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Priority Communication

A green approach for arylation of phenols using iron catalysis in water under aerobic conditions

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ABSTRACT

The first efficient iron-catalyzed coupling of aryl iodides with phenols was developed exclusively with water as solvent. The reaction is performed with low cost and readily available $FeCl_3{\cdot}6H_2O$ and DMEDA catalytic system providing diaryl ethers in good to excellent yields. The effectiveness of this reaction was further revealed by compatibility with a wide range of functional groups. Moreover, the procedure is rendered simple as this transformation is carried out in the presence of air. Thus, the protocol represents a facile, economical and eco-friendly procedure to access diaryl ethers.

1. Introduction

Diaryl ethers are common structural motifs that find widespread applications in numerous fields such as life sciences, chemical, pharmaceutical, polymer and material industries [1]. Many natural products bearing diaryl ether linkage exhibit remarkable physiological activities [2] and these scaffolds are also very useful structures for the design and synthesis of drugs and drug precursors [3]. Traditional copper promoted Ullmann reaction of aryl halides with sodium phenoxides [4] has limited applications due to the harsh reaction conditions. Nowadays, the transition metal-catalyzed O-arylation of phenols constitutes the most general and straightforward strategy for the formation of diaryl ethers [5]. Palladium has been widely used as catalyst for the coupling reaction in combination with phosphine ligands [6]. After that various transition metals such as Cu [7], Ni [8], and Co [9] have been reported as efficient catalysts for this transformation. Out of these metals, iron an abundant, economical and environmentally friendly metal shows increasing and promising catalytic abilities in many organic transformations. In 2008, Bolm's group successfully developed an iron-catalyzed C—O cross-coupling of phenols with aryl iodides which uses anhydrous $FeCl_3$/TMHD (2,2,6,6-tetramethyl-3,5-heptanedione) catalyst and Cs_2CO_3 base in DMF under argon atmosphere [10]. Even though the synergistic effects of copper and iron have been explored after this [11], no Fe-catalytic systems are reported for the C—O bond forming reactions. Aside from the reliability of these methods, there are some limitations for the existing protocols due to the involvement of organic solvents and requirement of inert atmosphere [7e,12].

In fact, over the last decade metal-catalyzed processes in green media have been an area of increasing interest both from economical perspective and in terms of environmental impacts. Thus, water has been the ideal choice of solvent due to its non-toxicity, low cost, and availability compared with organic solvents. In connection with the ongoing research in our group [13] dealing with iron-catalyzed carbon-sulfur [14] and carbon-carbon [15] bond formations in the presence of water, we judged it certainly appealing to extend the protocol for carbon-oxygen bond forming reactions also. Considering the lack of green chemical methods to synthesize aryl ethers, we herein report the first iron-catalyzed O-arylation of phenols using aryl halides in the presence of water under aerobic conditions.

2. Results and discussion

Initially, 4-iodoacetophenone and phenol were chosen as the model substrates to perform and optimize the C—O coupling reaction. The studies showed that the nature of the ligand and the base

