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Controllable Highly Stereoselective Reaction of *in situ* Generated Magnesium Dienolate Intermediates with Different Electrophiles

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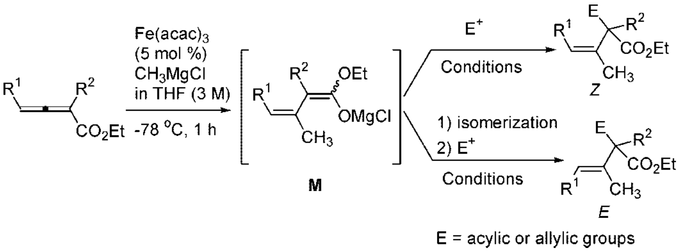
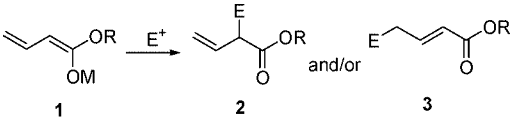
ABSTRACT



In this paper, we have described an efficient controllable stereoselective α-acylation and -allylation reaction of the magnesium dienolate intermediates generated *in situ* from the Fe(III)-catalyzed reaction between 2,3-allenoates and Grignard reagents with different electrophiles to afford 2-acylated or allylated 3(*Z*)- or (*E*)-alkenoates depending on the nature of the electrophiles and reaction conditions. The distinct stereoselectivity may be caused by the isomerization of metallic *Z*-1,3-dienoate to *E*-1,3-dienoate via the intermediacy of *anti*-allylic MgCl and *syn*-metallic species.

1,3-Dienolates **1** are useful intermediates in organic synthesis, in which both the α- and γ-position may react with electrophiles to afford the corresponding β,γ- or α,β-unsaturated products **2** or **3** (Scheme 1).[1–3] It has been reported that the reaction of 2-lithiated 3(*Z*)- or (*E*)-alkenoates with water,[4a] alkyl iodide,[4a,b] or aldehyde[4b] afforded the α-protonated, alkylated, or aldolated 3(*Z*) or (*E*)-alkenoate with moderate to high stereoselectivity. However, to the best of our knowledge, there is no report on stereocontrollable reaction of the same metal dienolate with different electrophiles to afford β,γ-unsaturated (*E*)- or (*Z*)-alkenoates in high regio- and stereoselectivity, respectively. On the other hand, recently an iron-catalyzed conjugate addition reaction of 2,3-allenoates with Grignard reagents affording 3(*Z*)-alkenoates

Scheme 1. Reaction of 1,3-Dienolates



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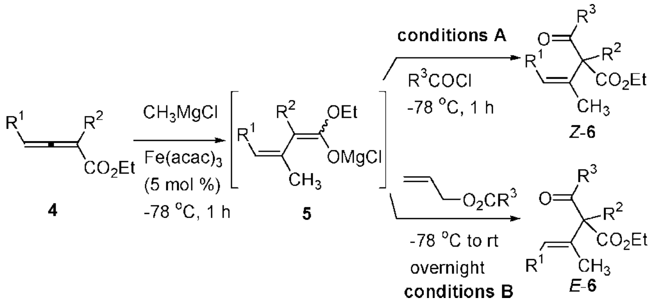
(1) (a) Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1. (b) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (c) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440.

(2) For some recent typical examples of reactions of dienolate at α-position, see: (a) Reutrakul, V.; Jaratjaroonphong, J.; Tuchinda, P.; Kuhakarn, C.; Kongsaeree, P.; Prabpai, S.; Pohmakotr, M. *Tetrahedron Lett.* **2006**, *47*, 4753. (b) Davis, F. A.; Qi, H.; Sundarababu, G. *Tetrahedron* **2000**, *56*, 5303. (c) Bazán-Tejeda, B.; Bluet, G.; Broustal, G.; Campagne, J.-M. *Chem.−Eur. J.* **2006**, *12*, 8358. (d) Alexander, P. A.; Marsden, S. P.; Subtil, D. M. M.; Reader, J. C. *Org. Lett.* **2005**, *7*, 5433. (e) Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603. (f) Otaka, A.; Yukimasa, A.; Watanabe, J.; Sasaki, Y.; Oishi, S.; Tamamura, H.; Fujii, N. *Chem. Commun.* **2003**, 1834.

