

Iron(II) Chloride-mediated Addition of Dialkylmagnesium to Carbonyl Compounds

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Addition reactions to carbonyl compounds with a complex reagent, prepared from organomagnesium and iron(II) chloride, were examined. The reagent works as effective nucleophile to an easily enolizable ketone such as β -tetralone; it also added to keto ester chemoselectively.

Since the pioneering works by Tamura and Kochi, iron salt has been utilized as a catalyst or mediator for cross-coupling reaction between organomagnesium/lithium and organic halides.^{1,2} In addition to the cross-coupling, iron-catalyzed carbometallation reactions have been also reported.³ On the contrary, only a limited number of examples was reported concerning for the reaction with carbonyl compounds. For example, treatment of cyclohexenones with a complex reagent prepared from methyl Grignard and iron(III) chloride underwent regioselective deprotonation to afford dienolate; that with dimethyliron prepared from methyl lithium and iron(II) chloride resulted in 1,4-addition reaction.⁴ A few examples of 1,2-addition of organoiron reagents to ketones had been also shown by Kauffmann and co-worker.⁵ We would like to report our findings about effective nucleophilic reactions of the reagent from iron(II) chloride–dialkylmagnesium with carbonyl compounds.

The addition of organoiron species was examined by the reaction with β -tetralone. The substrate has been recognized as a representative easily enolizable ketone, which is hard to be converted into carbinol via nucleophilic alkylation by the Grignard or organolithium reagent alone (eq 1).⁶ Actually, as shown in Entries 1 and 2 in Table 1, treatment of β -tetralone with MeMgI and Me₂Mg resulted in recovery of starting material **1** in 70 and 65% yields respectively because of enolization. On the other hand, pretreatment of these organomagnesium species with iron(II) chloride in THF for 5 min at 0 °C showed an improvement for yield of the adduct (Entries 4 and 5). A combination of iron(II) chloride with dimethylmagnesium gave the adduct in 70% yield (Entry 5). The result showed that an addition of iron(II) chloride facilitates the addition of methyl group

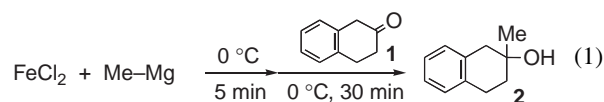
Table 1. Reaction of organoiron species with β -tetralone (**1**, eq 1)^a

Entry	Me–Mg	FeCl ₂ ^b	2 /%	1 (Recov)/%
1	MeMgI (1.5 equiv)	—	24	70
2	Me ₂ Mg (1.5 equiv)	—	34	65
3	MeMgI (1.5 equiv)	2.0 equiv	12	84
4	MeMgI (3.0 equiv)	2.0 equiv	41	54
5	Me ₂ Mg (1.5 equiv)	2.0 equiv	70	30

^aKetone (**1**, 1.0 mmol) was used. ^bAnhydrous FeCl₂ (2.0 mmol) was dispersed in anhydrous THF (6.0 mL) through sonication using Brenson ultrasonic cleaner for 20 min. Organomagnesium (ether solution) was added dropwise at 0 °C, and the resulting mixture was stirred for 5 min at 0 °C.

to carbonyl group of β -tetralone. The efficiency of the preparation of organic transition-metal with diorganomagnesium compare to organomagnesium halide had been already demonstrated.^{6b} It has been well known that such an addition reaction to easily enolizable ketones with organomagnesium reagents was shown in the combination with lanthanoid metal(III) salt. That is, in these transformations, iron(II) chloride was shown to be compatible with expensive lanthanoid metal salts. An attempt to perform the addition reaction with a catalytic amount of iron(II) chloride was failed.

To make a comparison, other fourth periodical transition-metal salts were examined in the same addition reaction. As shown in Figure 1, iron(II) chloride–dimethylmagnesium gave the best result among them. A combination with β -titanium(III) chloride⁷ showed a compatible result. Except these two metal salts, others have not shown positive effect which improves the yield of the adduct **2**. Recently, it was reported that Grignard reagent in the presence of zinc(II) chloride is one of the most nucleophilic species, but the zinc-mediated reagent is still impossible to make addition reaction to easily enolizable β -tetralone.⁸



The methyl–iron reagent, prepared from iron(II) chloride and dimethylmagnesium, was examined for the reaction with other ketones as shown in Figure 2. A sterically hindered ketone **3a** and an enone **3b** were converted to the corresponding carbinols in good yields.⁹ It is notable that an addition reaction of the ketone **3c**, carrying ester group, proceeded effectively with being intact to ester group.¹⁰

The dialkylmagnesium–iron(II) chloride reagent was extended from dimethyl- to dibutylmagnesium and iron(II) chloride one. Different from dimethylmagnesium case, butyl group has a possibility of β -elimination to form metal–hydride. As shown in eq 2, treatment of iron(II) chloride with dibutylmagnesium followed by an addition of β -tetralone resulted in a formation of the reduced product **6**.

