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## ARTICLE

# Chromium-Catalyzed Transformations with Grignard Reagents: New Opportunities for Cross-Coupling Reactions

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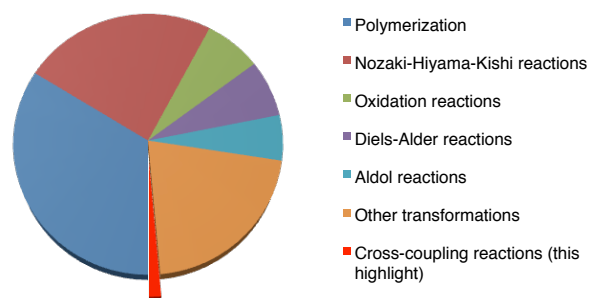
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Beyond classic Nozaki-Hiyama-Kishi reactions, a low-cost and low-toxicity chromium(II) salt is shown recently to have the capability to catalyze the cross-couplings of C–X and C–H bonds with Grignard reagents. It is a remarkable progression and would point out new direction for future development on chromium catalysis, as well as opening new opportunities for discovery of new cross-coupling reactions. This highlight typically focused on these advances in chromium-catalyzed transformations by use of Grignard reagents.

Chromium ranks among the most abundant elements on earth.<sup>1</sup> As early as 1910s, Hein performed a pioneering study by the treatment of chromium(III) chloride with phenyl Grignard reagent for the synthesis of bis(arene)chromium species.<sup>2</sup> However, up to 1970s that Nozaki and Hiyama uncovered an interesting chromium-mediated addition of organic halides to aldehydes,<sup>3</sup> that so-called “Nozaki-Hiyama-Kishi” reactions,<sup>4</sup> the employment of this transition metal in organic synthesis has received increasing attention of chemists.<sup>5</sup> Unfortunately, the studies on that stage mainly focused on the exploration of organochromium reagent-mediated stoichiometric reactions. Remarkable advance by use of chromium salts as catalysts to promote organic transformation was achieved by the group of Fürstner.<sup>6</sup> Since then, chromium catalysis has attracted broad interests and various useful synthetic strategies, including polymerization,<sup>7</sup> oxidation,<sup>8</sup> aldol<sup>9</sup> and Diels-Alder reactions,<sup>10</sup> have been developed. These transformations generally feature particular advantages such as good compatibility with sensitive functional groups and high stereoselectivity, rendering them widespread employed in total synthesis as key steps for the preparation of sophisticated natural products.<sup>11</sup> Despite these achievements, chromium-catalyzed organic reactions still remain to be undeveloped as compared to other transition metal catalysis, and considerable efforts in the field can be dedicated to disclose new transformations and broaden the reaction scope. Transition metal-catalyzed cross-coupling reactions have emerged as a powerful tool to organic synthesis, which allows chemists to assemble basic chemical bonds for buildup valuable structural motifs with diversified interests.<sup>12</sup> These reactions traditionally depended largely on precious palladium and toxic nickel and copper catalysts. Recent efforts have been devoted into the development of sustainable synthetic strategies such as environmentally-benign iron-catalyzed transformations as an alternation.<sup>13</sup> It is noting to mention that, analogous with iron(II) chloride, chromium(II) chloride also exhibits a lower toxicity,

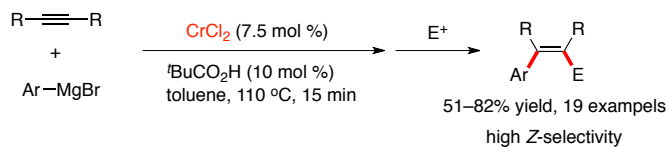
although high-valent chromium(VI) salts are found to have highly toxicity.<sup>14</sup> Obviously, the employment of this attractive metal salt in uncovering new cross-coupling strategies would attract broad interests. It may open fascinating opportunities to disclose new synthetic methodologies. Unfortunately, cross-coupling reactions enabled by chromium catalysts have rarely been investigated. In this context, we want to highlight recent breakthroughs achieved by Knochel and co-workers on chromium-catalyzed cross-coupling reactions of C–X(H) bonds with Grignard reagents, allowing for effectively construction of C–C bonds with a fast conversion rate under ambient conditions.<sup>14,15</sup>