10.1021/ol8012815 CCC: $40.75

Table 1. Reaction of *in situ* Generated Dienolate **5** with Acyl Chlorides or Allyl Carboxylic Esters[a]



entry	R¹	R²	R³	conditions A yield of Z-**6** (%)[b]	 ratio (Z/E)[c]	conditions B yield of E-**6** (%)[b]	 ratio (E/Z)[c]
1	Ph	Me (**4a**)	Me	68 (*Z*-**6a**)	>99/1	50 (*E*-**6a**)	95/5
2	Ph	Me (**4a**)	Bn	87 (*Z*-**6b**)	>99/1	47 (*E*-**6b**)	>98/2
3	Ph	Me (**4a**)	Ph	70 (*Z*-**6c**)	>99/1	57 (*E*-**6c**)	>98/2
4	Ph	*n*-Pr (**4b**)	Me	69 (*Z*-**6d**)	>99/1	50 (*E*-**6d**)	>98/2
5	p-FC_6H_4	Me (**4c**)	Me	76 (*Z*-**6e**)	>99/1	69 (*E*-**6e**)	98/2
6	p-ClC_6H_4	Me (**4d**)	Me	84 (*Z*-**6f**)	>99/1	50 (*E*-**6f**)	98/2
7	p-BrC_6H_4	Me (**4e**)	Me	87 (*Z*-**6g**)	>99/1	62 (*E*-**6g**)	97/3

[a] Conditions A: acyl chloride (2 mmol) was added to the solution of *in situ* generated magnesium dienolate (0.4 mmol) at −78 °C. Conditions B: allyl carboxylic acid ester (2 mmol) was added to the solution of *in situ* generated magnesium dienolate (0.4 mmol) at −78 °C followed by warming up to rt naturally. [b] Isolated yield. [c] Tatio was determined by ^1H NMR analysis of the crude products.

with very high regio- and stereoselectivity has been reported by this group.[5] In this paper, we wish to report our recent observation that the magnesium 1,3(*Z*)-dienolate intermediates *in situ* generated in this reaction may react with different electrophiles to afford α-allylated or acylated 3(*Z*)- or (*E*)-alkenoates highly stereoselectively under different reaction conditions.

As originally noted,[5] the reaction of the *in situ* generated magnesium dienolate intermediate **5a** with acyl chloride at −78 °C afforded α-acylated alk-3(*Z*)-enoate *Z*-**6a** in 61% yield (Conditions A). The configuration of the carbon−carbon double bond was determined by NOE analysis (Figure 1).

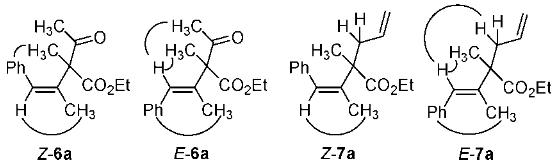


Figure 1. NOE Study of the *Z*- and *E*-Isomers of **6a** and **7a**.

Further screening led us to observe that the reaction of the *in situ* generated magnesium dienolate **5a** with allyl acetate afforded α-acylated alk-3(*E*)-enoate *E*-**6a** in 50% yield with a reversal stereoselectivity (E/Z = 95/5),[6] which was also established by NOE analysis (Figure 1) (Conditions B, entry 1, Table 1). Some such examples are shown in Table 1. It can be noted that R¹ may be aryl, R² may be alkyl, and R³ may be alkyl, benzyl, or phenyl. In conclusion, under Conditions A, the reaction with acyl chloride provided the *Z*-**6** in 68−87% yields with *Z/E* ratio >99/1 while the corresponding opposite stereoisomers *E*-**6** may be formed under the Conditions B with *E/Z* ratio of ≥95/5.

