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Ferric Chloride Hexahydrate-Catalyzed Highly Regio- and Stereoselective Conjugate Addition Reaction of 2,3-Allenoates with Grignard Reagents: An Efficient Synthesis of β,γ-Alkenoates

Guobi Chai,[a] Zhan Lu,[a] Chunling Fu,[a] and Shengming Ma[a,*]

[a] Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, People's Republic of China
Fax: (+86)-21-6260-9305; e-mail: masm@mail.sioc.ac.cn

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Abstract: Ferric chloride hexahydrate was shown to be an efficient catalyst for the conjugate addition of 2,3-allenoates with alkyl-, aryl-, or vinyl-Grignard reagents to synthesize polysubstituted β,γ-unsaturated alkenoates with high regio- and stereoselectivity. The *in situ* formed magnesium dienolate may readily react with different electrophilic reagents under different reaction conditions with or without a catalyst to construct an allylic quaternary carbon at the α-position of the ester group and a stereocontrollable retention of the carbon-carbon double bond.

Keywords: allenes; esters; Grignard reagents; iron; Michael addition

Introduction

Substituted β,γ-unsaturated alkenoates bearing a nonconjugated double bond are widely found in biologically active natural products such as actiniarin A methyl ester,[1a] 4-hydroxycinnamate derivatives,[1b] cytochalasin Q,[1c] and, thus, they have caught the attention of many synthetic organic and pharmaceutical chemists.[1] It is not so easy to synthesize this type of compounds due to the possible migration of the C=C double bond to the conjugated α,β-position and the stereoselectivity referring to the formation of the C=C double bond.[2] On the other hand, allenes, especially those with electron-withdrawing groups, have become of great interest in synthetic organic chemistry owing to the high reactivity of the allene moiety.[3] In the past decades, the conjugate addition of organometallic reagents to 2,3-allenoates has proven to be an efficient way to synthesize β,γ-unsaturated carbonyl compounds *via* the α-protonation of the *in situ* formed metallic dienolates:[4] addition reactions of lithium dialkylcuprates or dialkenylcuprate with simple 2,3-allenoates[4a] or 2,3-allenoates with functional groups such as hydroxy,[4b] methoxycarbonyl,[4c] or ethylthio groups[4d] afford β,γ-unsaturated alkenoates with good regio- and stereoselectivity; the reaction of an organolithium with 2,3-allenoates in the presence of CuCN·2 LiCl (0.5 equiv.)[4e,f] also affords β,γ-unsaturated alkenoates with good regio- and stereoselectivity.

However, these reactions are limited to the use of stoichiometric or substoichiometric organocuprate reagents; further improvements in this area are obviously desirable. Particularly, in the view of industrial applications, an environmentally friendly and cheap catalytic system is important. In this context, iron is one of the best choices.[5,6] In our previous work, we utilized the anhydrous iron salt $Fe(acac)_3$ to catalyze the conjugate addition reaction of 2,3-allenoates with Grignard reagents, affording β,γ-unsaturated alkenoates with high regio- and stereoselectivity.[7]

Compared with $Fe(acac)_3$, $FeCl_3{\cdot}6H_2O$ is surely more readily available and extremely cheap. However, there are very limited reports concerning its applications as a catalyst.[8] In this context, we present our recent surprising observation on the use of simple $FeCl_3{\cdot}6H_2O$ as an alternative catalyst for the conjugate addition reaction of 2,3-allenoates with various Grignard reagents to afford β,γ-unsaturated alkenoates. Furthermore, highly stereocontrollable α-acylation and allylation reactions of the *in situ* generated magnesium dienolate intermediate were achieved by

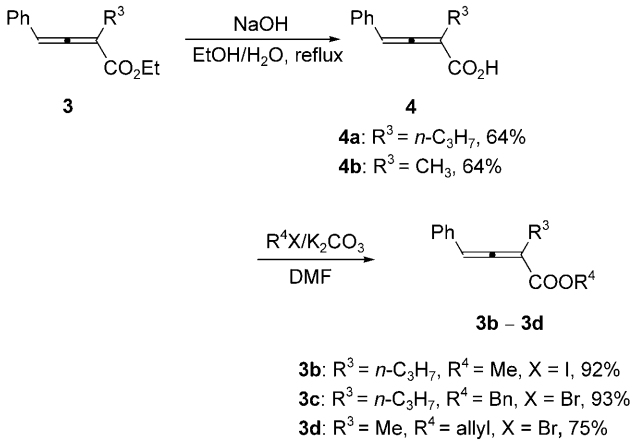
variations of the electrophiles and reaction conditions.[9,10]

Results and Discussion

Synthesis of 2,3-Allenoates 3

2,3-Allenoates **3a** and **3e–3o** can be prepared from the corresponding Wittig reagents with acyl chlorides **2** in the presence of Et_3N (Scheme 1).[11]

2-Alkyl-4-phenyl-2,3-butadienoates **3b–3d** can be prepared from the esterification of corresponding 2,3-allenoic acids **4** (Scheme 2).[12]



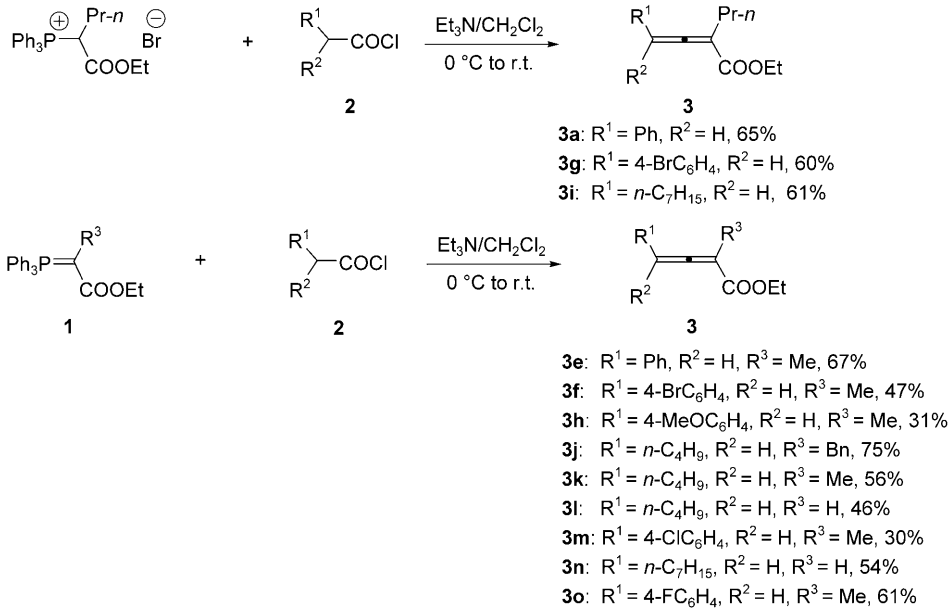
Scheme 2. Synthesis of 2,3-allenoates **3b–3d**.

$FeCl_3{\cdot}6H_2O$-Catalyzed Highly Regio- and Stereoselective Conjugate Addition Reaction of 2,3-Allenoates with Grignard Reagents

Initially, we accidentally attempted the reaction of ethyl 4-phenyl-2-propyl-2,3-butadienoate **3a** with methylmagnesium chloride under the catalysis of 5 mol% of $FeCl_3{\cdot}6H_2O$ and the same conditions utilized in our previous work.[7] To our surprise, ethyl 3-methyl-4-phenyl-2-propyl-3(*Z*)-butenoate *Z*-**5a** was afforded in 93% yield highly selectively (entry 1, Table 1). The stereochemistry was established by NOE analysis (Figure 1).

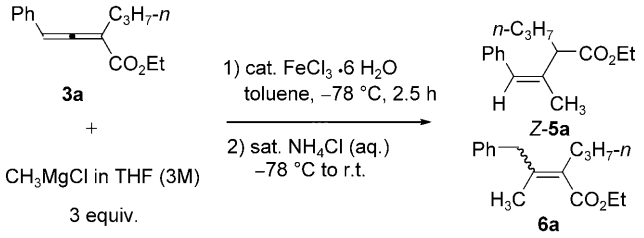
Next, 2 mol% of $FeCl_3{\cdot}6H_2O$ was used and a similar result was obtained (entry 2, Table 1). However, when we reduced the loading of $FeCl_3{\cdot}6H_2O$ further to 0.5 mol%, the reaction was quite slow, resulting in a very low yield of *Z*-**5a** (entry 3, Table 1). Only 13% of *Z*-**5a** was formed when no catalyst was used with **3a** being recovered in 84% yield (entry 4, Table 1). In all cases, the formation of the *E* isomer of the conjugate addition product was not observed; the α,β-unsaturated conjugated isomer 3-methyl-4-phenyl-2-propyl-2-butenoate **6a** was formed to the extent of $\leq$1.2% (entries 1–4, Table 1). Obviously, compared with the results from $Fe(acac)_3$, although the formation of α,β-unsaturated enoate **6a** is slightly higher,[7] $FeCl_3{\cdot}6H_2O$ is more efficient and high yielding (compare entries 1 and 2 with entries 5 and 6, Table 1).

With the optimized reaction conditions in hand, we explored the substrate scope of the $FeCl_3{\cdot}6H_2O$-catalyzed conjugate addition reaction of 2,3-allenoates with alkyl-Grignard reagents as shown in Table 2. R^1



Scheme 1. Synthesis of 2,3-allenoates **3a** and **3e–3o**.

Table 1. Effect of catalyst on the Fe(III)-catalyzed conjugate addition of 2,3-allenoate **3a** with methylmagnesium chloride.[a]



Entry	$FeCl_3 \cdot 6H_2O$ [mol%]	Yield of *Z*-**5a** [%][b]	Recovery of **3a** [%][b]	Yield of **6a** [%][b]
1	5	93	–	0.7
2	2	98	–	0.7
3	0.5	46	46	1.2
4	–	13	84	0.9
5	5[c]	81	–	0.8

[a] The reaction was conducted using 0.4 mmol of the 2,3-allenoate, 3 equiv. of the Grignard reagent (3 M solution in THF) in 5 mL of toluene at −78 °C.

