LETTERS

High-Throughput Screening Protocol for the Coupling Reactions of Aryl Halides Using a Colorimetric Chemosensor for Halide Ions

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(5) Supporting Information

ABSTRACT: Mercury complex of 4-(2-pyridylazo)resorcinol (PAR-2Hg²⁺), a halide-ion chemosensor, was prepared and its efficiency as a tool for high-throughput screening (HTS) of transition-metal-catalyzed coupling reactions was investigated. It showed a high selectivity for halide ions. When the PAR– $2Hg^{2+}$ complex was used in the Suzuki coupling reaction and C–H activated coupling reaction with aryl bromides, the quantitative and qualitative conversions of aryl halides were obtained from the reaction mixture color change.



The development of efficient reaction methodologies is an important topic in pharmaceutical and fine chemical industries.1 Among many organic reactions, transition-metalcatalyzed coupling reactions have been widely used in synthetic chemistry.² Modified coupling reactions and new conceptually advanced methods are being continuously developed.³ Because of the demand for the fast analysis of reaction leads to synthetic methodology development, several high-throughput screening (HTS) methods have been developed.⁴ Recently, Hartwig and MacMillan independently reported efficient screening methods for efficient unbiased screening methods using GC-MS.⁵ Gas chromatography,⁶ high-performance liquid chromatography,⁷ mass spectrometry,⁸ and NMR spectroscopy⁹ are convenient for this purpose as they do not require prefunctionalization for analysis. However, the analysis times highly depend on the automation and still require minutes per sample. The fluorescence method has a fast analysis time; however, special fluorescent substrates are needed.¹⁰ The colorimetric method is also a good method; however, it does not provide quantitative information about the yield or conversion of a reaction.¹¹

To solve these problems, we previously developed colorimetric analysis methods using Au nanoparticles and paper-based colorimetric iodide sensors (PBCIS). Although these methods were used efficiently for screening transition-metal-catalyzed coupling reactions, they are limited to aryl iodides.¹² In the coupling reactions of aryl halides, aryl bromides are most frequently used; aryl chlorides are inexpensive, but challenging substrates. Therefore, HTS methods should be developed for coupling aryl halides such as aryl iodides, aryl bromides, and aryl chlorides.

To achieve this objective, we developed a chemosensor for halide ions. Organic dye-metal ion complexes have been developed as ligand-exchange-based chemosensors for various anions, including phosphate derivatives, halides, and cyanide.¹³

In particular, diphenylcarbazone–Hg²⁺ complex has been used as a chemosensor for halide ions.¹⁴ However, the chemosensor cannot be used in HTS for the coupling reactions of aryl halides because it rapidly decomposes in assay solutions.^{14b} The instability of a chemosensor can affect the reproducibility and accuracy of HTS. Previously, the mercury complex of 4-(2pyridylazo)resorcinol (PAR-2Hg²⁺) was used as a chemosensor for cyanide ions with a high binding affinity to Hg²⁺ ion and high stability in an assay solution.¹⁵ The PAR–2Hg²⁺ complex can be expanded to detect halide ions because halide ions exhibit high binding affinity to $Hg^{2+,16}$ We envisioned that PAR-2Hg²⁺ would be converted to free PAR in the presence of halide ions, and the ligand exchange reaction would change the assay solution color. This would allow a general screening protocol for the coupling reactions of aryl halides by easily measuring the color changes even though it has some limitations 17 (Scheme 1).

Scheme 1. Schematic Representation of the Halide Probe Based on a High-Throughput Screening Method for the Coupling Reaction of Aryl Halides





The PAR–2Hg²⁺ complex was prepared by mixing PAR (50 μ M) and Hg²⁺ (100 μ M) in a pH 7.2 phosphate buffer solution (EtOH/H₂O = 1:1 v/v, Tween 20 0.1%) because the color change of PAR was directly proportional to the Hg²⁺ concentration, and the stoichiometry of PAR–2Hg²⁺ is 2:1 (metal to ligand ratio).¹⁸ To evaluate the PAR–2Hg²⁺ complex as a chemosensor for halide ions, its optical properties (change in the absorbance) were measured in the presence of Br⁻. The absorbance intensity of the PAR-2Hg²⁺ complex increased at 408 nm and decreased at 506 nm with the increase in Br⁻ concentration (Figure 1). The chemosensor also exhibited a



Figure 1. (a) Absorbance spectra were measured after adding various concentrations of Br⁻ to a pH 7.2 phosphate buffer 0.01 M solution (EtOH/H₂O = 1:1, Tween 20 0.1%) containing PAR (50 μ M) and Hg²⁺ (100 μ M). Inset: plot of absorbance intensities at 408 nm vs various concentrations of Br⁻. (b) Absorbance spectra at 408 nm were measured after adding various anions (1 mM) to a pH 7.2 phosphate buffer solution 0.01 M (EtOH/H₂O = 1:1, Tween 20 0.1%) containing PAR (50 μ M) and Hg²⁺ (100 μ M).

