The drastic effect of cobalt and chromium catalysts in the borylation of arylzinc reagents†

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A new synthetic approach to arylboronic esters from arylzinc reagents with boryl electrophiles $\text{MeOB(OR)₂}$ has been developed. Furthermore, this protocol could be applied to the cyclization/borylation of alkylnaryl iodides to afford cyclized vinylboronic esters.

Arylboronic esters are recognized as being indispensable building blocks in organic synthesis because of their stability and wide range applicability to C–X ($X = C, N$ and O) bond-forming reactions in chemical, medicinal and materials science.1 Over the past 20 years, transition-metal-catalysed borylations of aryl (pseudo)halides with diborons, hydroboranes or metal–boryl reagents have been developed using Pd, Rh, Ni, Cu, Zn, Fe and Co complexes.2 These methods facilitate the concise synthesis of arylboronic esters bearing useful functional groups (route a, Scheme 1). More recently, the synthetic strategies used to produce arylboronic esters have shifted to favour the direct C–H borylation of arenes, which has been rapidly evolved by precious metal catalysts such as Rh and Ir (route b).3,4 Moreover, very recently, the direct borylations have been also accomplished by using abundant and inexpensive transition-metal catalysts.5 In contrast, transition-metal-free borylation protocols, such as electrophilic borylations of electron-rich arenes (route c),5 the Sandmeyer-type borylation (route d),7 and boryl substitution reactions with boryl-silanes8 or borylzincates9 (route e), have been frequently reported, although there are still problems with these strategies, such as their narrow substrate scope, loss of the boron component and/or the scarcity of suitable boron sources.

A classical but powerful method for the synthesis of arylboronic esters is the substitution of aryllithium or arylmagnesium reagents with trialkylboric esters.10 This method, however, suffers from poor functional group tolerance. Conversely, compared with the above organometallics, organozinc compounds are highly compatible with a broad range of polar functional groups due to the relatively weak ionic character of the C–Zn bond, which may undergo chemoselective transformation.12 However, the nucleophilicity of organozine reagents is quite low; therefore, their reactions with organic electrophiles often require the use of transition-metal catalysts.12 Despite their high potential for the development of tractable organic transformations, the borylation of organozine reagents using easy-to-handle boric esters has not been reported,13 except for highly electrophilic B-chlorocatecholborane and subporphyrins.14

Transmetalation is a highly effective route to drastically changing the reactivity of an organometallic species. For example, Takagi reported that highly nucleophilic arylchromium intermediates,15 afforded by the reaction of arylzinc reagents with chromium(II) salts, underwent addition to aldehydes under mild conditions. A similar strategy of changing the nucleophilicity of organometallics via transmetalation has been demonstrated in the Nozaki–Hiyama–Kishi reaction.16 Here we report the marked additive effect of low-valence cobalt and chromium catalysts in

![Scheme 1](image-url)
the borylation of arylzinc reagents with MeOBr(OR)₂ as the boryl electrophile in the presence of TMSCl (route f). Furthermore, this protocol could be applied to the direct synthesis of arylboronic esters from ubiquitous aryl halides under CoBr₂, xantphos and CrCl₃(thf)₃ catalyst systems in the presence of Zn.

We began by examining the borylation of the preformed 4-MeC₆H₄ZnI-LiCl with 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-one (2a, MeOBrpin) as model substrates in the presence of TMSCl (1.2 equiv.) at 60 °C for 16 h. These results are summarized in Table 1. As expected, the aryloboration reaction was sluggish in the absence of the ligand (entry 1); however, the presence of dppe afforded 3aa in 53% yield (entry 12).

