



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



Ayoung Pyo^{a,†}, Sudeok Kim^{b,†}, Manian Rajesh Kumar^a, Aleum Byeun^a, Min Sik Eom^b, Min Su Han^{b,*}, Sunwoo Lee^{a,*}

^a Department of Chemistry, Chonnam National University, Gwangju 500-757, Republic of Korea

^b Department of Chemistry, Chung-Ang University, Seoul 156-756, Republic of Korea

ARTICLE INFO

Article history:

Received 7 June 2013

Revised 5 July 2013

Accepted 9 July 2013

Available online 17 July 2013

Keywords:

High-throughput screening

Palladium

Hydrodehalogenation

Aryl iodides

Aryl bromides

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 Cs₂CO₃ were the best catalyst and base, respectively. Aryl iodides and bromides were hydrodehalogenated to produce the reduced arenes using Pd(OAc)₂ and Pd(PPh₃)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.

© 2013 Elsevier Ltd. All rights reserved.

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

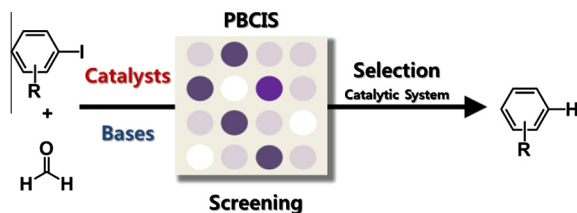
their persistent toxic effect.⁶ It is known that the activity of the carbon-halogen bond in aryl halide is lower than that in alkyl halide, because the bond dissociation energies of C–X (X = I, Br, Cl, F) in aryl halides are higher than those in alkyl halides. As a result, aryl halides are hard to degrade 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 nickel¹¹ 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 H₂,¹² 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).

* Corresponding authors. Tel.: +82 62 530 3385.

E-mail addresses: mshan@cau.ac.kr (M.S. Han), sunwoo@chonnam.ac.kr (S. Lee).

† These authors contributed equally to this work.



Scheme 1. Optimization of hydrodehalogenations by using PBCIS.

Table 1
Pd-catalyzed hydrodehalogenation^a

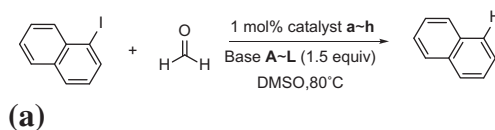
Entry	Pd (mol %)	Mol %	Conversion (%)	Yield ^b (%)
1	Pd ₂ (dba) ₃	1.0	100	93
2	Pd(PPh ₃) ₄	1.0	100	96
3	PdCl ₂	1.0	100	99
4	Pd(OAc) ₂	1.0	100	99
5	PdCl ₂	0.1	73	73
6	Pd(OAc) ₂	0.01	100	99
7	Pd(OAc) ₂	0.005	100	95
8	Pd(OAc) ₂	0.001	35	32

^a Reaction conditions: 1-iodonaphthalene (0.3 mmol), paraformaldehyde (0.3 mmol), and Cs₂CO₃ (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, PdCl₂ (a), Pd(OAc)₂ (b), NiCl₂ (c), Ni(OAc)₂ (d), CuCl (e), CuCl₂ (f), FeCl₃ (g), and CoBr₂ (h) were employed. Five kinds of weak inorganic bases [Cs₂CO₃ (A), K₂CO₃ (B), Na₂CO₃ (C), K₃PO₄ (D), and K₂HPO₄ (E)], four kinds of organic bases [DBU (F), Et₃N (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 Cs₂CO₃, K₂CO₃, and Et₃N 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, PdCl₂ and Pd(OAc)₂ were chosen. In addition, Pd₂(dba)₃ and Pd(PPh₃)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 Cs₂CO₃.²¹ Their conversions and



(a)



(b)

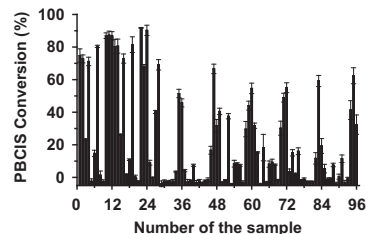


Figure 1. Screening of catalysts and bases for the hydrodehalogenation using PBCIS. Catalyst: a–h, Base: A–L. (a) Picture of the PBCIS results of the reactions. (b) The extent of conversion of 1-iodonaphthalene was determined by equation [conversion (PBCIS)% = (–1.0506) × (grayscale intensity – 243.9713)]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

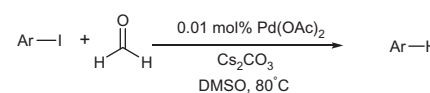
product yields were monitored by gas chromatography with an internal standard.

