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Iron-catalysed cross-coupling of haloxydrins with aryl aluminium reagents: A protecting-group-free strategy attaining remarkable rate enhancement and diastereinduction

Shintaro Kawamura, a,b Tatsuya Kawabata, a,b Kentaro Ishizuka a and Masaharu Nakamura a,b

Non-protected haloxydrins are cross-coupled with aryl aluminium reagents to produce aryl alkanols in the presence of the iron-bisphosphate catalysts. Remarkable reaction rate enhancement and diastereinduction are realized by the in situ generated aluminium alkoxides, offering a new method for the reactivity and selectivity control of the iron-catalysed cross-coupling reaction.

The directing effect of non-protected hydroxyl groups (called neighbouring group participation when the directing group is near the reaction centre) is recognized as a classical, yet powerful chemical tool in organic synthesis for controlling stereo-, regio-, and chemoselectivities as well as reaction rate. This synthetic control may also be expected to be operative in cutting-edge cross-coupling technology, but there have been very few reports on attempts to actively implement it in designing such reactions. In addition to the paucity of systematic research efforts, the increasing interest in protecting-group-free syntheses prompted us to investigate the cross-coupling reactions of protected/non-protected haloxydrins to eventually find the novel reactivity of organoaluminium reagents for iron-catalysed cross-coupling reactions. Herein, we report a new cross-coupling reaction of non-activated alkyl chlorides and aryl aluminium reagents, in which the free hydroxyl group, or more precisely, in situ generated aluminium-alkoxide, facilitated the reaction and enhanced the diastereoselectivity.

We have reported previously that the cross-coupling reactions of alkyl halides with various organometallic reagents proceed efficiently in the presence of the iron-bisphosphine catalysts (FeCl₂–SciOPPs, Fig. 1). However, we did not observe sufficient reactivity of the catalyst when a free hydroxyl group was present in the coupling substrates or when a free alcohol substrate was added to the reaction mixture. We assumed that catalyst poisoning resulted from the formation of inert iron-alkoxide species.

In contrast to the previous observations, we found unexpectedly the iron-catalysed cross-coupling reaction of a non-protected chlorohydrin proceeded readily when using aryl aluminate as the nucleophile. It should be noted that primary alkyl chlorides usually show low reactivity in iron-catalysed cross-coupling reactions (regardless of the presence of a free hydroxyl group), and require certain elaborate catalysts. Thus, we first reinvestigated the iron-bisphosphate-catalysed cross-coupling of various phenyl metal nucleophiles by using 6-chloro-1-hexanol 3 as a model substrate, in order to confirm the unexpected unique reactivity of aryl aluminates (Scheme 1 and Table 1).

Scheme 1. Iron-catalysed cross coupling reaction of protected or non-protected haloxydrins with various phenyl metal reagents

As shown in entry 1, PhMgBr gave the desired cross-coupling product 4a in only 4% yield, along with the formation of 5-hexen-1-ol and 1-hexanol in ca. 30% combined yield. The reaction with diphenylzinc, Ph₂Zn 2MgCl₂ (5b) was sluggish, giving 4a in 6% yield (entry 2). Triphenylzincate (Ph₃Zn·MgBr, 5c) gave the product in a higher yield than the neutral diphenylzinc; however, the yield and selectivity of the reaction were both low (entry 3). When diphenylborate (Ph₂B(pin)Li, 5d) was used, no desired product was obtained (entry 4). While neutral phenyl aluminium (Ph₃Al·3MgCl₂, 5e) resulted in almost complete recovery of haloxydrin 3a, the reaction with phenyl aluminate (Ph₃Al·MgCl, 5f) proceeded smoothly and selectively to give the desired 4a in 91% yield (entries 5 and 6). We suspected that the efficient reaction might be explained by the formation of a heteroleptic aluminate species (e.g., Ph₃AlOR·MgCl), which generates an anionic iron (ferrate) or Fe/Al mixed cluster species that exhibits the unprecedented reactivity (see mechanistic discussion). The reaction of the protected chlorohydrin 3b with phenyl aluminate, thus, gave a 1:1 mixture of the coupling product and the alkane by-product in only 40% combined yield (entry 7), and the results of the reactions using the other phenyl metal reagents were almost the same as those reported previously.
Table 1. Reactivity differences between various phenyl metal reagents and effect of protection of hydroxyl group on the reactivity