### Table 1: Effect of cobalt and chromium salts in the borylation of 4-tolZnI-LiCl with MeOBrpin (2a)\(^\text{a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives (mol%)</th>
<th>Zn (x equiv.)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>CrCl₃(thf)₃ (20)</td>
<td>—</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>CrCl₂ (20)</td>
<td>—</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>CoBr₂/xantphos (10), CrCl₃(thf)₃ (20)</td>
<td>2.0</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>CoBr₂/xantphos (10), CrCl₃(thf)₃ (20)</td>
<td>0.5</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>CoBr₂/xantphos (10), CrCl₃(thf)₃ (20)</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>7</td>
<td>CrCl₃(thf)₃ (20)</td>
<td>2.0</td>
<td>Trace</td>
</tr>
<tr>
<td>8</td>
<td>CoBr₂/xantphos (10)</td>
<td>2.0</td>
<td>Trace</td>
</tr>
<tr>
<td>9</td>
<td>CoBr₂/xantphos (10), CrCl₃(thf)₃ (20)</td>
<td>—</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>CoBr₂/xantphos (10), CrCl₃(thf)₃ (20)</td>
<td>—</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>CoBr (10)(^c)</td>
<td>—</td>
<td>Trace</td>
</tr>
<tr>
<td>12</td>
<td>CoBr/dppe (10)(^c), CrCl₃ (20)</td>
<td>—</td>
<td>53</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were carried out in the presence of TMSCl (1.2 equiv.).  
\(^b\) NMR yield.  
\(^c\) The borylation was performed after reduction with 20 mol% zinc powder to form the low-valence cobalt complex.

From 4-tolyl iodide (Table 2, entry 1), without TMSCl, the desired boronic ester 3aa was obtained in low yield (27%), even with a longer reaction time (entry 2). This result indicates robust Cr-O bond formation during the reaction, because the bond appears to be difficult to cleave in the catalytic cycle without the aid of TMSCl. Chromium complexes ligated by nitrogen ligands, such as 2,2’-bipyridyl (bpy) and 1,10-phenanthroline (1,10-phen), inhibit the borylation in THF solvent (entries 6 and 7). However, the borylation proceeded in acetonitrile with the replacement of xanthos with 1,10-phen, albeit with a slightly lower yield (entry 5).

Having established the optimum conditions (Table 2, entry 1), we explored the substrate scope through the Co/Cr-catalysed borylation of various aryl bromides (Table 3). Electron-neutral (1b and 1c) and -rich aryl bromides (1d, 1e and 1f) are efficiently converted to the corresponding aryloboronic acid pinacol esters 3 in 66–71% yields (entries 1–5). However, electron-deficient aryl halides with inductively and/or resonance withdrawing substituents were less reactive (entries 6, 8, 10, 12, 14 and 17). In particular, the strongly electron-deficient aryl bromides bearing CN (1j) and CF₃ (1k, 1m) substituents were markedly less reactive towards trapping with 2a (entries 12, 14 and 17). Fortunately, a significant improvement was achieved by the replacement of 2a with 2-methoxy-5,5-dimethyl-1,3,2-dioxaborinane (MeOBrne, 2b), which is a less sterically hindered electrophile compared to 2a. This boronate preferentially afforded the desired boronic esters 3jb, 3kb and 3mb in good yields (entries 13, 15 and 18).

The borylation reaction presumably involves the generation of aryl cobalt and aryl chromium intermediates. In contrast, the migratory insertion of an alkynyl into both aryl-metal complexes has been established. Based on these findings and our previous results, we assumed that if these aryl-metal complexes are active in alkyne-insertion reactions to form a vinyl-metal species,
and the products undergo a substitution reaction with boryl electrophiles under identical conditions to those presented above, a useful three-component reaction (carboboration) could be developed. The carboboration of alkynes is a very important process for the regio- and stereoselective synthesis of multi-substituted olefins.\textsuperscript{29} Similar catalytic reactions for alkynes\textsuperscript{13,30} have been reported; however, all examples employed carbon electrophiles. The transformation using boryl electrophiles has never been demonstrated, except in cases employing Grignard reagents.\textsuperscript{31} Our initial attempts at the addition/borylation of 4-octyne with 4-tolyl bromide \(1a\) and MeOBpin \(2a\) under identical conditions failed, wherein the major product is arylboronic ester \(3aa\). This may be because the reaction of the \textit{in situ} generated aryls-metal species with the boryl electrophile is fast compared to the intermolecular reaction with the alkyne. Based on these experimental results, we next attempted the cyclisation/borylation of alkyne aryl iodides \(4\) (Scheme 2). Having refined the conditions,\textsuperscript{32} the desired cyclisation/borylation was accomplished, affording the cyclised vinylboronic esters \(5a, 5b\) and \(5c\) in 50, 41 and 43\% yields, respectively (Scheme 2). The stereochemistry of the products was determined by NOE measurements, which clearly indicated \textit{syn}-carboboration. In addition, an alkynyl aryl iodide tethered with nitrogen also reacted to afford the corresponding boronic ester \(5d\) in 26\% yield.

