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Title(English)	New Iron-Mediated Synthetic Reactions: Grignard Addition to Enynoates and C–H Bond Peroxygenation
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種別(和文)	論文要旨
Type(English)	Summary

（博士課程）
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論 文 要 旨

THESIS SUMMARY

専攻： Department of	生体分子機能工学	専攻	申請学位（専攻分野）： Academic Degree Requested	博士 Doctor of	（工学）
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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

This thesis, entitled "New Iron-Mediated Synthetic Reactions: Grignard Addition to Enynoates and C-H Bond Peroxygenation," describes the development of new synthetic reactions catalyzed or mediated by iron reagents.

Chapter 1 "Introduction": The recent research in the field of conjugate addition of Grignard reagents and C–H bond functionalization in organic synthesis, the development of iron reagents in currently organic chemistry, and the latest contribution from our laboratory are briefly summarized. In addition, the importance of the studies described in this thesis from the scientific and practical point of view is discussed.

Chapter 2 "Iron-Catalyzed Synthesis of Allenes from 2-Alken-4-ynoates and Grignard Reagents": Conjugate addition of methyl or aryl Grignard reagents to 2-alken-4-ynoates was nicely catalyzed by iron(II) chloride ($FeCl_2$) to proceed in a 1,6-selective manner, giving 5-methyl(or aryl)-3,4-alkadienoates after hydrolysis. Alternatively, deuteration and the treatment with an electrophile gave the deuterated and alkylated products. For example, *tert*-butyl (*E*)-2-undecen-4-ynoate, methylmagnesium bromide, and $FeCl_2$ (10 mol%) afforded magnesiated intermediate, which upon hydrolysis, deuteriolysis, or reaction with acetone gave *tert*-butyl 5-methyl-3,4-undecadienoate, *tert*-butyl 2-deuterio-5-methyl-3,4-undecadienoate, or *tert*-butyl 5-methyl-2-(1-methyl-1-hydroxyethyl)-3,4-undecadienoate in good yields. Additionally, this reaction is applicable to 3-substituted-2-alken-4-ynoates to give tetra-substituted allenes. For example, ethyl (*Z*)-7-(*tert*-butyldimethylsilyloxy)-3-[(triisopropylsilyloxy)methyl]-2-hepten-4-ynoate, 2-bromophenylmagnesium halide, and $FeCl_2$ (10 mol%) afforded ethyl 5-(2-bromophenyl)-7-(*tert*-butyldimethylsilyloxy)-3-[(triisopropylsilyloxy)methyl]-3,4-heptadienoate, which would be a good starting material for the synthesis of an alkaloid, meloscine. Thus, this method allows the preparation of allenes without tedious operations and could be utilized for the synthesis of natural products.

Chapter 3 "Iron-Mediated Three-Component Coupling Reaction between 2-Alken-4-ynoates, *tert*-Alkyl Grignard Reagent, and 1-Bromo-1-alkyne": As mentioned in Chapter 2, *tert*-butylmagnesium chloride or 1-alkynyl Grignard reagents did not add to 2-alken-4-ynoate at its 2- nor 5-position in the presence of an iron salt. However, when a mixture of 2-alken-4-ynoate, 1-bromo-1-alkynes, and $FeCl_2$ was treated with *tert*-BuMgCl, a new one-pot three-component coupling reaction between these starting

materials took place to give 2-(*tert*-butyl)-3,4-alkadien-6-ynoates. For example, *tert*-butyl (*E*)-2-undecen-4-ynoate, 1-bromo-1-octyne, $FeCl_2$ (1 equiv), and *tert*-BuMgCl afforded *tert*-butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate in a good yield. This reaction has quite unusual aspects: (i) clean incorporation of a sterically demanding *tert*-alkyl group, (ii) formal addition of *tert*-alkyl Grignard reagents in an *anti*-Michael fashion, and (iii) that the reaction course does not involve an anionic addition, but most likely consists of a radical pathway. These characteristics are unique in the standpoint of the role of iron reagents in organic synthesis. In conjunction with this transformation, we also found a copper-mediated *anti*-Michael addition of a *tert*- or *sec*-alkyl Grignard reagent to 2-alken-4-ynoates to give an allenylmetal species, which was then alkylated with 1-bromo-1-alkynes to give the same product as those of the aforementioned iron-mediated reactions. For example, *tert*-butyl (*E*)-2-undecen-4-ynoate, *tert*-BuMgCl, and copper(I) bromide dimethylsulfide complex ($CuBr \cdot SMe_2$) afforded the metalated intermediate resulting from the uptake of *tert*-BuMgCl, which upon alkylation with 1-bromo-1-octyne gave the same three-coupling reaction product as above. These Fe- or Cu-mediated reactions could be used complementarily: iron reagents are less toxic and expensive than copper reagents and the laboratory operation of the iron-mediated reactions is simpler, while the copper-mediated reaction covers somewhat wider product variation.

Chapter 4 “Synthesis of *tert*-Butyl Peroxyacetals from Benzyl, Allyl, or Propargyl Ethers via Iron-Promoted C–H Bond Functionalization”: C–H bond functionalization of benzyl, allyl, or propargyl ethers with *tert*-butyl hydroperoxide (*tert*-BuO_2H) was achieved with an iron catalyst to give aryl, olefinic, or acetylenic peroxyacetals which are otherwise tedious to prepare. For example, benzyl butyl ether, *tert*-BuO_2H, and tris(acetylacetonato)iron(III) ($Fe(acac)_3$, 10 mol%) afforded butyl (*tert*-butylperoxy)(phenyl)methyl ether in a good yield. In addition, benzylic, allylic, or propargylic acetals were found good substrates for this transformation to afford peroxyorthoesters. For example, 2-phenyl-1,3-dioxolane was treated with *tert*-BuO_2H in the presence of $Fe(acac)_3$ to give 2-(*tert*-butylperoxy)-2-phenyl-1,3-dioxolane in an excellent yield. Hence, this reaction provides a simple and new synthetic method of organic peroxides, which are generally difficult to prepare, by using an iron catalyst.

Chapter 5 “Summary”: New iron-mediated synthetic reactions, including 1,6- or α-selective conjugate addition of Grignard reagents to enynoates, its extension to three-component coupling reaction between 2-alken-4-ynoates, 1-bromo-1-alkynes, and *tert*-alkyl Grignard reagent, and C–H bond fuctionalization at α position to the ether oxygen, have been disclosed in this thesis. Through these results, the role of iron reagents in organic synthesis and possible synthetic application of the products obtained by these methods are also discussed.