high selectivity for Br⁻ over other anions such as AcO⁻, CO₃²⁻, F⁻, and PO₄³⁻ in the coupling reactions of aryl halides. The dynamic ranges of PAR–2Hg²⁺ for the detection of Cl⁻ and I⁻ are different because of different affinities of halide ions to Hg²⁺ compared to Br⁻, whereas the other optical properties of the chemosensor for Cl⁻ and I⁻ were similar to those for Br⁻.¹⁹ The detection of Cl⁻ equally worked at high concentration.²⁰

This indicates that the chemosensor can detect Cl⁻, Br⁻, and I⁻ and determine the concentration of halide ions released after the coupling reactions of various aryl halides. Therefore, the coupling reaction of aryl halides can be easily evaluated by measuring the color changes of the chemosensor. To evaluate the capability of PAR-2Hg²⁺ in measuring the conversion of aryl halides in coupling reactions, the Pd-catalyzed Suzuki coupling reaction was selected as the model reaction.

The results are summarized in Table 1. 4-Iodotoluene, 4bromoanisole, and 4-chlorobenzonitrile were used as aryl halides and reacted with phenylboronic acid in the presence of a Pd catalyst. Three types of bases (K3PO4, K2CO3, and KOAc) and solvents (DMSO, DMF, and THF) were used. Four types of ligands were investigated. After 3 h reaction time, distilled water and EtOAc (1:5 v/v) were added to the reaction mixture. The reaction mixtures were analyzed by using PAR-2Hg²⁺ and GC. All the samples were diluted and treated with PAR-2Hg²⁺; the resulting solutions were analyzed by UV/vis spectroscopy. The conversions of aryl halides were determined from the titration curves of the halide ions. All the conversions obtained from halide-sensor analysis exhibited good correlation with those obtained from the GC analysis (Table 1). Moreover, the conversion of aryl halide was determined from the solution color without using any instrument. The conversion increased as the solution changed from red to yellow. The results indicate the following: (1) The PAR-2Hg²⁺ provided information about

Table 1. Conversion Yields from PAR–2Hg²⁺ Complex and Gas Chromatography in Suzuki Reaction^a

entry	ArX	ligand	UV abs. ^e	$\operatorname{conv}(\%)^a$	$\operatorname{conv}(\%)^{e}$	yield (%) ^e
1	1	L1	1.009	55	47	40
2	1	L4	1.403	94	92	95
3	1	L5	1.137	67	75	75
4	1	L7	1.010	55	64	67
5	1	L11	0.312	$0(-14)^{f}$	6	2
6	1	L12	1.178	71	75	73
7	2	L1	1.037	37	53	49
8	2	L4	1.174	55	56	49
9	2	L5	1.178	55	56	50
10	2	L7	1.261	74	92	95
11	2	L11	0.862	23	20	19
12	2	L12	1.118	46	49	43
13	3	L1	0.383	0	3.3	0.7
14	3	L4	1.371	55	44.8	54
15	3	L5	0.497	4	4.5	3
16	3	L7	1.277	45	53.7	63
17	3	L11	0.691	11	2.5	0
18	3	L12	0.399	1	0.3	0

^{*a*}Reaction conditions: ArX (0.3 mmol), PhB(OH)₂ (0.3 mmol), Pd(OAc)₂ (0.003 mmol), ligand (0.003 mmol), base (0.45 mmol), solvent (1.0 mL), 3 h. ^{*b*}See Figure 2a. ^{*c*}Absorbance at 408 nm. ^{*d*}The value was calculated from the titration curves of halide ions. ^{*c*}Determined by gas chromatography using an internal standard. ^{*f*}The value below 0 was treated as 0% conversion.

both the quantitative and qualitative conversions of aryl halides in the coupling reactions. (2) The halide sensor well tolerated Pd, ligand, base, and organic solvent. Therefore, $PAR-2Hg^{2+}$ can be used as a suitable sensor for the conversion of aryl halides such as aryl iodides, aryl bromides, and aryl chlorides in coupling reactions. Moreover, this protocol was evaluated for the screening of Williamson ether synthesis using alkyl chlorides and phenol derivatives. It was found that this protocol was also suitable for the sensor for the conversion of alkyl halides.²⁰