[b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethylbenzene as the internal standard.

[c] $Fe(acac)_3$ was used as catalyst instead of $FeCl_3 \cdot 6H_2O$.[7]

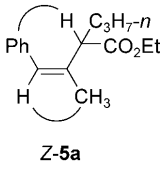
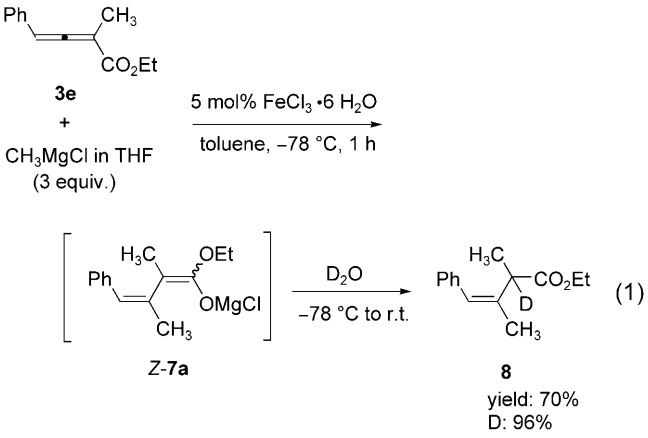


Figure 1. NOE study of *Z*-**5a**.

could be aryl or alkyl groups; R^2 could be H, Bn or alkyl groups; R^3 could be alkyl, Bn or allyl groups. The reaction may proceed with primary (entries 1–12, Table 2), secondary, and tertiary Grignard reagents (entries 13–15, Table 2). However, in some cases such as substrates **3g**, **3i** and **3j**, the reaction requires 5 mol% of $FeCl_3 \cdot 6H_2O$ for a complete conversion of the starting 2,3-allenoates (entries 7, 9 and 10, Table 2).

The highly regio- and stereoselective addition reaction of 2,3-allenoates with vinylmagnesium halides (entries 1–3, Table 3) or phenylmagnesium chloride (entries 4–7, Table 3) can also be performed to afford the conjugated dienes or 3-phenyl-substituted β,γ-alkenoates. 2-Thienylmagnesium bromide may also be reacted with **3e** to obtain the corresponding product *E*-**5w** in 63% yield (entry 8, Table 3).

Treatment of the conjugate addition reaction mixture with D_2O afforded **8** in 70% yield with 96% D incorporation, indicating the intermediacy of the magnesium 1,3(*Z*)-dienolate *Z*-**7a** [Eq. (1)].

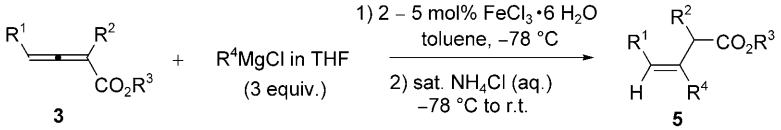


Stereocontrollable α-Acylation and Allylation Reactions of the *in situ* Generated Magnesium Dienolate Intermediates with Electrophiles

As a result, the magnesium 1,3-dienolate **7a** may undergo a coupling reaction with acetyl chloride to afford *Z*-**9a** in 65% yield with an *Z*/*E* ratio of >99% (conditions A, entry 1, Table 4). Similarly,[10] the reaction of the *in situ* generated magnesium dienolate **7a** with allyl acetate at −78 °C followed by warming up to room temperature afforded α-acylated 3(*E*)-alkenoate *E*-**9a** in 50% yield with a reversed stereoselectivity (*E*/*Z* = 93/7) (conditions B, entry 1, Table 4). The stereochemistry was also established by NOE analysis. It should be noted that the formation of the α-allylated product was not observed based on the ^{1}H NMR analysis of the crude reaction mixture. The *in situ* generated dienolates from the reactions of **3f**, **3m** and **3o** also reacted with acetyl chloride or allyl acetate affording the corresponding products *Z*-**9** or *E*-**9** with high stereoselectivity, respectively (conditions A and B, entries 3, 5 and 7, Table 4). In the *Z*-acylation reactions of the *in situ* generated magnesium dienolate **7**, $FeCl_3 \cdot 6H_2O$ and $Fe(acac)_3$ both exhibited very high stereoselectivity (>99/1) (conditions A, compare entries 1, 3, 5 and 7 with 2, 4, 6 and 8, Table 4). However, in the *E*-acylation reactions of the *in situ* generated magnesium dienolate **7**, the results obtained with $Fe(acac)_3$ are better than those with $FeCl_3 \cdot 6H_2O$ (conditions B, compare entries 1, 3, 5 and 7 with 2, 4, 6 and 8, Table 4).