Furthermore, we are quite happy to observe that under the catalysis of $Pd(PPh_3)_4$, instead of forming the α- acylated 3(*E*)-alkenoate **6**, the reaction of magnesium dienolate **5a** with allylic acetate afforded the α-allylated alk-3(*Z*)-enoate *Z*-**7a** in 67% yield with high stereoselectivity (Z/E = 96/4), which was established by NOE study of *Z*-**7a** (Figure 1) (Conditions C, entry 1, Table 2). The structure of the products *Z*-**7** was further established by the X-ray diffraction study of *Z*-**7h**[7] (Figure 2). Obviously, the oxidative addition reaction of $Pd(PPh_3)_4$ with allyl acetate forms a π-allyl palladium species, which reacted with the magnesium dienolate to provide the corresponding α-allylated products.[8] The reaction of the magnesium dienolates with 2- or

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(3) For some recent typical examples of reactions of dienolate at γ-position, see: (a) Denmark, S. E.; Heemstra, J. R., Jr. *J. Org. Chem.* **2007**, *72*, 5668. (b) Denmark, S. E.; Xie, M. *J. Org. Chem.* **2007**, *72*, 7050. (c) Denmark, S. E.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 1038. (d) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800. (e) Saito, S.; Nagahara, T.; Shiozawa, M.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6200. (f) Denmark, S. E.; Heemstra, J. R., Jr. *Synlett* **2004**, 2411.

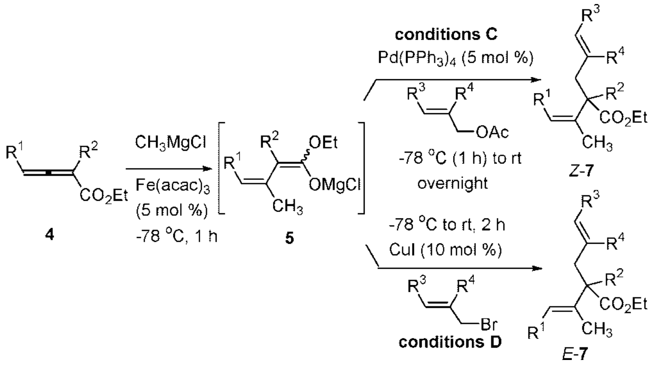
(4) (a) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163. (b) He, Y.; Yang, H.; Yao, Z. *Tetrahedron* **2002**, *58*, 8805.

(5) Lu, Z.; Chai, G.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 14546.

(6) Solomons, T. W. G.; Fryhle, C. B. *Organic Chemistry*, 7th ed.; John Wiley & Sons: New York, 2000; pp 880−883.

(7) Crystal data for compound *Z*-**7h**: $C_{23}H_{26}O_2$, Mw 334.46, triclinic, $P\bar{1}$, Mo Kα, final R indices [$I > 2\sigma(I)$], $R1 = 0.0812$, $wR2 = 0.2081$, a = 8.2770 (6) Å, b = 8.6143 (7) Å, c = 14.1523 (13) Å, α = 103.444 (2)°, β = 91.662 (2)°, γ = 95.1097 (19)°, V = 976.23 (14), Z = 2, number of reflections measured/unique 4336/1886 (R_{int} = 0.028) number of observations 4336 [$I > 2\sigma(I)$], parameter 227, CCDC 676332.