We attempted to use $PAR-2Hg^{2+}$ in the coupling reactions of aryl bromides in C–H activation.²¹ We selected heterocyclic substrates such as benzoxazoles, benzothiazoles, N-methylindoles, and benzothiophenes for C-H activated coupling reactions with aryl bromides. We envisioned that PAR-2Hg²⁻ would act as a simple and fast tool to determine the optimized conditions for the coupling reactions of aryl bromides and C-H activated substrates. Twelve types of ligands (L1-L12) and bases (B1–B12) were selected for the coupling reaction because it is important to find a suitable ligand and base for this reaction. Using these ligands and bases, the coupling reactions were conducted in the presence of $Pd(OAc)_2$ (5 mol %) and t-BuCO₂H (10 mol %) in DMF at 120 °C for 15 h (Figure 2a). The reaction mixture was diluted with water, and the resulting solution was treated with PAR-2Hg²⁺ solution. Figure 2b shows the colorimetric results of 96 reactions. These samples were analyzed by UV/vis spectroscopy, and the conversion of 4bromotoluene was determined using the colorimetric change of PAR-2Hg²⁺. We found that all the conversions correlated well with those obtained from the GC analysis.²²

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Figure 2. (a) Conditions for ligands and bases in the coupling of azoles with 4-bromotoluene. (b) Detected colors in colorimetric assay. A: L1–L12 with K_3PO_4 . B: B1–B12 with dppbz. C: L1–L12 with Cs_2CO_3 . D: B1–B12 with dppbz. E: L1–L12 with Cs_2CO_3 . F: B1–B12 with phen. G: L1–L12 with K_3PO_4 . H: B1–B12 with Xantphos.

From the HTS results, the best ligand and base were selected for each substrate as follows; dppbz (L6) and K_3PO_4 for benzoxazoles (condtion I), dppbz (L6) and Cs_2CO_3 for benzothiazoles (condtion III), phen (L11) and Cs_2CO_3 for *N*methylindoles (condtion III), and Xantphos (L7) and K_3PO_4 for benzothiophenes (condtion IV). The coupling reactions were carried out under these conditions, and the desired products were isolated. As expected, substrates 7, 8, and 9 afforded the corresponding products, 2-*p*-tolylbenzoxazole (12a), 2-*p*tolylbenzothiazole (13a), and 2-*p*-tolyl-1-methylindole (14a), in good yields. Benzothiophene (10) afforded the coupled product 15a in 69% yield.²³

By comparing with previous reports,²⁴ we found that dppbz (L6) increased the yields of the products in the reactions of azoles 7 and 8. However, phen (L11) ligand was superior to other phosphine ligands in the reaction of *N*-methylindole (9). The coupling reactions with benzothiophene showed lower yields. With these optimized conditions, the substrate scope was investigated. Diverse aryl bromides were used in the coupling reactions with benzoxazoles, benzothiazoles, *N*-methylindoles, and benzothiophenes. The results are summarized in Scheme 2. The reactions with benzoxazole, 4-bromobenzonitrile (11b), 4'bromoacetophenone (11c), 4'-bromobiphenyl (11d), and 1bromonaphthalene (11e) afforded the desired coupled products 12b, 12c, 12d, and 12e with good-to-excellent yields.

The coupling of benzothiazole with **11c** afforded **13c** in 88% yield; however, the coupling reactions with aryl halides such as 3-bromoquinoline, 1-bromo-4-tert-butylbenzene, and 1-bromo-



Scheme 2. Coupling Reactions with Aryl Bromides and C-H

2,4,5-trimethylbenzene afforded the corresponding products in 65%, 71%, and 61% yields, respectively. For *N*-methylindole, aryl bromide **11c** afforded the product in 58% yield, and substrates **11i** and **11j** afforded the desired coupled products in moderate-to-good yields. The coupling of benzothiophene and 3-bromopyridine afforded the corresponding product in 48% yield.

In summary, the PAR-2Hg^{$\hat{2}+$} complex was used as a chemosensor for halide ions; the sensor exhibited a high selectivity for halide ions. The conversions of aryl iodides, aryl bromides, and aryl chlorides in Suzuki coupling reactions were determined using PAR-2Hg²⁺; the conversions of aryl halides obtained using this sensor by UV/vis spectroscopy correlated well with those obtained from GC analysis using an internal standard. Moreover, the colorimetric change in the reaction mixture provided information about the conversions of aryl halides. We used PAR-2Hg²⁺ for the HTS of the coupling reactions with aryl bromides and C-H activated substrates such as benzoxazoles, benzothiazoles, N-methylindoles, and benzothiophenes. When 96 samples of coupling reactions were treated with PAR-2Hg²⁺, the conversions of aryl bromides were easily determined from the colorimetric change and UV/vis spectroscopy. The results provided information about the suitable ligand and base in each coupling reaction.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00300.

Experimental procedures (chemosensor and coupling reactions) and spectral data for the products (PDF)

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Notes

The authors declare no competing financial interest.

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(22) Conversion data from the coupling reaction in Figure 2 were presented in Supporting Information (Table S1).

(23) C-H activated coupling reactions with a ole and 4-bromotoluene was presented in Supporting Information (Table S2).

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