Furthermore, we were again quite happy to observe that under the catalysis of $Pd(PPh_3)_4$, the reaction of magnesium dienolate **7a** with allyl acetate afforded the α-allylated 3(*Z*)-alkenoate *Z*-**10a** exclusively in 75% yield with high stereoselectivity (*Z*/*E* = 98/2) (conditions C, entry 1, Table 5). The configuration of the C=C double bond in this compound was established again by NOE analysis. Likewise, under the catalysis of CuI, the reaction with allyl bromide afforded the opposite stereoisomer *E*-**10a** in 52% yield

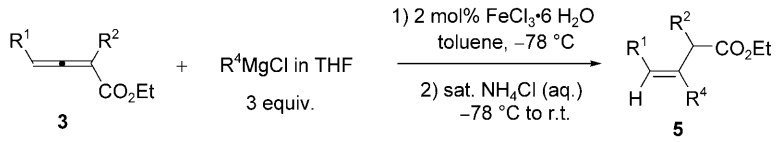
Table 2. $FeCl_3 \cdot 6H_2O$-catalyzed conjugate addition of alkylmagnesium chlorides to 2,3-allenoates.[a]



Entry	R^1	R^2	R^3	R^4	Time [h]	Yield of **5** [%][b]
1	Ph	*n*-Pr	Et (**3a**)	Me	2.5	88 (*Z*-**5a**)
2	Ph	*n*-Pr	Me (**3b**)	Me	2.4	89 (*Z*-**5b**)
3	Ph	*n*-Pr	Bn (**3c**)	Me	3.5	78 (*Z*-**5c**)
4	Ph	Me	allyl (**3d**)	Me	3	72 (*Z*-**5d**)
5	Ph	Me	Et (**3e**)	Me	3.5	62 (*Z*-**5e**)
6	*p*-BrC_6H_4	Me	Et (**3f**)	Me	3	87 (*Z*-**5f**)
7[c]	*p*-BrC_6H_4	*n*-Pr	Et (**3g**)	Me	2.4	99 (*Z*-**5g**)
8	*p*-$MeOC_6H_4$	Me	Et (**3h**)	Me	1	67 (*Z*-**5h**)
9[c]	*n*-C_7H_{15}	*n*-Pr	Et (**3i**)	Me	3	85 (*Z*-**5i**)
10[c]	*n*-C_4H_9	Bn	Et (**3j**)	Me	3	89 (*Z*-**5j**)
11	*n*-C_4H_9	Me	Et (**3k**)	Me	2	76 (*Z*-**5k**)
12	*n*-C_4H_9	H	Et (**3l**)	*n*-C_5H_{11}[d]	3.5	61 (*Z*-**5l**)
13	Ph	Me	Et (**3e**)	*c*-Hex	2	79 (*Z*-**5m**)
14	*n*-C_7H_{15}	*n*-Pr	Et (**3i**)	*s*-Bu[d]	1.5	85 (*Z*-**5n**)
15	Ph	Me	Et (**3e**)	*t*-Bu	1.5	81 (*E*-**5o**)

[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 $FeCl_3 \cdot 6H_2O$ in 5 mL of toluene at −78 °C, unless otherwise stated.
[b] Isolated yield.
[c] 5 mol% of $FeCl_3 \cdot 6H_2O$ was used.
[d] Alkylmagnesium bromides were used.

Table 3. $FeCl_3 \cdot 6H_2O$-catalyzed conjugate addition of aryl or vinyl magnesium halides with 2,3-allenoates.[a]

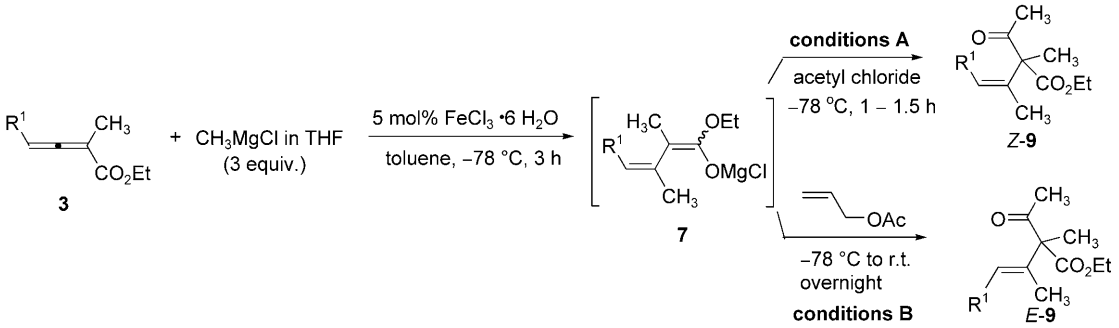


Entry	R^1	R^2	R^4	Time [h]	Yield of **5** [%][b]
1[c]	Ph	*n*-Pr (**3a**)	vinyl	1.5	84 (*Z*-**5p**)
2	*p*-ClC_6H_4	Me (**3m**)	vinyl[d]	3	85 (*Z*-**5q**)
3	*n*-C_4H_9	Me (**3k**)	vinyl	3	75 (*Z*-**5r**)
4	*p*-$MeOC_6H_4$	Me (**3h**)	Ph	3	81 (*E*-**5s**)
5	*n*-C_4H_9	H (**3l**)	Ph	2.5	64 (*E*-**5t**)
6	*n*-C_7H_{15}	H (**3n**)	Ph	3	60 (*E*-**5u**)
7	*n*-C_4H_9	Me (**3k**)	Ph	3	70 (*E*-**5v**)
8[e]	Ph	Me (**3e**)	2-thienyl[d]	11	63 (*E*-**5w**)