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ph₃M (equiv)</th>
<th>Yield (%)</th>
<th>RSM (%)</th>
<th>4a or 4b</th>
<th>4a or 4b alkene</th>
<th>RSm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMeBr (5a)</td>
<td>12</td>
<td>17</td>
<td>63</td>
<td>3a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ph₂MgBr (6b)</td>
<td>6</td>
<td>0</td>
<td>89</td>
<td>3b</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph₂MgBr (6c)</td>
<td>13</td>
<td>20</td>
<td>30</td>
<td>3c</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>Ph₂MgCl (6d)</td>
<td>0</td>
<td>9</td>
<td>91</td>
<td>3d</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ph₂MgCl (6e)</td>
<td>0</td>
<td>0</td>
<td>&gt;99</td>
<td>3e</td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td>Ph₂MgCl (6f)</td>
<td>91</td>
<td>6</td>
<td>0</td>
<td>3f</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ph₂MgCl (6g)</td>
<td>20</td>
<td>1</td>
<td>20</td>
<td>3g</td>
<td>52</td>
</tr>
</tbody>
</table>

Reactions were carried out at 80 °C for 12 h on 0.5 mmol scale. The yields were determined by 1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard and confirmed by GLC analysis using undecane as an internal standard. The cross-coupling products 4a and 4b were obtained in entries 1–7, respectively. 20 mol% MgBr₂ was added as a co-catalyst. The reaction almost stopped for 12 h. The reaction of phenylaluminates prepared by transmetalation from AlCl₃ and Ph₂MgBr gave the same result as that prepared from Ph₂MgCl.

For the further study of the influence of alkoxide in the reaction, 1-hexanol was added to the iron-catalysed cross-coupling reaction of the protected halohydrin 3b with phenylaluminate 5f (Scheme 2). Although the reactions in the absence of alcohol gave the cross-coupling product in low yield (Table 1, entry 7, and Scheme 2), stoichiometric or even 20 mol% 1-hexanol dramatically improved the yield of the desired product in high yield. The in situ generated aluminium alkoxide did not cause any catalyst poisoning, but enhanced the reaction. This observation also clearly indicates that the formation of aluminium alkoxide species is a key to the observed high catalytic activity.

Scheme 2. Rate enhancement by in situ generated aluminium alkoxide

Fig 2 shows a plausible catalytic cycle inferred from the abovementioned results and previous reports published by us and others. In the initial step, the precatayst complex FeCl₃(TMS-SciOPP) is transformed into intermediate A through transmetalation with an aryl alumininate (Ar₃AlOR MgX). The intermediate A, which is reminiscent of the bis(m-oxo)phenyl-aluminium–phenyltinanium complex and iron chloride–aluminium-tert-butoxide complexes, is proposed here as a catalytically active species because of its expected high reactivity towards non-activated alkyl chlorides. Subsequently, homolytic cleavage of the C–Cl bond proceeds to give an alkyl radical and the ferrate intermediate B. This is followed by the recombination of the resulting elusive alkyl radical with the aryl group on intermediate B, which occurs in a solvent cage to give the cross-coupling product and intermediate C. Finally, intermediate A is regenerated by transmetalation between intermediate C and the aryl alumininate.

We next focused on the stereoinduction by the hydroxyl group in the electrophilic coupling partner. For the further study, 3a or 3b was added as a co-catalyst and effect of catalyst and the ferrate intermediate B. This is followed by the recombination of the resulting elusive alkyl radical with the aryl group on intermediate B, which occurs in a solvent cage to give the cross-coupling product and intermediate C. Finally, intermediate A is regenerated by transmetalation between intermediate C and the aryl alumininate.

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We next focused on the stereoinduction by the hydroxyl group in the electrophilic coupling partner. For the further study, 3a or 3b was added as a co-catalyst and effect of catalyst and the ferrate intermediate B. This is followed by the recombination of the resulting elusive alkyl radical with the aryl group on intermediate B, which occurs in a solvent cage to give the cross-coupling product and intermediate C. Finally, intermediate A is regenerated by transmetalation between intermediate C and the aryl alumininate.
The aluminium alkoxide: it is likely to exist in the form of aluminium alkoxide oligomers, thereby acting as a sterically demanding substituent.  

In summary, we have demonstrated the unique iron-catalysed cross-coupling reaction between halohydrins and arylalumminates. The aluminium alkoxide generated in situ through deprotonation of the hydroxyl group of halohydrin by arylaluminate did not cause the expected catalyst poisoning; instead, to the contrary to the initial expectation, the reaction rate was enhanced, and high-level diastereoselectivity was induced, thus providing a first illustration of the synthetic potential of this protective-group-free strategy in catalytic cross-coupling reactions.

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Notes and references

Supporting Information (SI). (d) The result of the reaction of phenyl metal reagents was shown in SI. (e) The yield and reaction rates were almost the same regardless of the structures of aluminium alkoxides. See SI. (f) Neutral FeAr-SciOPPs, which are the reactive species in the cross-coupling of alkyl halides previously reported by us (ref. 5), showed poor reactivities toward primary alkyl chlorides. (g) A radical clock experiment is reported in SI. (b) The aluminium alkoxide did not improve the diastereoselectivity as shown in SI. (i) The starting material was recovered (ca. 80%).

1 For selected papers on neighbouring group participation, see:


