Cross-Coupling Reactions of Alkyl Halides with Aryl Grignard Reagents Using a Tetrachloroferrate with an Innocent Countercation

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Abstract: Bis(triphenylphosphoranylidene) ammonium tetrachloroferrate, (PPN)[FeCl 4] (1), was evaluated as a catalyst for cross-coupling reactions. 1 exhibits high stability toward air and moisture and is an effective catalyst for the reaction of secondary alkyl halides with aryl Grignard reagents. The PPN cation is considered as an innocent counterpart to the iron center. We have developed an easy-to-handle iron catalyst for “ligand-free” cross-coupling reactions.

Keywords: Iron; ferrate salt; cross-coupling reaction; alkyl halide; Grignard reagent

Transition-metal-catalyzed cross-coupling reactions between organic electrophiles and organometallic reagents represent one of the most powerful strategies for the construction of carbon-carbon bonds. Since the discovery of cross-coupling reactions, palladium and nickel complexes have been extensively studied as catalysts, and continuous improvements have resulted in the development of highly efficient catalytic systems. Considerable attention has also been focused on the use of iron catalysts in these reactions, given that iron is an ideally suited practical transition metal owing to its low cost, low toxicity, and abundance. The first discovery of FeCl 3-catalyzed cross-coupling reactions was reported by Kochi in 1971. In 1998, Cahiez used an iron/NMP (NMP = N-methylpyrrolidinone) system, in which NMP serves as a co-solvent that has a beneficial impact on reactions involving alkenyl electrophiles. Subsequently, Fürstner improved this Fe(acac) 3/NMP (acac = 2,4-pentanedionato) system for reactions using aryl chlorides and triflates.

So far, various catalyst systems have been developed combining iron sources such as FeCl 3 and Fe(acac) 3 with donor molecules such as amines, phosphines, N-heterocyclic carbenes (NHCs) as ligands and/or additives. In addition, well-defined iron complexes have also been developed as catalysts for the coupling reactions. Moreover, it has been reported that Fe(acac) 3 itself acts as an effective catalyst for the coupling reactions. Fe(acac) 3 is commercially available and stable toward air and moisture. It is thus an easy-to-handle iron source for the preparation of iron complexes and catalysts. While FeCl 3 is arguably one of the most basic iron sources, it is unfortunately hydroscopic. Therefore, the development of easy-to-handle iron sources for large-scale industrial processes remains highly desirable.

Iron-containing imidazolium salts, generally classified as ionic liquids, show high stability toward air and moisture. In addition, these salts act as efficient catalysts for cross-coupling reactions. In these catalytic systems, the formation of iron-NHC species as the catalytically active species by in-situ deprotonation of the azolium cation with a Grignard reagent cannot be ruled out. Therefore, we were interested in the development of easy-to-handle iron catalysts and the realization of “ligand-free” iron catalysis for cross-coupling reactions. Herein, we report the cross-coupling of alkyl halides with aryl Grignard reagents catalyzed by (PPN)[FeCl 4] (1), i.e., a tetrachloroferrate bearing the innocent cation bis(1H-imidazol-1-yl)imidazolium.
(triphenylphosphoranylidene)ammonium (PPN), (Scheme 1).

Tetrachloroferrate was prepared according to a literature method, i.e., by treating anhydrous FeCl$_3$ with an equimolar amount of bis(triphenylphosphoranylidene)ammonium chloride ([PPN]Cl) in MeOH at room temperature. Salt 1 was obtained in 91% yield as a yellow solid (Scheme 2) and characterized by elemental analyses and X-ray diffraction study (Figure 1). Interestingly, 1 is not hydroscopic and is highly stable toward air and atmospheric moisture.[15,16] Moreover, 1 showed good solubility in THF and NMP, whereas it was poorly soluble in ethereal solvents such as Et$_2$O, tert-butyl methyl ether (MTBE), 1,2-dimethoxyethane (DME), and cyclopentyl methyl ether (CPME).

In order to evaluate the catalytic activity of 1, the cross-coupling reaction of bromocyclohexane (2a) with 1.2 equivalents of phenylmagnesium bromide was carried out in the presence of 5 mol% of 1 in various solvents (Table 1). In the case of THF, the cross-coupled product, phenylecyclohexane (3a), was obtained in 26% yield, together with the homo-coupled product from phenylmagnesium bromide (biphenyl) in 36% yield (entry 1). In this case, 33% of the starting material (2a) was recovered. When the mixed solvent THF/NMP (9/1; v/v) was used, 3a was obtained in 27% yield (entry 2). Using NMP as the solvent furnished 3a in 22% yield (entry 3). Subsequently, we investigated the reaction using the aforementioned ethereal solvents, albeit 1 is poorly soluble in these solvents. In Et$_2$O, the yield of 3a increased to 58% yield, but the reaction did not reach completion (entry 4). MTBE and DME were not suitable solvents, i.e., 3a was obtained merely in low yield (28% and 34%; entries 5 and 6). As shown in entry 7, CPME provided the best results, affording 3a in 94% yield together with small amounts of biphenyl (10% yield based on PhMgBr). This catalytic protocol based on 1 was also successful on the gram-scale (7 mmol of 2a).