Although the actual role of the cobalt catalyst is still unclear, the arylchromium(II) species seems to trigger the borylation step. Thus, the reaction of 4-MeC\(_6\)H\(_4\)CrCl\(_2\) (prepared via the reaction of the 4-MeC\(_6\)H\(_4\)Li with CrCl\(_3\)(thf))\textsuperscript{33} with MeOBpin afforded \(3aa\) in only 3\% GC yield.\textsuperscript{34} In contrast, the reaction of the 4-MeC\(_6\)H\(_4\)Cr provided \(3aa\) in 67\% yield.

In conclusion, we have reported a drastic additive effect for increasing the reactivity of arylzinc reagents, enabling the borylation of unreactive arylzinc compounds to afford various aryloboronic esters. In addition, we found that this protocol could be applied to a more practical route to borylation starting from ubiquitous aryl halides. The easy-to-operate procedure avoids the preparation of air- and moisture-sensitive arylzinc reagents, making it more practical for aryloboronic ester synthesis. Furthermore, cyclisation/borylation of arylalkynyl iodides was accomplished by the modified catalytic system to give cyclized vinylboronic esters, in which carboboration proceeded in an exclusively \textit{syn}-addition manner. Control experiments revealed the important roles of low-valence cobalt and chromium in the borylation. This suggests that a key intermediate is an aryl

\begin{table}
\centering
\caption{Substrate scope for the Co/Cr-catalysed borylation of aryl halides}
\begin{tabular}{cccc}
\hline
Entry & \(Ar-X\) & Time/h & Product & yield\textsuperscript{a}/\% \\
\hline
1 & \(Ph-Br\) & 1b & 16 & 3ba 71 \\
2 & & 1c & 16 & 3ca 66 \\
3 & Me\(_2\)N-Br & 1d & 16 & 3da 66 \\
4 & & 1e & 16 & 3ea 67 \\
5\textsuperscript{b} & & 1f & 48 & 3fa 68 \\
6 & MeOBr & 1g & 16 & 3gb 38 \\
7\textsuperscript{c} & & 1h & 16 & 3ga 66 \\
8 & F-Br & 1i & 16 & 3hb 75 \\
9\textsuperscript{d} & MeO\(_2\)C-Br & 1j & 48 & 3ia 68 \\
10 & & 1k & 48 & 3ib 74 \\
11\textsuperscript{e} & NC\(_2\)Br & 1l & 48 & 3ja 38 \\
12\textsuperscript{f} & F\(_2\)C\(_2\)Br & 1m & 48 & 3jb 83 \\
13\textsuperscript{g} & F\(_3\)C-Br & 1n & 48 & 3ka 23 \\
14\textsuperscript{h} & & 1o & 48 & 3kb 83 \\
15\textsuperscript{i} & Me\(_3\)Si-Br & 1p & 24 & 3lb 92 \\
16\textsuperscript{j} & & 1q & 48 & 3ma Trace \\
17 & MeO\(_2\)CBr & 1r & 48 & 3mb 84 \\
18\textsuperscript{k} & F\(_2\)C & 1s & 48 & 3na 65 \\
19\textsuperscript{l} & & 1t & 48 & 3nb 66 \\
20\textsuperscript{m} & F\(_2\)O\(_2\)CBr & 1u & 48 & 3na 66 \\
21 & Me\(_2\)NBr & 1v & 48 & 3oa 72 \\
22\textsuperscript{n} & S-Br & 1w & 48 & 3pb 80 \\
\hline
\end{tabular}
\textsuperscript{a} Isolated yield. \textsuperscript{b} 2 equivalents of the boryl electrophile were employed. \textsuperscript{c} MeOB(nep) was used instead of MeOB(pin).
\end{table}

\begin{scheme}
\caption{Substrate scope for the Co/Cr-catalysed cyclisation/borylation.}
\end{scheme}
chromium(II) species, although more data are required in order to understand the mechanistic details of the reaction. Further studies on the mechanism and synthetic applications of the Co/Cr catalyst system are currently underway in our laboratory.

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Notes and references