Table 2. Transition Metal-Catalyzed Allylation Reactions of *in situ* Generated Dienolates **5** with Different Allylic Reagents[a]



					conditions C		conditions D	
entry	R^1	R^2	R^3	R^4	yield of *Z*-**7** (%)^b	ratio (*Z*/*E*)^c	yield of *E*-**7** (%)^b	ratio (*E*/*Z*)^c
1	Ph	Me (**4a**)	H	H	67 (*Z*-**7a**)	96/4	51 (*E*-**7a**)	96/4
2	*p*-FC$_6$H$_4$	Me (**4c**)	H	H	74 (*Z*-**7b**)	94/6	72 (*E*-**7b**)	97/3
3	*p*-ClC$_6$H$_4$	Me (**4d**)	H	H	66 (*Z*-**7c**)	96/4	71 (*E*-**7c**)	97/3
4	*p*-BrC$_6$H$_4$	Me (**4e**)	H	H	80 (*Z*-**7d**)	93/7	65 (*E*-**7d**)	97/3
5	*p*-MeOC$_6$H$_4$	Me(**4f**)	H	H	72 (*Z*-**7e**)	98/2	53 (*E*-**7e**)	97/3
6	Ph	Me (**4a**)	H	Ph	61 (*Z*-**7f**)	89/11	58 (*E*-**7f**)	>99/1
7	Ph	*n*-Pr (**4b**)	H	Ph	58 (*Z*-**7g**)	91/9	39 (*E*-**7g**)	>99/1
8	Ph	Me (**4a**)	Ph	H	77 (*Z*-**7h**)	94/6	39 (*E*-**7h**)	–^{d}

[a] Conditions C: Pd(PPh$_3$)$_4$ (5 mol %) and allylic acetate (5 equiv) were added to the solution of *in situ* generated magnesium dienolate (0.4 mmol) at −78 °C for 1 h followed by warming up to rt naturally. Conditions D: CuI (10 mol %) and allylic bromide (5 equiv) were added to the solution of *in situ* generated magnesium dienolate (0.4 mmol) at rt. [b] Isolated yield. [c] Ratio was determined by ^{1}H NMR analysis of the crude products. [d] Other isomer was not isolated.

3-substituted allylic acetate under the catalysis of Pd(PPh$_3$)$_4$ all afforded the α-allylated *Z*-products *Z*-**7** in 58−77% yields with an *Z/E* ratio of 89/11~94/6 (Conditions C, entries 6−8, Table 2). Quite surprisingly, under the catalysis of CuI, the related reaction with allyl bromide afforded the opposite stereoisomer *E*-**7a** in 51% yield (*E/Z* = 96/4), which was confirmed by NOE study (Figure 1)(Conditions D, entry 1, Table 2).[9] Based on the results shown in Table 2, it should also be noted that the reversed *E*-stereoselectivity (Conditions D) is higher than the original *Z*-stereoselectivity (Conditions C). Not only simple allyl bromide but also 2- or 3-substituted allylic bromides react with the magnesium dienolates **5** under the catalysis of CuI to afford the corresponding stereoreversed α-allylated *E*-products with high selectivity (Conditions D, entries 6−8, Table 2).

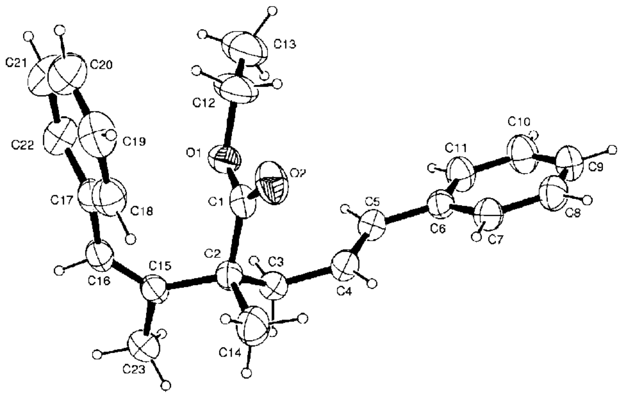


Figure 2. ORTEP structure of *Z*-**7h**.