In this case, the reaction proceeded efficiently to give 3a in 88% yield, even when the amount of 1 was reduced to 1 mol% (entry 8).

To demonstrate the efficiency of 1 as a catalyst for such cross-coupling reactions, we investigated the

### Table 1. Optimization of the conditions for the cross-coupling of bromocyclohexane (2a) with phenylmagnesium bromide catalyzed by 1.$^{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>3a (%)$^{[b]}$</th>
<th>Biphenyl (%)$^{[c]}$</th>
<th>Recovery of 2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>26</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>THF/NMP</td>
<td>27</td>
<td>17</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>NMP</td>
<td>22</td>
<td>14</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>Et$_2$O</td>
<td>58</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>MTBE</td>
<td>28</td>
<td>22</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>DME</td>
<td>34</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>CPME</td>
<td>94</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>8$^{[e]}$</td>
<td>CPME</td>
<td>88</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

$^{[a]}$ The reaction was carried out using 2a (0.5–1.0 mmol) and PhMgBr (0.6–1.2 mmol, 1.2 equiv.) in the presence of 1 (5 mol%) at room temperature.

$^{[b]}$ The yield of 3a is based on 2a and was determined by gas-liquid chromatography (GLC) analysis using undecane as the internal standard.

$^{[c]}$ The yield of biphenyl is based on PhMgBr and was determined by GLC analysis using undecane as the internal standard.

$^{[d]}$ THF/NMP = 9/1 (v/v).

$^{[e]}$ The reaction (7.0 mmol scale of 2a) was carried out for 1.5 h using 1 mol% of 1.

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**Scheme 1.** The cross-coupling reactions catalyzed by (PPN)[FeCl$_4$] (1) reported in this work.

**Scheme 2.** Preparation of catalyst (PPN)[FeCl$_4$] (1).

**Figure 1.** ORTEP drawing of (PPN)[FeCl$_4$] (1) with thermal ellipsoids at 30% probability. All hydrogen atoms have been omitted for clarity.
substrate scope with a variety of alkyl halides and aryl Grignard reagents under the optimized reaction conditions, and the results are summarized in Table 2. Using p-tolylmagnesium bromide, 3b was obtained in 95% yield (entry 1). p-Methoxyphenylmagnesium bromide afforded 3c in 90% yield (entry 2), while p-dimethylaminophenylmagnesium bromide furnished a slightly lower yield of 3d (78%, entry 3). p-Fluorophenylmagnesium bromide, which bears an electron-withdrawing substituent, afforded 3e in 63% yield (entry 4). Next, we investigated the influence of different electrophiles. The reaction between iodocyclohexane (2b) and PhMgBr furnished 3a in 69% yield (entry 5). In the case of chlorocyclohexane (2c), the yield of 3a decreased to 41% (entry 6). Bromocycloheptane (2d) was also tolerated as a coupling partner, affording 3f in 50% yield (entry 7). The reaction of acyclic alkyl bromide 2e generated 3g in 81% yield, whereas the iodo analogue 2f provided 3g in 53% yield (entries 8 and 9). As shown in entry 10, the siloxy substituent on the alkyl chain remained intact and the product was obtained in 72% yield. o-Tolylmagnesium bromide gave the corresponding product 3i in moderate yield[7b] (entry 11). We next examined the reaction with primary alkyl halides. The reaction using 1-bromodecane (2h) proceeded sluggishly to give coupling product 3j in 30% yield under concomitant formation of decane (15%) and 1-decene (40%). Furthermore, 15% of bromide 2h was recovered (entry 12). In the case of 1-iododecane (2i), the corresponding product (3j) was obtained in 32% yield. Moreover, benzylmagnesium bromide furnished 3k in 75% yield (Scheme 3).[8b,g–i]

To gain insight into the reaction mechanism,[18] we investigated the coupling reaction using trans-4-benzyloxycyclohexyl bromide (2j) and (bromomethyl)cyclopropane (2k) as electrophiles under standard conditions (Schemes 4 and 5). Treatment of 2j with PhMgBr afforded a mixture of stereoisomers 3l in 69% yield (trans:cis = 74:26). In the case of 2k, the simple coupled product 3m was not detected, whereas ring-opened product 3n was obtained in 13% yield. Overall, these results indicated that the cross-coupling reaction catalyzed by 1 likely involves radical species.[7b,8a,c,e,g]

Furthermore, we examined the isolation of any potentially formed iron species. However, all attempts to obtain such species were unsuccessful. Although the actual structure of the intermediates in our catalytic system is not clear at this point, we assume that the [FeCl₄]⁻ anion of 1 plays an important role in the

