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Iron-Catalyzed Highly Regio- and Stereoselective Conjugate Addition of 2,3-Allenoates with Grignard Reagents

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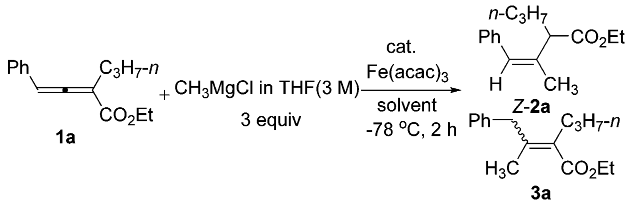
Iron, one of the most inexpensive metals, has recently attracted great attention in organic synthesis.[1] Iron catalysts have been applied to various reactions, such as addition,[2] oxidation,[3] coupling,[4] cyclization,[5] allylic alkylation,[6] etc.[7] We know that it is not so easy to prepare β,γ-unsaturated alkenoates due to the possible migration of the C−C double bond to the conjugated α,β-position. In principle, conjugate addition of 2,3-allenoates would be the most convenient method.[8] Addition reactions of lithium dialkylcuprates or dialkenylcuprate with simple 2,3-allenoate[9a] or 2,3-allenoates with functional groups, such as hydroxyl,[9b] methoxycarbonyl,[9c] or 4-ethylthio groups,[9d] afforded β,γ-unsaturated alkenoates with good regio- and stereoselectivity; the reaction of organolithium with 2,3-allenoates using CuCN•2LiCl (0.5 equiv) also afforded β,γ-unsaturated alkenoates with high regio- and moderate stereoselectivity (86/14).[9e,f] However, these reactions require a stoichiometric or substoichiometric amount of organocuprate reagents. To the best of our knowledge, there is no report on the catalytic conjugate addition of 2,3-allenoates with easily available organometallic reagents. Herein, we wish to report an iron-catalyzed conjugate addition of 2,3-allenoates with Grignard reagents in excellent regio- and stereoselectivity.

First, we used ethyl 2-(*n*-propyl)-4-phenylbutadienoate **1a** as the substrate. The results of its reaction with methyl magnesium chloride (3 equiv) at −78 °C in different solvents are summarized in Table 1. With 20 mol % of Fe(acac)$_3$, ethyl 2-(*n*-propyl)-3-methyl-4-phenylbut-3-enoate (*Z*)-**2a** was afforded in 78% yield with a *Z/E* ratio of 96/4 in THF; the yield of 2-(*n*-propyl)-3-methyl-4-phenylbut-2-enoate **3a** was at the extent of 0.5% (entry 2, Table 1). In the absence of Fe(acac)$_3$, no reaction occurred (entry 1, Table 1). However, when CH$_2$Cl$_2$ or *n*-hexane was used as the solvent, the yield of **2a** was lower with a poor stereoselectivity (entries 3 and 4, Table 1). Fortunately, it was found that Et$_2$O or toluene is a very nice solvent for this reaction (entries 5 and 7, Table 1). With 5 mol % of the catalyst, the yield and stereoselectivity of the reaction in toluene were somewhat higher than those in Et$_2$O (compare entries 6, 8, and 9, Table 1). It was also quite interesting to note that the reaction with 1.2 equiv of methyl magnesium chloride afforded **2a** with a lower stereoselectivity (*Z*/*E* = 91/9) (entry 10, Table 1).[10] Furthermore, the reaction could even afford **2a** in 73% yield with just 0.5 mol % of Fe(acac)$_3$ (entry 12, Table 1). In the absence of Fe(acac)$_3$, the reaction in toluene was very slow (entry 13, Table 1). It should be noted that under the catalysis of 20 mol % of CuCl$_2$ the reaction in toluene afforded (*Z*)-**2a** and **3a** in 82 and 3% yields, respectively (entry 14, Table 1).

