. When the amount of palladium was decreased to 0.1 mol %, $PdCl_2$ afforded a 73% yield of the product (entry 5). The employment of 0.01 and 0.005 mol % of $Pd(OAc)_2$ produced naphthalene in 99% and 95% yields, respectively (entries 6 and 7). However, the product yield was decreased to 32% when the amount of $Pd(OAc)_2$ was decreased to 0.001 mol % (entry 8). Based on these results, the optimized conditions of the hydrodehalogenation of aryl iodides involve aryl iodides (1.0 equiv) and paraformaldehyde (1.0 equiv) reacted with $Pd(OAc)_2$ (0.01 mol %) and Cs_2CO_3 (1.5 equiv) in DMSO at 80 °C for 12 h. In addition, when the reaction was conducted in the presence of formaline instead of paraformaldehyde, the desired hydrodehalogenated product was formed. A variety of aryl iodides were reacted with paraformaldehyde under the optimized conditions to explore them further. The results are summarized in Table 2.

Alkyl and alkoxy-substituted aryl iodides were converted into the hydrodehalogenated arenes in good yields (entries 1–6). Halo-substituted aryl iodides were transformed into the deiodinated arenes in good yields (entries 7–9). The hydrodebromination did not proceed in these reaction conditions (entry 9). Aryl iodides bearing the amino or ester group produced the corresponding product in good yields (entries 10 and 11). 4-Nitro iodobenzene was converted to nitrobenzene without the reduction of the nitro group (entry 12). Heteroaromatic iodides such as 2-iodothiophene and 2-iodopyridine also produced the hydrodeiodinated arenes in good yields (entries 13 and 14).

Next, we attempted to apply this reaction method to the aryl bromides. However, the hydrodehalogenated product was formed in low yield in the presence of $Pd(OAc)_2$. To increase the yield of