Iron-catalyzed conversion of unactivated aryl halides to phenols in water

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ABSTRACT

Although iron is low-cost and environmentally friendly, there is no report about iron-catalyzed conversion of unactivated aryl halides to phenols. In this Letter, a new method for the present conversion was developed with iron compounds as the catalyst and water as the solvent. The suggested method allowed a series of unactivated aryl bromides and aryl iodides to be converted into the corresponding substituted phenols in moderate to high yields.

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Phenols are structural motifs frequently occurring in such diverse compounds as pharmaceuticals, agrochemicals, and naturally occurring compounds.[1] They also have served as versatile intermediates in preparing aryl ethers.[2] Therefore, effective methods for the synthesis of phenols would be valuable.[3] One of the most classical methods for the preparation of phenols is the conversion of aryl halides to phenols with palladium[4] or copper[5] salts as the catalysts. Compared with these catalysts, iron is lower-cost and more environmentally friendly.[6] Although the coordination chemistry of iron has been widely developed in the past decades, iron is underrepresented as the homogeneous catalyst compared to the other transition metals.[6g] So the use of iron as the catalyst has recently drawn increasing attention in some fields including hydration of alkynes,[6a] cross-couplings,[6g,7] cycloadditions,[8] oxidation,[9] and hydrogenation.[10]

To our knowledge, there is no report about iron-catalyzed conversion of unactivated aryl halides to phenols. In addition, the use of water as the solvent is still a highly desirable goal from environmental and economic perspectives.[11] Thus our attention was drawn to the development of an effective iron catalyst for such a conversion in water. The results are reported here.
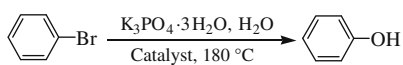
In our initial study, bromobenzene was chosen as a model substrate to demonstrate the catalytic effectiveness of FeCl$_3$ in water. Control experiments showed that no product was obtained in the absence of FeCl$_3$ (Table 1, entry 1). In the case of no ligand, only a small amount of desired product was obtained (Table 1, entry 2). An addition of *N,N*'-dimethylethylenediamine (DMEDA) as the ligand improved significantly the catalytic activity of FeCl$_3$, and

the desired product was obtained in 80% yield (Table 1, entry 3). 1,2-Ethylenediamine was also an effective ligand, while other bidentate nitrogen ligands such as 2,2'-bipyridine, *o*-phenylenediamine, 1,10-phenanthroline were almost inactive (Table 1, entries 4–7). Interestingly, a small amount of diphenyl ether by-product was detected in almost all the cases, which was possibly rationalized by assuming that the initially formed phenol was reacted with alkyl halides to afford the diphenyl ether product (Scheme 1). These results implied that it was possible to explore a protocol for targeting symmetrical diaryl ethers. Unfortunately, our attempts to obtain diphenyl ether in high yield were not successful by changing reaction conditions.

With the above results in mind, a series of iron sources were screened to ascertain the optimal pre-catalyst with DMEDA as the ligand and water as the solvent. As seen from Table 1, FeCl$_3$, ferric acetylacetonate and γ-Fe$_2$O$_3$ were suitable pre-catalysts for the conversion of aryl halides to phenols (Table 1, entries 3, 8, and 12). It was surprising that ferrocene could also be used as the iron-based catalyst to catalyze the reaction (Table 1, entry 10). We could not yet give a reasonable explanation for such an unusual phenomenon. Considering the fact that FeCl$_3$ was most inexpensive and commercially available, we performed all the following reactions with FeCl$_3$ as the pre-catalyst. In the absence of inorganic base, the phenol product was obtained in a very low yield (Table 1, entry 14), revealing that an addition of the inorganic base was necessary. Of the bases screened, K$_3$PO$_4$ turned out to be the most effective one (Table 1, entries 3, 15, and 16). In view of the poor solubility of the substrate in water solvent, tetrabutylammonium bromide (TBAB) was additionally used as a phase transfer agent to improve the reaction. As expected, such a modification caused a slight increase in the yield of the phenol product (Table 1, entry

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Table 1
Iron-catalyzed conversion of bromobenzene to phenol[a]