**Scheme 1** Schematic illustration of the known examples on the chromium-catalyzed transformations.

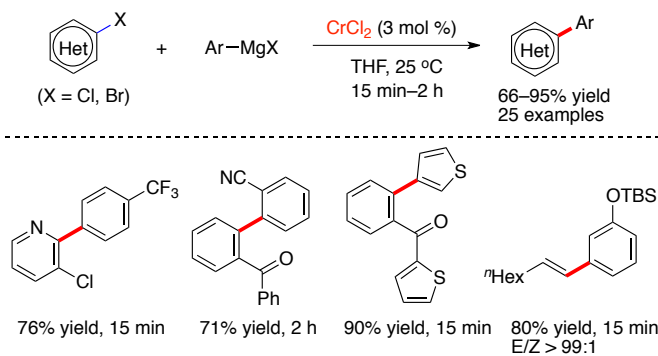
The challenge associated with chromium-promoted cross-coupling reactions may ascribe to the difficulty in the insertion of unactivated chemical bonds into a high-valent chromium species. In contrast, a low-valent complex tends to undergo an oxidative addition to generate an organochromium intermediate, which is thought to be produced in the assistance of nickel, iron or cobalt salts.<sup>16</sup> Note that Fürstner and Shi demonstrated that

the use of manganese powder as reductant in combination with TMSCl allows the achievement of chromium-catalyzed Nozaki-Hiyama-Kishi reactions.<sup>6</sup> In particular, insight from recent advances on low-valent iron and cobalt-catalyzed reactions described by the groups of Fürstner, Nakamura, Yoshikai and Cook,<sup>17</sup> the treatment of a chromium salt with Grignard reagent may allow facily the formation of a low-valent chromium as a catalytically active species, rendering the step of oxidative addition to occur effectively leading to related cross-coupling products.<sup>18</sup>



**Scheme 2** Chromium-catalyzed selective arylation of alkynes (Oshima et al.).<sup>19</sup>

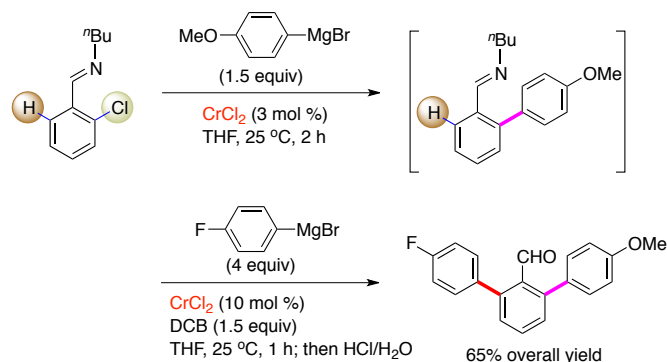
Although the employment of Grignard reagents in chromium-promoted arylation of alkynes was described by Oshima and Yorimitsu (Scheme 2),<sup>19</sup> Knochel and co-workers revealed that chromium(II) chloride, for the first time, was found to have the capability to promote the Kumada cross-coupling reactions between aromatic halides and Grignard reagents (Scheme 3).<sup>14</sup> Interestingly, the reaction allows to proceed at room temperature and achieves satisfactory results in short reaction times. Notably, as compared with other first-low transition metal catalysts, only formation of homo-coupling side product in less than 1% yield was observed in this transformation. It was proved that various nitrogen-containing heterocyclic and aromatic halides can be arylated effectively, while alkenyl iodides are suitable partners to couple efficiently with aromatic Grignard reagents. A variety of functionalities such as chloride, fluoride, alkoxy, alkoxy carbonyl and amino are well compatible with the catalytic system.



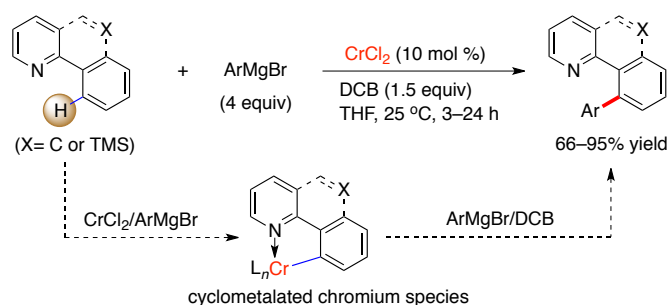
**Scheme 3** Chromium-catalyzed cross-coupling transformations of aromatic and alkenyl halides with Grignard reagents (Knochel et al.).<sup>14</sup>

Interestingly, by consecutive treatment of imino-protected 2-chlorobenzaldehyde with two different aryl Grignard reagents via one-pot operation, the formation of a bisarylated compound was observed (Scheme 4).<sup>15</sup> It reveals that the *ortho*-C–H bond on the aromatic motif was successfully functionalized by chromium in combination with a stoichiometric amount of 2,3-dichlorobutane (DCB) oxidant. The authors demonstrated that benzo[*h*]quinolines, 2-(2-trimethylsilylphenyl)pyridines and 2-

trimethylsilylphenyl-substituted oxazolines allow undergoing this conversion smoothly leading to the desired coupling products in good to excellent yields (Scheme 5). To our knowledge, it is the first example to demonstrate that chromium salts, like commonly effectively transition metal catalysts such as Pd, Rh, Ir, Ni, Co and Fe in the C–H activation reactions,<sup>20</sup> enable promoting the functionalization of unactivated C–H bonds in the assistance of auxiliary, despite that chromium-mediated C–H bond cleavage has been illustrated previously by Smith and co-workers in the achievement of an unexpected cyclometalated chromium complex.<sup>21</sup> Further application of this transformation in the rapid construction of functionalized (terphenyl)pyridine scaffolds was described by the treatment of the resulting TMS-bearing arylated products with ICl followed by a Negishi cross-coupling.