Pd₂(dba)₃ and Pd(PPh₃)₄ showed 100% conversion of 1-iodonaphthalene, however, the yields of products were 93% and 96%, respectively (entries 1 and 2). Both PdCl₂ 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 %, PdCl₂ 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 Cs₂CO₃ (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

Table 2
Pd-catalyzed hydrodeiodination of aryl iodides^a



Entry	Ar-I	Product	Yield (%)
1			98
2			72
3			85
4			95
5			85
6			84
7			94
8			95
9			91
10			42
11			81
12			80
13			82
14			83

^a Reaction condition: aryl iodide (5.0 mmol), paraformaldehyde (5.0 mmol), Cs₂CO₃ (7.0 mmol), and Pd(OAc)₂ (0.0005 mmol) were reacted in DMSO at 80 °C for 12 h.

the product, Pd(PPh₃)₄ was employed in place of Pd(OAc)₂, with expectations that PPh₃ works as a good ligand. As expected, most aryl bromides were transformed into the corresponding hydrodehalogenated one, as shown in Table 3.

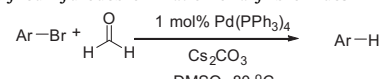
Bromobenzene was transformed into benzene in 98% yield (entry 1). Alkyl or alkoxy-substituted aryl bromides showed good yields (entries 2–7). 1- and 2-Bromonaphthalene afforded naphthalene in 93% and 87% yields, respectively (entries 8 and 9). Aryl bromides bearing alcohol and ester groups were also hydrodebrominated in good yields (entries 10 and 11).

To investigate the role of paraformaldehyde, the hydrodehalogenation of 1-iodonaphthalene was conducted with paraformaldehyde-*d*₂. As shown in Scheme 2, deuterated naphthalene was formed in 95% yield.

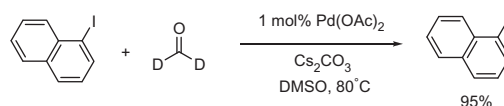
To explain the high activity of Pd(OAc)₂ toward aryl iodides without the additional ligand, the palladium residue was analyzed by TEM. It showed that nanoparticles of palladium were formed in the reaction mixture.²² It has been reported that paraformaldehyde works as a reducing agent for the formation of palladium nanoparticles.²³ Based on these results, we suggest that paraformaldehyde is the hydrogen source and the reducing agent for the formation of nanoparticles.

We propose the reaction mechanism as shown in Scheme 3. Pd(0) is the active catalytic species, which reacted with aryl

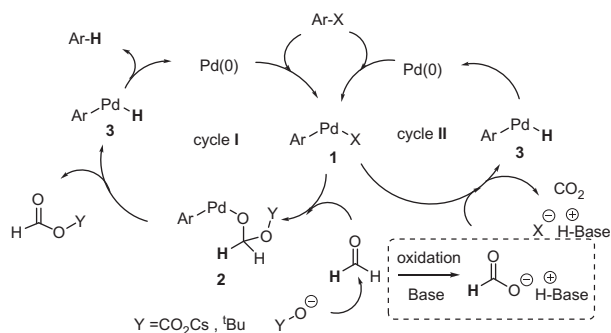
Table 3
Pd-catalyzed hydrodebromination of aryl bromides^a



Ar-Br	Product	Yield (%)
		entry 1 (98%)
		entry 2 (92%)
		entry 3 (99%)
		entry 4 (99%)
		entry 5 (85%)
		entry 6 (81%)
		entry 7 (93%)
		entry 8 (87%)
		entry 9 (91%)
		entry 10 (87%)
		entry 11 (91%)



Scheme 2. The reaction of 1-iodonaphthalene and D₂CO.