[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 $FeCl_3 \cdot 6H_2O$ in 5 mL of toluene at −78 °C. Freshly prepared vinyl-Grignard reagent was needed.
[b] Isolated yield.
[c] 5 mol% of $FeCl_3 \cdot 6H_2O$ was used.
[d] Magnesium bromide was used.
[e] This reaction was conducted at room temperature as no reaction occurred at −78 °C.

(*E*/*Z* = 96/4) (conditions D, entry 1, Table 5). The configuration of the C=C double bond in this compound was also established by NOE analysis. The *in situ* generated dienolates from the reaction of **3f**, **3m** and **3o** also reacted with allyl acetate under the catalysis of $Pd(PPh_3)_4$ or allyl bromide under the catalysis of CuI affording the corresponding products *Z*-**10** or *E*-**10** with high stereoselectivity, respectively (conditions C and D, entries 3, 5 and 7, Table 5). In the α-allylation of magnesium dienolate intermediates with allyl ace-

Table 4. Reaction of *in situ* generated magnesium dienolate **7** with acetyl chloride or allyl acetate.[a]



Entry	R^1	Conditions A		Conditions B	
		Yield of *Z*-**9** [%][b]	Ratio (*Z*/*E*)[c]	Yield of *E*-**9** [%][b]	Ratio [*E*/*Z*][c]
1	Ph (**3e**)	65 (*Z*-**9a**)	>99/1	50 (*E*-**9a**)	93/7
2[d]	Ph (**3e**)	68 (*Z*-**9a**)	>99/1	50 (*E*-**9a**)	95/5
3	*p*-BrC_6H_4 (**3f**)	70 (*Z*-**9b**)	>99/1	45 (*E*-**9b**)	95/5
4[d]	*p*-BrC_6H_4 (**3f**)	87 (*Z*-**9b**)	>99/1	62 (*E*-**9b**)	97/3
5	*p*-ClC_6H_4 (**3m**)	82 (*Z*-**9c**)	>99/1	55 (*E*-**9c**)	96/4
6[d]	*p*-ClC_6H_4 (**3m**)	84 (*Z*-**9c**)	>99/1	50 (*E*-**9c**)	98/2
7	*p*-FC_6H_4 (**3o**)	77 (*Z*-**9d**)	>99/1	50 (*E*-**9d**)	94/6
8[d]	*p*-FC_6H_4 (**3o**)	76 (*Z*-**9d**)	>99/1	69 (*E*-**9d**)	98/2

[a] *Conditions A:* 2 mmol of acetyl chloride were added to 0.4 mmol of the *in situ* generated magnesium dienolate at −78 °C. *Conditions B:* 2 mmol of allyl acetate were added to 0.4 mmol of the *in situ* generated magnesium dienolate at −78 °C followed by warming up to room temperature naturally. The formation of 6–31% hydrolysis product was observed by ^{1}H NMR analysis of the crude reaction mixture.

[b] Isolated yield.

[c] The ratio was determined by ^{1}H NMR analysis of the crude products.

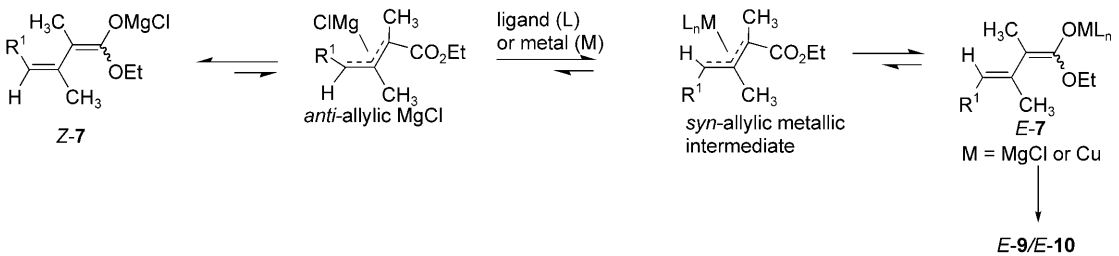
[d] $Fe(acac)_3$ was used instead of $FeCl_3{\cdot}6H_2O$.

tate under the catalysis of $Pd(PPh_3)_4$, the amounts of α-acylated product 3(*E*)-alkenoate *E*-**9** are in the order of ≤0.9%, if any, based on the ^{1}H NMR analysis of the crude reaction mixture. In all cases, $FeCl_3{\cdot}6H_2O$ exhibited better or similar stereoselectivity (conditions C and D, compare entries 1, 3, 5 and 7 with 2, 4, 6 and 8, Table 5).