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**Table 2.** Substrate scope of the cross-coupling reaction of alkyl halides with aryl Grignard reagents catalyzed by 1.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyl-X</th>
<th>2</th>
<th>Coupling product</th>
<th>Yield (%)</th>
<th>[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>2b</td>
<td>3b</td>
<td>95 (R = Me)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>2c</td>
<td>3c</td>
<td>90 (R = CMe₃)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>2a</td>
<td>3d</td>
<td>78 (R = NMe₂)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>2e</td>
<td>3e</td>
<td>63 (R = F)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>2b</td>
<td>3a</td>
<td>69 (X = i)[f]</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2c</td>
<td>2c</td>
<td>3a</td>
<td>41 (X = Ci)[f]</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2d</td>
<td>2d</td>
<td>3f</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2e</td>
<td>2f</td>
<td>3g</td>
<td>81 (X = Br)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2f</td>
<td>2f</td>
<td>3i</td>
<td>53 (X = i)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2g</td>
<td>2g</td>
<td>3h</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2a</td>
<td>2a</td>
<td>3j</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2h</td>
<td>2i</td>
<td>3j</td>
<td>30 (X = Br)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2i</td>
<td>2i</td>
<td>3j</td>
<td>32 (X = i)</td>
<td></td>
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<tr>
<td></td>
<td>2a</td>
<td>2a</td>
<td>3j</td>
<td>30 (X = Br)</td>
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<td>2i</td>
<td>2i</td>
<td>3j</td>
<td>32 (X = i)</td>
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<tr>
<td></td>
<td>2h</td>
<td>2i</td>
<td>3j</td>
<td>30 (X = Br)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2i</td>
<td>2i</td>
<td>3j</td>
<td>32 (X = i)</td>
<td></td>
</tr>
</tbody>
</table>

[a] The reaction was carried out using alkyl halides 2 (0.5–1.0 mmol) and an aryl Grignard reagent (1.2–1.5 equiv.) in the presence of 1 (5 mol%) at room temperature.

[b] Isolated yield.

[c] The yield of 3a is based on 2b or 2c and was determined by GLC analysis using undecane as the internal standard.

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**Scheme 3.** Coupling reaction of 2a with benzylmagnesium bromide catalyzed by 1.

**Scheme 4.** Coupling reaction of 2j with PhMgBr catalyzed by 1.

**Scheme 5.** Coupling reaction of 2k with PhMgBr catalyzed by 1: radical clock experiment.
catalytic cycle. When other iron salts such as FeCl₄⁻, FeCl₃, or Fe(acac)₃ were employed as catalysts under otherwise identical reaction conditions, the coupled product 3a was obtained in 90%, 93%, and 94% yield, respectively (Scheme 6). These results indicate that both 1 and these other iron compounds afford similarly active iron species via the reduction of a Grignard reagent in the catalytic cycle. Accordingly, we assume that the PPN cation in 1 does not engage in the catalytic reaction, i.e., the PPN cation can be considered as an innocent counterpart to the iron center.

In conclusion, we have reported (PPN)[FeCl₄] (1) as an efficient catalyst for the coupling reactions of secondary alkyl halides with aryl and benzyl Grignard reagents under mild reaction conditions. 1 exhibits high stability toward air and atmospheric moisture. The results described in this paper thus promote the development of “ligand-free” iron-catalyzed reactions. Further investigations into the (i) mechanistic aspects of this catalytic system, including the role of the counterion, ferrate, and the solvent, (ii) the coupling of various organometallic reagents with organic electrophiles, and (iii) the development of novel organic transformations are currently in progress in our group.

### Experimental Section

**Preparation for (PPN)[FeCl₄] (1):** A Schlenk tube was charged with anhydrous FeCl₃ (0.608 g, 3.75 mmol), bis(triphenylphosphoranylidene)ammonium chloride ((PPN)Cl, 2.18 g, 3.80 mmol) and dry MeOH (45 mL) at room temperature. After stirring overnight, the solvent was removed in vacuo. The residue was washed with hexane to give 1 as a yellow solid (2.50 g, 91%). IR (Diamond-ATR, neat): 2359, 1436, 1264, 1182, 1112, 1027, 997, 720, 688, 530, 495, 373 cm⁻¹. Anal. calcd for C₉₆H₁₆₂Cl₄FeNP₄: C, 58.73; H, 4.11; N, 1.90, found C, 58.74; H, 4.12; N, 1.84.

**General procedure for the cross-coupling reactions:** A Schlenk tube was charged with 1 (5 mol%), CPME (5 mL), the respective alkyl halide (0.50 mmol), and a Grignard reagent (1.2–1.5 equiv.) at room temperature. The coupling reaction was carried out at room temperature for 1–24 h. After quenching with HCl (1 M, 2.0 mL), the aqueous layer was extracted with Et₂O (5 × 3 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous MgSO₄. After filtration and removal of all volatiles from the filtrate, the residue was purified by column chromatography on silica gel.

### References


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- Air- and moisture stable salt
- Easy preparation
- Ligand free
- Mild reaction conditions
- Radical pathway

R^1
R^2
\[ \text{BrMg} \rightarrow R^3 \]

R^1
R^2
\[ \text{N}_2 \text{PPh}_3 \text{PPh}_3 \text{[FeCl}_4 \text{]} \]

CPME

\[ \text{up to 95\%} \]

R^3 = Aryl, Bn