β -TiCl ₃	VCl ₃	CrCl ₃	MnCl ₂	FeCl ₂
68%	34%	4%	10%	70%
CoCl ₂	NiCl ₂	CuCl	ZnCl ₂	GaCl ₃
<1%	<1%	6%	<1%	<1%

Figure 1. The yields of **2** in the reaction of β -tetralone and the reagent prepared from the fourth periodical transition-metal salt–dimethylmagnesium.

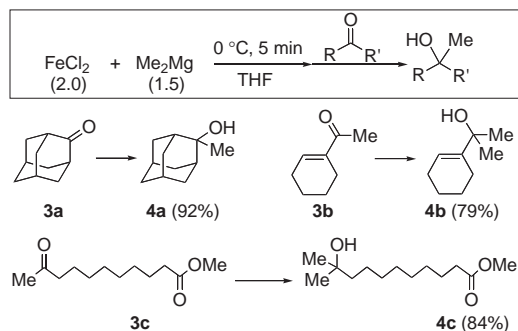


Figure 2. Addition of methyl-iron reagent to ketones.

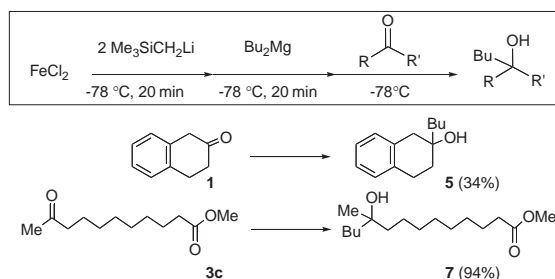
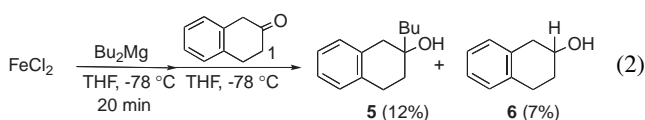
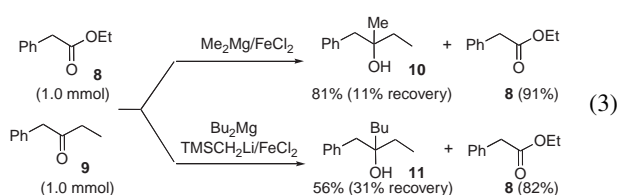


Figure 3. Addition of butyl-iron reagent to ketones.



In order to prevent a formation of metal-hydride species, sterically bulky group, which may interfere β -elimination, was introduced. As shown in Figure 3, iron(II) chloride was treated with 2 equiv of trimethylsilylmethylithium¹¹ at -78°C for 20 min and followed by an addition of dibutylmagnesium at the same temperature. After the procedure, a carbonyl compound was added at the same temperature. The nucleophilic adduct of butyl group to β -tetralone **5** was obtained in 34% yield with 60% recovery of **1**. In this case, the reduced product **6** was not detected. Without the addition of iron salt, a reaction of **1** with dibutylmagnesium in THF afforded the adduct **5** in 7% yield. The amount of trimethylsilylmethylithium was crucial, as the reaction with **1** using 1 equiv of trimethylsilylmethylithium in Figure 3 resulted the formation of **5** in 30% and **6** in 31%. The chemoselectivity was also observed in this reagent. The keto ester **3c** was converted into carbinol **7** chemoselectively.

In eq 3, the highlighted examples, which include the alkylation to easily enolizable ketone with chemoselectivity, were shown. An equimolar mixture of ethyl phenylacetate (**8**) and benzyl ethyl ketone (**9**) was treated with the iron reagents. In both cases, alkylation proceeded on ketone without detectable effect to ester.



The reactive species prepared from dialkylmagnesium and iron(II) chloride is supposed to be ate-complex.^{6b,12,13} Although our reagent is not optimized completely like the lanthanoid reagent system, it is notable that the reactivity is compatible with a combination of dialkylmagnesium and lanthanoid(III) salt.

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