A possible mechanism has been proposed for the inversion of the configuration of the C=C bond for the formation of *E*-**9** and *E*-**10** (Scheme 3). The dienolate intermediate *Z*-**7** may isomerize to the delocalized π-allylic intermediate, i.e., *anti*-allylic-MgCl, which may isomerize to the more stable *syn*-allylic metallic intermediate due to the steric effect between the coordinated metal and the methyl/R^1 groups.[10,13] The coordination of the C=C bond in the allylic carboxylate or allylic bromide with the metal or the presence of the more bulky Cu^+ instead of Mg^{2+} would further increase this steric effect leading to the isomerization of the *in situ* generated intermediate *Z*-**7** to the thermodynamically more stable *E*-**7**. Subsequent reaction with the allylic carboxylate or allylic bromide leads to the formation of *E*-**9** or *E*-**10**.[14]

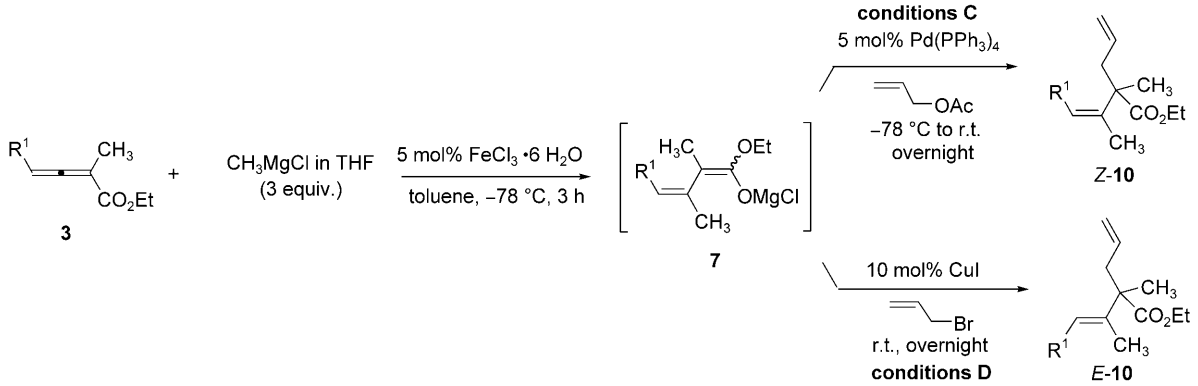
Conclusions

In summary, we have developed an efficient $FeCl_3{\cdot}6H_2O$-catalyzed method to synthesize trisubstituted β,γ-unsaturated *Z*-alkenoates with high regio-



Scheme 3. Possible mechanism for the formation of *E*-**9** and *E*-**10**.

Table 5. Transition metal-catalyzed allylation reactions of *in situ* generated dienolate **7** with different allyl reagents.[a]



Entry	R^1	Conditions C		Conditions D	
		Yield of *Z*-**10** [%][b]	Ratio (*Z*/*E*)[c]	Yield of *E*-**10** (%)[b]	Ratio (*E*/*Z*)[c]
1	Ph (**3e**)	76 (*Z*-**10a**)	98/2	52 (*E*-**10a**)	96/4
2[d]	Ph (**3e**)	67 (*Z*-**10a**)	96/4	51 (*E*-**10a**)	96/4
3	*p*-BrC_6H_4 (**3f**)	70 (*Z*-**10b**)	97/3	71 (*E*-**10b**)	>99/1
4[d]	*p*-BrC_6H_4 (**3f**)	80 (*Z*-**10b**)	93/7	65 (*E*-**10b**)	97/3
5	*p*-ClC_6H_4 (**3m**)	72 (*Z*-**10c**)	97/3	63 (*E*-**10c**)	97/3
6[d]	*p*-ClC_6H_4 (**3m**)	66 (*Z*-**10c**)	96/4	71 (*E*-**10c**)	97/3
7	*p*-FC_6H_4 (**3o**)	69 (*Z*-**10d**)	96/4	69 (*E*-**10d**)	98/2
8[d]	*p*-FC_6H_4 (**3o**)	74 (*Z*-**10d**)	94/6	72 (*E*-**10d**)	97/3

[a] *Conditions C:* 5 mol% of $Pd(PPh_3)_4$ and 2 mmol of allyl acetate were added to 0.4 mmol of the *in situ* generated magnesium dienolate at −78 °C followed by warming up to room temperature naturally. *Conditions D:* 10 mol% of CuI and 2 mmol of allyl bromide were added to 0.4 mmol of the *in situ* generated magnesium dienolate at room temperature.

[b] Isolated yield (see the experimental section for the details). The formation of 1–13% hydrolysis product was observed by ^1H NMR analysis of the crude reaction mixture.

[c] The ratio was determined by ^1H NMR analysis of the crude products.