Scheme 3. Proposed mechanism.

halides to form the oxidative adduct **1**. Paraformaldehyde, which is activated by a base, reacted with palladium complex **1** to form complex **2**. The β-hydride elimination produced the hydro aryl palladium complex **3**, and then the reductive elimination afforded the hydrodehalogenated product. In addition, we could rule out the mechanism of cycle **II**, which contains the reaction of formic acid formed from the oxidation of paraformaldehyde, from the fact that hydrodeiodinated product was formed in 45% yield when benzaldehyde was employed instead of paraformaldehyde.

In summary, we have employed the PBCIS for the high-throughput screening for developing the palladium-catalyzed hydrodehalogenation of aryl halides using paraformaldehyde as a hydride source. PBCIS was proven to be a fast and simple tool for hydrodeiodination, and showed that Pd(OAc)₂ and Cs₂CO₃ are the best catalyst and base, respectively, for the hydrodeiodination. These conditions showed good yields in a variety of aryl iodides. With aryl bromides, Pd(PPh₃)₄ afforded the desired hydrodebrominated products in good yields. It is noteworthy that paraformaldehyde is stable, easy to handle and store, and an inexpensive hydride source. To the best of our knowledge, this is the first example of paraformaldehyde being employed as a hydride source in the hydrodehalogenation.

Experimental section

The reaction flask was charged with an appropriate amount of aryl iodides (5.0 mmol), paraformaldehyde (150 mg, 5.0 mmol), Cs_2CO_3 (351 mg, 7.0 mmol), and $\text{Pd}(\text{OAc})_2$ (0.0005 mmol from stock solution). And then DMSO (15.0 mL) was added. The flask was sealed and heated at 80 °C for 12 h. The reaction mixture was cooled, and an aliquot was taken and dissolved in Et_2O for GC–MS analysis. The products were confirmed by GC–MS and the data of authentic sample.

Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (2012R1A1B3000871) and Priority Research Centers Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2009-0093817).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.07.071>.