Thus, we defined 2 mol % of Fe(acac)$_3$, 3 equiv of Grignard reagents, and toluene as the solvent at −78 °C as the standard reaction conditions. The typical results shown in Table 2 indicated that the reaction is quite general, forming β,γ-unsaturated alkenoates with very high regio- and stereoselectivity. R^1 may be alkyl or aryl; R^2 may be H, alkyl, or benzyl; R^3 may be alkyl or Bn. In addition to primary alkyl Grignard reagent, secondary alkyl Grignard reagent may also be applied to afford corresponding products in good yields (entries 10−13, Table 2). The reaction of **1i** and **1j** with phenyl magnesium chloride afforded the products in the same yields (63%) (entries 14 and 15, Table 2). Vinyl magnesium chloride may also be used in the reaction (entries 16 and 17, Table 2).

Table 1. Effects of Solvent and the Amount of Catalyst on Iron-Catalyzed Conjugate Addition of 2,3-Allenoate **1a**



entry	mol % of catalyst	solvent	yield of (*Z*)-**2a** (%) (*Z/E*)[c]	**1a** recovered[c] (%)	yield[c] of **3a** (%)
1	−	THF	−	77	−
2	20	THF	78 (96/4)	−	0.5
3	20	CH$_2$Cl$_2$	50 (74/26)	2	3
4	20	*n*-hexane	50 (83/17)	6	1.5
5	20	Et$_2$O	81 (98/2)	−	1.1
6	5	Et$_2$O	77 (99/1)	−	0.4
7	20	toluene	71 (98/2)	−	1
8	10	toluene	75 (99/1)	−	0.4
9	5	toluene	81 (>99/1)	−	0.8
10[a]	5	toluene	76 (91/9)	−	1.5
11	2	toluene	82 (>99/1)	2	0.3
12[b]	0.5	toluene	73 (>99/1)	6	1.5
13	−	toluene	29 (>99/1)	56	2
14[d]	20	toluene	82 (>99/1)	−	3

[a] CH$_3$MgCl (1.2 equiv) was applied. [b] The reaction time was 5 h. [c] Determined by NMR. [d] CuCl$_2$ used instead of Fe(acac)$_3$.

In terms of mechanism, the reaction of Fe(acac)$_3$ with Grignard reagent R^{4}MgX may form the iron−magnesium ate complex **4**.[4d,f] The subsequent conjugate addition with the electron-deficient α,β-carbon−carbon double bond in 2,3-allenoates would form 1,3-dienolate intermediate **7** highly stereoselectively, probably due to the steric interaction between the R^1 and R^4 group in the transition state **6**. Upon transmetalation of **7** with R^{4}MgX, magnesium 1,3-dienolate **8**[2g] was formed with the regeneration of the catalytically active species **4** (Scheme 1).

The in situ formation of magnesium dienolate may be trapped with D$_2$O to afford the 2-D-3-methyl-4-phenyl-2-propyl-3-butenoate **9** in 89% yield with a D incorporation of 97% (Scheme 2).

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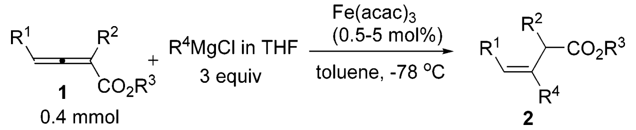
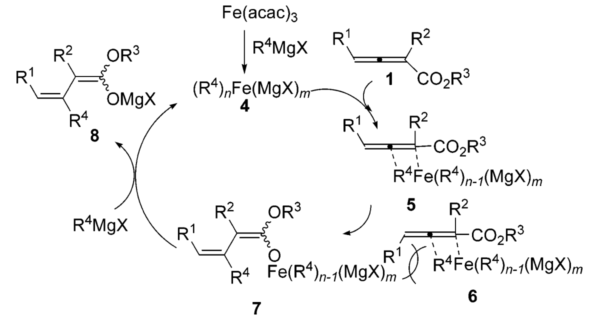
Table 2. Iron-Catalyzed Carbomagnesiation of 2,3-Allenoates[a]