**Scheme 4** Chromium-promoted consecutive arylations for the introduction of two distinctive aryl scaffolds.



**Scheme 5** Cr-catalyzed arylation by use of Grignard reagents via chelation-assisted C–H activation (Knochel et al.).<sup>15</sup>

Despite the fact that the mechanism for the chromium-promoted C–H arylation has not been mentioned by the authors, analogous with cobalt and iron-catalyzed C–H transformations by use of Grignard reagents,<sup>17</sup> a low-valent chromium complex can be considered as a catalytically active species to be involved in the transformation,<sup>18</sup> which may allow to coordinate with the imino auxiliary followed by a *ortho*-C–H bond cleavage leading to a five-membered metallacycle species. The role of Grignard reagents in the reaction may not only be addressed in serving as nucleophilic partner to couple with C–H bond, but likely also to permit access to a low-valent chromium species in the reaction pathway.

## Conclusion and perspective

1 Taking account of the inexpensive and low-toxicity profiles of  
2 chromium(II) chloride that are similar with that of iron salts,  
3 the use of this salt in developing efficient synthetic strategies  
4 would provide an alternation and beneficial complementary to  
5 traditional transition metal catalysis. It may offer an opportunity  
6 for the discovery new reactions. In particular, as compared to  
7 cobalt and iron-promoted cross-couplings by using Grignard  
8 reagents, these protocols own unique features such as forming  
9 small amount of homo-coupling products and proceeding with  
10 fast reaction rates. Despite these advances, chromium-catalyzed  
11 cross-coupling reactions are still in their infancy, significant  
12 efforts would be dedicated to shed light on the mechanism for  
13 uncovering new transformations and expanding reaction scope.  
14 Without doubt, the exploration of efficient synthetic methods  
15 by use of Grignard reagent as a reductant or base rather than a  
16 coupling partner will become preliminary important for future  
17 development.

## 18 Acknowledgements

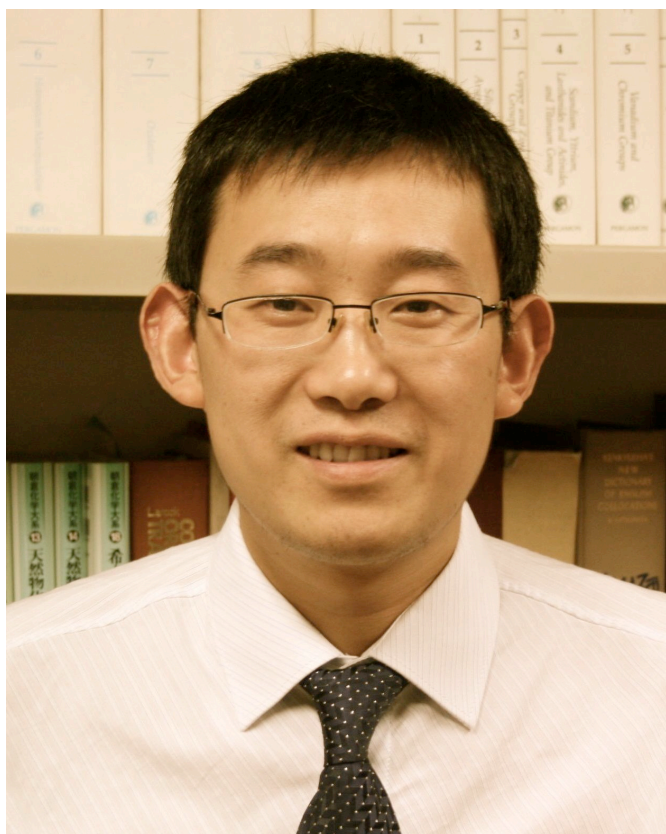
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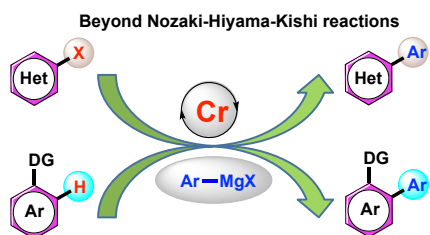
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TOC:



Recent advances in chromium-catalyzed cross-couplings of C-X and C-H bonds with Grignard reagents are highlighted.