References and notes

- (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1335–1338; (b) Stambuli, J. P.; Hartwig, J. F. *Curr. Opin. Chem. Biol.* **2003**, *7*, 420–426.
- Cremer, G. D.; Sels, B. F.; De Vos, D. E.; Hofkens, J.; Roeffaers, M. B. *Chem. Soc. Rev.* **2010**, *39*, 4703–4717.
- (a) Vicennati, P.; Bensen, N.; Wagner, A.; Créminon, C.; Taran, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 6863–6866; (b) Rozhkov, R. V.; Davisson, V. J.; Bergstrom, D. E. *Adv. Synth. Catal.* **2008**, *350*, 71–75; (c) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677–2678; (d) Sashuk, V.; Schoeps, D.; Plenio, H. *Chem. Commun.* **2009**, 770–772.
- (a) Jung, E.; Kim, S.; Kim, Y.; Seo, S. H.; Lee, S. S.; Han, M. S.; Lee, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 4386–4389; (b) Kim, S.; Jung, E.; Kim, M. J.; Pyo, A.; Palani, T.; Eom, M. S.; Han, M. S.; Lee, S. *Chem. Commun.* **2012**, *48*, 8751–8753.
- Selvam, P.; Mohapatra, S. K.; Sonavane, S. U.; Jayaram, R. V. *Appl. Catal. B* **2004**, *49*, 251–255.
- (a) Zhou, W.; Fu, D.; Sun, Z. *Res. Environ. Sci.* **1991**, *6*, 9–12; (b) Castro, C. E. *Rev. Environ. Contam. Toxicol.* **1998**, *155*, 1–67; (c) Morra, M. J.; Borek, V.; Koolpe, J. J. *Environ. Qual.* **2000**, *29*, 706–715.
- (a) Morris, P. J.; Mohn, W. W.; Quenson, J. F.; Tiedje, J. M.; Boyd, S. A. *Appl. Environ. Microbiol.* **1992**, *58*, 3088–3094; (b) Dichiarante, V.; Fagnoni, M.; Albin, A. *Green Chem.* **2009**, *11*, 942–945; (c) Shiraishi, Y.; Takeda, Y.; Sugano, Y.; Ichikawa, S.; Tanaka, S.; Hirai, T. *Chem. Commun.* **2011**, *47*, 7863–7865.
- (a) Leung, S. H.; Edington, D. G.; Griffith, T. E.; James, J. J. *Tetrahedron Lett.* **1999**, *40*, 7189–7191; (b) Viciu, M. S.; Grasa, G. A.; Nolan, S. P. *Organometallics* **2001**, *20*, 3607–3612; (c) Arcadi, A.; Cerichelli, G.; Chiarini, M.; Vico, R.; Zorzan, D. *Eur. J. Org. Chem.* **2004**, *16*, 3404–3407; (d) Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R. A., III; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685–692; (e) Iranpoor, N.; Firouzabadi, H.; Azadi, R. *J. Organomet. Chem.* **2010**, *695*, 887–890; (f) Huang, Y.; Liu, S.; Lin, Z.; Li, W.; Li, X.; Cao, R. *J. Catal.* **2012**, *292*, 111–117.
- (a) Guo, H.; Kannao, K.-I.; Takahashi, T. *Chem. Lett.* **2004**, *33*, 1356; (b) Czaplik, W. M.; Grupe, S.; Mayer, M.; von Wangelin, A. J. *Chem. Commun.* **2010**, *46*, 6350–6352; (c) Zhang, Z.; Cissoko, N.; Wo, J.; Xu, X. *J. Hazard. Mater.* **2009**, *165*, 78–86.
- (a) Fujita, K.; Owaki, M.; Yamaguchi, R. *Chem. Commun.* **2002**, 2964–2965; (b) Buil, M. L.; Esteruelas, M. A.; Niembro, S.; Oliván, M.; Orzechowski, L.; Pelayo, C.; Vallibera, A. *Organometallics* **2010**, *29*, 4375–4383.
- (a) Kuhl, S.; Schneider, R.; Fort, Y. *Adv. Synth. Catal.* **2003**, *345*, 341–344; (b) Desmarets, C.; Kuhl, S.; Schneider, R.; Fort, Y. *Organometallics* **2002**, *21*, 1554–1559; (c) Mochizuki, K.; Suzuki, M. *Inorg. Chem. Commun.* **2011**, *14*, 902–905.
- (a) Hara, T.; Mori, K.; Oshiba, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Green Chem.* **2004**, *6*, 507–509; (b) Monguchi, Y.; Kume, A.; Hattori, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* **2006**, *62*, 7926–7933; (c) Kume, A.; Monguchi, Y.; Hattori, K.; Nagase, H.; Sajiki, H. *Appl. Catal., B Environ.* **2008**, *81*, 274–282; (d) Chang, F.; Kim, H.; Lee, B.; Park, H. G.; Park, J. *Bull. Korean Chem. Soc.* **2011**, *32*, 1074–1076.
- (a) Chen, J.; Zhang, Y.; Yang, L.; Zhang, X.; Liu, J.; Li, L.; Zhang, H. *Tetrahedron* **2007**, *63*, 4266–4270; (b) Moon, J.; Lee, S. *J. Organomet. Chem.* **2009**, *694*, 473–477.
- Chelucci, G. *Tetrahedron Lett.* **2010**, *51*, 1562–1565.
- (a) Wang, X.-J.; Zhang, L.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5026–5028; (b) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491–3494.
- Zawisza, A. M.; Muzart, J. *Tetrahedron Lett.* **2007**, *48*, 6738–6742.
- Yang, J.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 12656–12657.
- Cellier, P. P.; Spindler, J. -F.; Taillefer, M.; Cristau, H. -J. *Tetrahedron Lett.* **2003**, *44*, 7191–7195.
- (a) Li, C.; Wang, L.; Li, P.; Zhou, W. *Chem. Eur. J.* **2011**, *17*, 10208–10212; (b) Chan, C.-W.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 3926–3929; (c) Adak, L.; Bhadra, S.; Ranu, B. C. *Tetrahedron Lett.* **2010**, *51*, 3811–3814.
- All extents of the conversion were described in Supplementary data.
- K_2CO_3 , Et_3N provided lower yields than Cs_2CO_3 in the large scale reaction.
- See Supplementary data.
- (a) Schmidt, E. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 400–413; (b) Heal, G. R.; McKayula, L. L. *Carbon* **1988**, *26*, 815–823; (c) Jin, H.; Park, S.-E.; Lee, J. M.; Ryu, S. K. *Carbon* **1996**, *34*, 429–431.