[d] $Fe(acac)_3$ was used instead of $FeCl_3{\cdot}6H_2O$.

and stereoselectivity. Primary, secondary and tertiary alkyl, vinylic or aromatic groups may be introduced by using the readily available Grignard reagents to the 3-position of 2,3-allenonates. Good to excellent yields were obtained with a catalytic loading of $FeCl_3{\cdot}6H_2O$. Compared with the results of $Fe(acac)_3$, $FeCl_3{\cdot}6H_2O$ is more efficient and high yielding with slightly higher yields for the formation of α,β-unsaturated enoate (compare entries 1 and 2 with entries 5 and 6, Table 1). Due to the cheap and easy handling nature of the catalyst, this catalytic system will have promising applications in organic synthesis. Furthermore, stereocontrollable α-acylation and allylation reactions of the *in situ* generated magnesium dienolate intermediates **7** were achieved with the use of different electrophiles and conditions: 2-acylated 3(*Z*)- and 3(*E*)-alkenotes **9** were formed when we used acetyl chloride or allyl acetate as the electrophiles; 2-allylated 3(*Z*)- and 3(*E*)-alkenotes **10** were formed when we used allyl acetate in the presence of $Pd(PPh_3)_4$ or allyl bromide in the presence of CuI as the electrophiles, respectively. In the *Z*-acylation reactions of the *in situ* generated magnesium dienolates **7**, $FeCl_3{\cdot}6H_2O$ and $Fe(acac)_3$ both exhibited very high stereoselectivity (>99/1) (conditions A, compare entries 1, 3, 5 and 7 with 2, 4, 6 and 8, Table 4) while in the *E*-acylation reactions of the *in situ* generated magnesium dienolate **7**, the results obtained with $Fe(acac)_3$ are better than those with $FeCl_3{\cdot}6H_2O$ (conditions B, compare entries 1, 3, 5 and 7 with 2, 4, 6 and 8, Table 4). On the other hand, $FeCl_3{\cdot}6H_2O$ exhibited better or similar stereoselectivity in the allylation reactions of the *in situ* generated magnesium dienolate **7** (conditions C and D, compare entries 1, 3, 5 and 7 with 2, 4, 6 and 8, Table 5). Further studies in this area are being conducted in our laboratory.

Experimental Section

Ethyl 3-Methyl-4-phenyl-2-propyl-3(*Z*)-butenoate (*Z*-5a); Typical Procedure for the Synthesis of Compounds 5

To a dried Schlenk tube were added $FeCl_3{\cdot}6H_2O$ (2.2 mg, 2 mol%, 0.008 mmol), **3a** (91.7 mg, 0.4 mmol), and toluene (5 mL) sequentially under a nitrogen atmosphere at room temperature. A solution of CH_3MgCl in THF (0.4 mL, 3 M,

1.2 mmol, 3 equiv.) was then added with a syringe to the reaction mixture within 3 min at −78 °C. After the reaction was over as monitored by TLC, the reaction mixture was quenched slowly with a saturated aqueous solution of NH_4Cl (1 mL) at −78 °C, followed by warming up to room temperature naturally and the addition of water (5 mL). After extraction with diethyl ether (30×3 mL), the organic layer was washed sequentially with diluted HCl (5%, aqueous), a saturated aqueous solution of $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 100/1) afforded the desired product *Z*-**5a** as a liquid;[7] yield: 86.2 mg (88%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 4H), 7.24–7.15 (m, 1H), 6.49 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.70 (t, J = 7.7 Hz, 1H), 1.84 (s, 3H), 1.80–1.65 (m, 1H), 1.65–1.25 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.23–1.01 (m, 2H), 0.76 (t, J = 7.4 Hz, 3H).

Ethyl 2-Acetyl-2,3-dimethyl-4-phenyl-3(*Z*)-butenoate (*Z*-9a); Typical Procedure for the Synthesis of Compounds *Z*-9

To a dried Schlenk tube were added $FeCl_3 \cdot 6H_2O$ (2.6 mg, 2.4 mol%, 0.010 mmol), **3e** (81.8 mg, 0.4 mmol), and toluene (5 mL) sequentially under a nitrogen atmosphere at room temperature. Then a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv.) was added with a syringe to the reaction mixture within 3 min at −78 °C. After the reaction was over as monitored by TLC, acetyl chloride (0.14 mL, d = 1.104 g mL^{-1}, 154.6 mg, 2 mmol, 5 equiv.) was slowly added dropwise at −78 °C. After the reaction was over (1.5 h) as monitored by TLC, the reaction mixture was quenched slowly with a saturated aqueous solution of NH_4Cl (1 mL) at −78 °C, followed by warming up to room temperature naturally. After extraction with diethyl ether (30×3 mL), the organic layer was washed sequentially with diluted HCl (5%, aqueous), a saturated aqueous solution of $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 100/1 ~ 20/1) afforded *Z*-**9a** as a liquid;[10] yield: 68.7 mg (65%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.08 (m, 5H), 6.65 (s, 1H), 3.90–3.68 (m, 2H), 2.04 (s, 3H), 1.91 (s, 3H), 1.50 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H).