Entry	Pre-catalyst	Ligand	Conv.[b] (%)	Yield[b] (%)
1	—	—	0	0
2	FeCl₃	—	5	2
3	FeCl₃	DMEDA	92	80
4	FeCl₃	1,2-Ethylenediamine	83	71
5	FeCl₃	2,2′-Bipyridine	6	0
6	FeCl₃	o-Phenylenediamine	17	7
7	FeCl₃	1,10-Phenanthroline	8	0
8	Ferric acetylacetonate	DMEDA	100	73
9	Ferric citrate	DMEDA	12	5
10	Ferrocene	DMEDA	100	62
11	Nano Fe₃O₄ (20 nm)	DMEDA	8	2
12	γ-Fe₂O₃ (20 nm)	DMEDA	83	71
13	FeSO₄·7H₂O	DMEDA	41	34
14[c]	FeCl₃	DMEDA	5	2
15[d]	FeCl₃	DMEDA	11	3
16[e]	FeCl₃	DMEDA	82	75
17[f]	FeCl₃	DMEDA	96	88
18	—	DMEDA	0	0

[a] Reaction conditions: iron salt (0.2 mmol), ligand (1 mmol), H₂O (3 mL), K₃PO₄·3H₂O (2 mmol), bromobenzene (1 mmol), 180 °C, 0.7 MPa, 20 h.
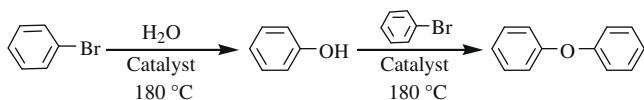[b] Determined by GC analysis using n-tetradecane as an internal standard.
[c] No K₃PO₄·3H₂O was used.
[d] 2 mmol Na₂CO₃ instead of K₃PO₄·3H₂O were used as the base.
[e] 2 mmol NaOH instead of K₃PO₄·3H₂O were used as the base.
[f] 1 mmol TBAB was added.

Scheme 1. Conversion of bromobenzene into diphenyl ether.

17). If iron source was absent, the reaction in the present of DMEDA could not proceed (Table 1, entry 18). A use of less than 100 mol % DMEDA would lead to a decrease in the yield of the phenol, which revealed that it was necessary to use as much as 100 mol % ligand. So 100 mol % DMEDA was used to perform all the following reactions. The effect of the loading amount of FeCl₃ on the reactions was also investigated, and it was found that a use of less than 20 mol % catalyst caused a significant decrease of the yield.

As described in previous literature,[12] the catalyzed N-, O- and C-arylation reactions ascribed to FeCl₃ could instead result from catalysis of trace quantities of copper salts in commercial FeCl₃. So our attention was drawn to clarifying the role of FeCl₃ in conver-

Table 2
Conversion of bromobenzene to phenol in the presence of FeCl₃ and Cu₂O[a]

Entry	Purity of FeCl₃ (%)	Cu₂O[b] (ppm)	GC yield (%)
1	>98	—	88
2	>99.99[c]	—	91
3	>99.99[c]	10	86
4	>99.99[c]	100	89
5	—	100	3

[a] Reaction conditions: FeCl₃ (0.2 mmol), DMEDA (1 mmol), H₂O (3 mL), K₃PO₄·3H₂O (2 mmol), bromobenzene (1 mmol), TBAB (1 mmol), 180 °C, 0.7 MPa, 20 h.
[b] Cu₂O was additionally added.
[c] Content of Cu salt in FeCl₃ was less than 10 ppm.

sion of bromobenzene to phenol. As shown in Table 2, a use of a high purity of FeCl₃ did not cause a significant change in the yield of phenol (entries 1 and 2), and the addition of copper salts had also a slight effect on the reaction (entries 3 and 4). Trace amount of copper salts gave a very low yield in the absence of FeCl₃ (Table 2, entry 5). These results revealed that conversion of bromobenzene to phenol in the presence of FeCl₃ was mainly ascribed to catalysis of Fe salt. According to some related reports,[6g] the catalytic active species may not be +3 but lower oxidation state of iron. Similar with copper catalyst for cross-coupling reactions,[13] iron catalyst in the catalytic cycle possibly takes part in successive oxidative addition, transmetallation, and reductive elimination reactions. The ordering of oxidative addition and transmetallation steps in the catalytic cycle is unknown, so either of two possibilities can take place.