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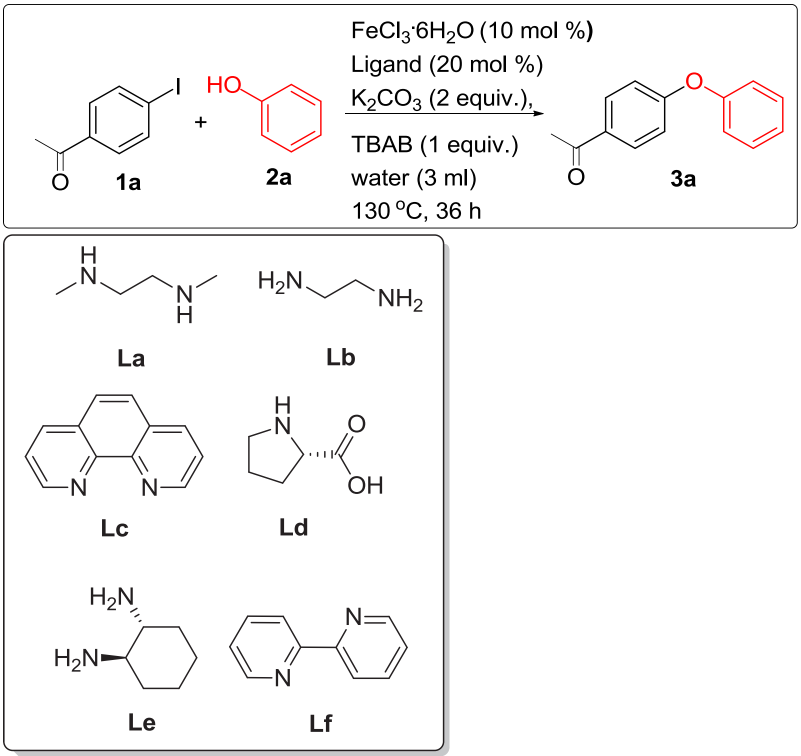
strongly influence the yield of the product and the results are summarized in Tables 1 and 2. In pure water (without Tetra butyl ammonium bromide), lower yield (<30%) of the desired product was detected in GC–MS analysis and the reactants were recovered from the reaction mixture. Tetra butyl ammonium bromide (TBAB) is also added in this reaction as phase transfer catalyst to facilitate the coupling reaction in water. We presume that the organophilic Bu_4N^+ cation may help the transport of hydrophilic negatively charged nucleophiles into the organic phase. Various cheaper and structurally simpler ligands were examined thereafter. The bidentate ligand N,N′-Dimethylethylene diamine (DMEDA) (**La**) showed good activity with 67% isolated yield of the product (Table 1, entry 1). Gratifyingly, ligands **Lb**, **Lc** and **Le** also showed good activity, but **Ld** and **Lf** could not provide satisfactory results (Table 1, entries 2–6).

After screening a variety of inorganic bases (i.e., K_2CO_3, K_3PO_4, Cs_2CO_3, NaOH and KOH), we found that Cs_2CO_3 gave the best result of 84% yield in water (Table 2, entries 1–5). The use of an organic base, triethylamine hardly provided detectable amount of the ether product (Table 2, entry 6). Lowering the reaction temperature or shortening the reaction time resulted in lower yields of the diaryl ether product **3a** (Table 2, entries 7–9). An attempt to reduce the catalyst loading to 5 mol% afforded the desired product only in 41% yield. Increasing the catalyst and ligand loadings to 15 mol% and 30 mol% respectively did not change the yields significantly (Table 2, entry 11). The 1:1 combination of catalyst and ligand delivered only 48% yield of **3a**. Further experiments in which the amount of Cs_2CO_3 was increased revealed no improvement in the yield of **3a** (Table 2, entry 13).

Interestingly, the aqueous solution containing the iron complex was recovered and reused under the optimized reaction condition. This was done by isolating the diaryl ether product by extracting the crude mixture with ethyl acetate and the recovered aqueous solution was used again to bring about each respective transformation up to three times. However after each run (1, 2, 3 runs), there is a clear decrease in the yield of the product (83%, 52% and 29% respectively). It should be pointed out that we recycled not only the iron complex but also the aqueous media itself as most of the reported catalyst reutilization involves separation and reactivation prior to reutilization.

The control experiments demonstrated that in the absence of $FeCl_3·6H_2O$ and DMEDA, no product was formed. In order to ensure the absence of other metal contamination in $FeCl_3·6H_2O$, we analyzed the metal impurities in the sample by ICP-MASS

Table 1
Ligand screening.[a]



Entry	Ligand	Yield[b] (%)
1	**La**	67
2	**Lb**	62
3	**Lc**	49
4	**Ld**	Traces
5	**Le**	45
6	**Lf**	Traces
7[c]	**La**	33
8[d]	**Lb**	65

[a] Reaction conditions: 4-iodoacetophenone (1 mmol), phenol (1.2 mmol), K_2CO_3 (2 equiv.), $FeCl_3·6H_2O$ (10 mol%), ligand (20 mol%), TBAB (1 equiv.), water (3 ml), 130 °C, 36 h.
[b] Isolated yield.
[c] 120 °C.
[d] Cs_2CO_3 base.