It has been reported that the *syn*-allylic metallic species is thermodynamically more stable as compared to the *anti*-allylic metallic species due to the steric interaction of the metal and the substituent(s) at the 1- and/or 3-positions,[10] thus, we reasoned that due to the presence of the carbon−carbon double bond, the *in situ* formed 1,3(*Z*)-dienoate[5] is prone to isomerize to the thermodynamically more stable 1,3(*E*)-dienoate via the intermediacy of *anti*-allylic MgCl and *syn*-allylic metallic species (Scheme 2).

When allylic acetate or allylic bromide with CuI was added as the electrophile at −78 °C, the carbon−carbon double bond[11] and/or the carbonyl oxygen may act as the coordination ligand to the metal, which increases the steric interaction between the coordinated metal and the substituent R^1 leading

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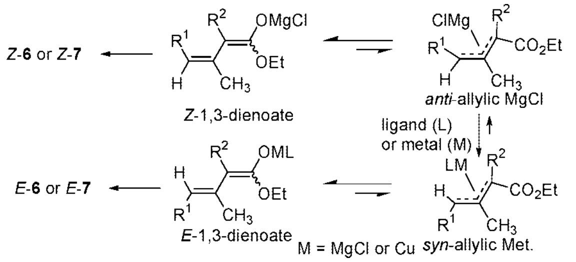
(8) (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (d) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (e) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(9) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698.

(10) For a review in this area, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. For some typical reports, see: (b) Akermark, B.; Hansson, S.; Vitagliano, A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4587. (c) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723.

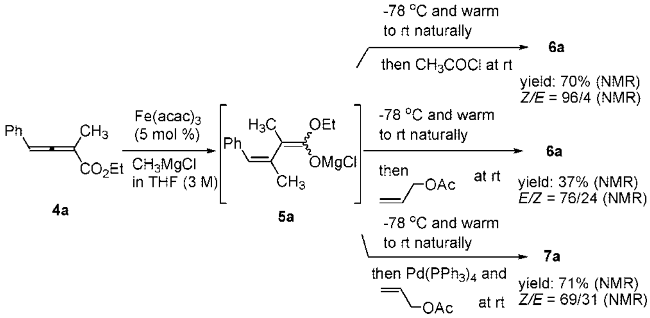
Scheme 2. Rationale for Observed Stereoselectivity



to the complete conversion of 1,3-(*Z*)-dienoate to 1,3(*E*)-dienoate. Subsequent reaction with the allylic carboxylate or allylic bromide leads to the formation of *E*-**6** and *E*-**7**. Of course, in the latter case the isomerization may also be promoted by the presence of Cu, which is more sterically demanding due to its relatively bigger radius.[12] The reaction with acyl chloride or allylic acetate under the catalysis of Pd is believed to be very fast, occurring before the *Z* to *E*-isomerization at lower reaction temperature, which was further confirmed by the fact that addition of acyl chloride or 5 mol% $Pd(PPh_3)_4$ and allylic acetate at rt led to the formation of an *E*/*Z* mixture (Scheme 3).

In summary, we have observed an efficient controllable stereoselective α-acylation or -allylation reaction of the *in situ* generated magnesium dienolate intermediate from the Fe-catalyzed conjugate addition of 4-aryl-2,3-allenoates and

Scheme 3. Mechanistic Study



Grignard reagents with acyl chloride, allyl carboxylic acid esters, allylic acetate catalyzed by $Pd(PPh_3)_4$, or allylic bromide catalyzed by CuI to afford alk-3(*Z* or *E*)-enoates highly stereoselectively. Further studies including the scope, synthetic application, and the mechanism for such an isomerization are being conducted in our laboratory.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For most recent reports on using optically active olefin as ligand in Rh- or Ir-catalyzed reactions, see: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fischer, C.; Sefieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (c) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336.

(12) The radius of Mg^{2+} is 0.65 Å and the radius of Cu^+ is 0.96 Å.