Next, our attention was turned to an examination of the scope and limitation of the present protocol by testing a series of unacti-

Table 3
Conversion of various aryl halides to phenols catalyzed by DMEDA/FeCl₃[a]

Entry	Substrate	Product	Yield[b] (%)
1	(phenyl)–Br	(phenyl)–OH	82
2	O₂N–(phenyl)–Br	O₂N–(phenyl)–OH	85
3	MeO–(phenyl)–Br	MeO–(phenyl)–OH	91
4	Me₃C–(phenyl)–Br	Me₃C–(phenyl)–OH	82
5	Me–(phenyl)–Br	Me–(phenyl)–OH	66
6	Me–(CMe₃,CMe₃-phenyl)–Br	Me–(CMe₃,CMe₃-phenyl)–OH	47
7	Br–(Bu-phenyl)–OH	HO–(Bu-phenyl)–OH	77
8	Br–(phenyl)–Br	HO–(phenyl)–OH	56
9	HO–(phenyl)–Br	HO–(phenyl)–OH	78
10	(naphthyl)–Br	(naphthyl)–OH	93
11	(naphthyl)–Br	(naphthyl)–OH	65
12	HO–(phenyl)–C(Me)(Me)–(phenyl)–Br	HO–(phenyl)–C(Me)(Me)–(phenyl)–OH	76
13	(phenyl)–I	(phenyl)–OH	83
14	MeO–(phenyl)–I	MeO–(phenyl)–OH	75
15	(naphthyl)–I	(naphthyl)–OH	87
16	O₂N–(phenyl)–I	O₂N–(phenyl)–OH	83

[a] Reaction conditions: FeCl₃ (0.2 mmol), DMEDA (1 mmol), H₂O (3 mL), K₃PO₄·3H₂O (2 mmol), aryl halide (1 mmol), TBAB (1 mmol), 180 °C, 0.7 MPa, 20 h.
[b] Isolated yield, the products were characterized by comparison of ¹H NMR and ¹³C NMR data with that in the literature.

vated aryl bromides.[14] The results were summarized in Table 3. In general, many aryl bromides were smoothly converted into the corresponding phenols. Moreover, the reactions were able to tolerate some functional groups such as hydroxyl, nitro, and methoxy groups. Although nitryl group had an ability to activate aryl bromides, our experimental result showed that 4-bromonitrobenzene with a nitryl group could not be converted into 4-nitrophenol in the case of no catalyst. Steric hindrance of the substituent in the substrate had a significant effect on the reactions. For example, bromobenzene gave the desired product in 82% yield, while 2,6-di-*tert*-butyl-4-methylphenol with two *tert*-butyl groups in the ortho-position of bromine gave a lower yield of 47% under the same conditions (Table 3, entries 1 and 6). α-Bromonaphthalene afforded the naphthol product in 93% yield, whereas β-bromo-naphthalene gave a lower yield of 55% (Table 3, entries 10 and 11), which suggested that bromine in β-position of naphthalene was more difficult to transform. The present method was also applicable to the reactions of aryl iodides. As shown in Table 3 (entries 13–16), several aryl iodides afforded the desired products in high yields from 75% to 90%.

In conclusion, an iron-catalyzed method for the conversion of unactivated aryl halides to phenols was developed with water as the solvent. After the reaction conditions were examined, it was found that DMEDA/FeCl$_3$ was the optimal catalytic system. By using the present method, a series of unactivated aryl bromides and aryl iodides were converted into the corresponding phenols in moderate to high yields.

Acknowledgments

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14. *General experimental procedure for Iron-catalyzed conversion of aryl halides to phenols:* FeCl$_3$ (0.2 mmol, purchased from Aladdin Reagent Co., purity >98%, Cu <10 ppm), ligand (1 mmol) and TBAF (1 mmol) were added to a 10 mL stainless steel autoclave containing H$_2$O (3 mL). After the mixture was stirred at room temperature for 5 min to give a homogeneous solution, K$_3$PO$_4$·3H$_2$O (2 mmol) and aryl halide (1 mmol) were added. Subsequently, the sealed autoclave was placed in a 180 °C oil bath stirred for 20 h (the pressure that created on the sealed autoclave was about 0.7 MPa). The desired product was extracted with 3 × 5 mL of diethyl ether. Evaporation of the solvent was followed by the GC analysis of the product. The product was purified by column chromatography. All the products are known compounds and were identified by comparison of their ^{1}H NMR and ^{13}C NMR data with the literature data.