Ethyl 2-Acetyl-2,3-dimethyl-4-phenyl-3(*E*)-butenoate (*E*-9a); Typical Procedure for the Synthesis of Compounds *E*-9

To a dried Schlenk tube were added $FeCl_3 \cdot 6H_2O$ (2.2 mg, 2 mol%, 0.008 mmol), **3e** (80.9 mg, 0.4 mmol), and toluene (5 mL) sequentially under a nitrogen atmosphere at room temperature. Then a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv.) was added with a syringe to the reaction mixture within 3 min at −78 °C. After the reaction was over as monitored by TLC, allyl acetate (0.22 mL, d = 0.928 g mL^{-1}, 204.2 mg, 2 mmol, 5 equiv.) was slowly added dropwise at −78 °C followed by warming up to room temperature naturally. After the reaction was over as monitored by TLC, the reaction mixture was quenched with a saturated solution of NH_4Cl (1 mL) at 0 °C, followed by warming up to room temperature naturally. After extraction with diethyl ether (30×3 mL), the organic layer was washed sequentially with diluted HCl (5%, aqueous), a saturated aqueous solution of $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 100/1 ~ 20/1) afforded *E*-**9a** as a liquid;[10] yield: 51.8 mg (50%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 3H), 6.41 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.30 (s, 3H), 1.88 (d, J = 1.2 Hz, 3H), 1.61 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

Ethyl 2-Allyl-2,3-dimethyl-4-phenyl-3(*Z*)-butenoate (*Z*-10a); Typical Procedure for the Synthesis of Compounds *Z*-10

To a dried Schlenk tube were added $FeCl_3 \cdot 6H_2O$ (1.9 mg, 1.8 mol%, 0.008 mmol), **3e** (81.8 mg, 0.4 mmol), and toluene (5 mL) sequentially under a nitrogen atmosphere at room temperature. Then a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv.) was added with a syringe to the reaction mixture within 3 min at −78 °C. After the reaction was over (3 h) as monitored by TLC, to the resulting reaction mixture were added sequentially $Pd(PPh_3)_4$ (22.4 mg, 0.02 mmol, 5 mol%) and allyl acetate (0.22 mL, d = 0.928 g mL^{-1}, 204.2 mg, 2 mmol, 5 equiv., dropwise) at −78 °C, followed by warming up to room temperature naturally. After the reaction was over as monitored by TLC, it was quenched with a saturated aqueous solution of NH_4Cl (1 mL) at 0 °C, followed by warming up to room temperature naturally. After extraction with diethyl ether (30×3 mL), the organic layer was washed sequentially with diluted HCl (5%, aqueous), a saturated aqueous solution of $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/CH_2Cl_2 = 8/1 ~ petroleum ether/ethyl acetate = 100/1) afforded *Z*-**10a** as a liquid;[10] yield: 79.1 mg (76%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.22 (m, 2H), 7.21–7.14 (m, 1H), 7.13–7.08 (m, 2H), 6.49 (s, 1H), 5.77–5.61 (m, 1H), 5.07–4.97 (m, 2H), 3.61 (dq, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 1H), 3.50 (dq, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 1H), 2.52–2.35 (m, 2H), 1.92 (d, J = 1.8 Hz, 3H), 1.28 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H).

Ethyl 2-Allyl-2,3-dimethyl-4-phenyl-3(*E*)-butenoate (*E*-10a); Typical Procedure for the Synthesis of Compounds *E*-10

To a dried Schlenk tube were added $FeCl_3 \cdot 6H_2O$ (2.1 mg, 1.9 mol%, 0.008 mmol), **3e** (80.2 mg, 0.4 mmol), and toluene (5 mL) sequentially under a nitrogen atmosphere at room temperature. Then a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv.) was added with a syringe to the reaction mixture within 3 min at −78 °C. After the reaction was over as monitored by TLC, the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h followed by sequential addition of CuI (7.9 mg, 0.04 mmol, 10 mol%) and allyl bromide (0.17 mL, d = 1.390 g mL^{-1}, 236.3 mg, 2 mmol, 5 equiv., dropwise). After the reaction was over as monitored by TLC, it was quenched with a saturated aqueous solution of NH_4Cl (1 mL) at 0 °C, followed by warming up to room temperature naturally. After extraction with diethyl ether (30×

3 mL), the organic layer was washed sequentially with diluted HCl (5%, aqueous), a saturated aqueous solution of $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/CH_2Cl_2 = 8/1) afforded *E*-**10a**[10] (yield: 42.5 mg) as a mixture of *E*-**10a** and ethyl 2,3-dimethyl-4-phenyl-3(*Z*)-butenoate *Z*-**5e** in a molar ratio by NMR of 94/6, content of *E*-**10a**: 95% by weight and a mixture of *E*-**10a**, *Z*-**5e** and *E*-**5e**, molar ratio by NMR: 86/6/8 (yield: 0.0141 g), content of *E*-**10a**: 88% by weight; combined yield: 52% as a liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 2H), 7.27–7.17 (m, 3H), 6.40 (s, 1H), 5.79–5.63 (m, 1H), 5.15–5.04 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 2.67–2.52 (m, 2H), 1.80 (d, J = 1.2 Hz, 3H), 1.37 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H).

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