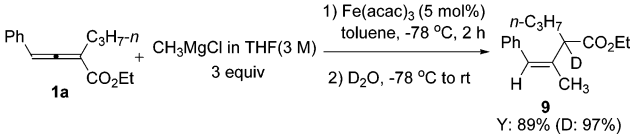
entry	R^1	R^2	R^3	R^4	time (h)	yield[d] of **2** (%)
1[b]	Ph	*n*-Pr	Et (**1a**)	Me	2	77 (**2a**)
2[c]	Ph	*n*-Pr	Me (**1b**)	Me	3	86 (**2b**)
3[b]	Ph	*n*-Pr	Bn (**1c**)	Me	2	84 (**2c**)
4	Ph	Me	Et (**1d**)	Me	1.5	88 (**2d**)
5	p-BrC$_6$H$_4$	*n*-Pr	Et (**1e**)	Me	1	88 (**2e**)
6[c]	p-BrC$_6$H$_4$	Me	Et (**1f**)	Me	1.5	88 (**2f**)
7[b]	n-C$_7$H$_{15}$	*n*-Pr	Et (**1g**)	Me	5	85 (**2g**)
8	n-C$_4$H$_9$	Bn	Me (**1h**)	Me	1.5	85 (**2h**)
9[b]	Ph	*n*-Pr	Et (**1a**)	*n*-Bu	1	70 (**2i**)
10[b]	Ph	*n*-Pr	Et (**1a**)	*c*-Hex	1.7	86 (**2j**)
11[b]	n-C$_7$H$_{15}$	*n*-Pr	Et (**1g**)	*c*-Hex	1	90 (**2k**)
12[b]	Ph	Me	Et (**1d**)	*c*-Hex	1	78 (**2l**)
13[b]	n-C$_7$H$_{15}$	*n*-Pr	Et (**1g**)	*s*-Bu[e]	1	94 (**1m**)
14	n-C$_4$H$_9$	H	Et (**1i**)	Ph	2	63 (**2n**)
15[b]	n-C$_7$H$_{15}$	H	Et (**1j**)	Ph	1	63 (**2o**)
16[b]	Ph	*n*-Pr	Et (**1a**)	vinyl	1	82 (**1p**)
17[b]	n-C$_7$H$_{15}$	*n*-Pr	Et (**1g**)	vinyl	1	86 (**1q**)

[a] The reaction was conducted using 0.4 mmol of 2,3-allenoates, 3 equiv of the Grignard reagents (solution in THF), and 2 mol % of Fe(acac)$_3$ in 5 mL of toluene at −78 °C. [b] Fe(acac)$_3$ (5 mol %) was used. [c] Fe(acac)$_3$ (0.5 mol %) was used. [d] Isolated yield. [e] *s*-Butyl magnesium bromide was used.

Scheme 1



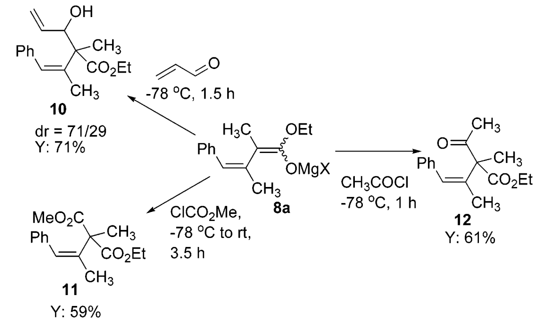
Scheme 2



This magnesium dienolate **8a** may also react with an aldehyde to afford the 1,2-addition product **10**. Its reaction with methyl chloroformate or acetyl chloride afforded 2-vinyl malonate derivative **11** or β-ketoester derivative **12** efficiently (Scheme 3).

In summary, we have developed an efficient regio- and stereospecific iron-catalyzed conjugate addition of 2,3-allenoates with 1°- and 2°-alkyl, phenyl, or vinyl Grignard reagents. This protocol introduces the R^4 group from the Grignard reagents to the β-position of the ester group with the R^4 group *trans* to the R^1 group at the 4-position in the remaining β,γ-carbon−carbon double bond. The in situ formed magnesium dienolate may also react with different electrophiles to prepare a series of compounds containing an allylic quaternary carbon at the α-position of the ester group. Further studies in this area are being conducted in our laboratory.

Scheme 3



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Supporting Information Available: Spectroscopic data and general procedure (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For details, see Table S1 in the Supporting Information.

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