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ARTICLE

Mg(OMe)2 Promoted Allylic Isomerization of γ-Hydroxy-α,β-Alkenoic Esters to The Synthesis of γ-Ketone Esters

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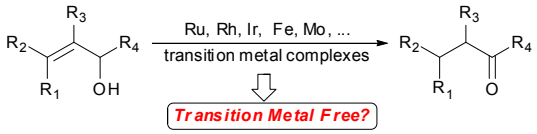
This work concerns the Mg (OMe)2 promoted allylic isomerization of γ-hydroxy-α, β-alkenoic esters with TMEDA as an additive. The isomerization proceeded under mild condition and afforded in high yield of γ-keto esters (up to 96%) within 2h. Both (Z)- and (E)-γ-hydroxy-α,β-alkenoic ester were tolerated under the reaction conditions. This transformation involves an in-situ formation of dienolate intermediate from easily accessible γ-hydroxy-α,β-alkenoic ester. The in-situ generated dienolate can reacted with benzaldehyde and provide a practical useful tandem allylic isomerization-Aldol reaction to more functionalized compounds.

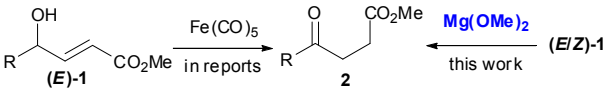
Introduction

Isomerization of allylic alcohol to the corresponding ketones or aldehydes represents an attractive one-step transformation in organic synthesis. [1] This atom-economic process [2] has received chemists' great attentions due to the multistep reduction-oxidation procedures as well as production of wastes could be avoided. During the past decades, people have made great efforts to develop various catalysts from over ten transition metals (Scheme 1). [3] These transition metal complexes are generally costly and/ or highly toxic. In the other hand, harsh conditions with strong acid, alkali and/or high temperature have always been conducted. Although less substituted allylic alcohols can more easily undergo the isomerization, substrate capability is still a challenging issue which needs to be overcome. [1c] Due to the strong dependence upon the substituent of allylic alcohol, electro-rich as well as less hindered allylic alcohols are favored substrates in most cases. On the contrary, allylic alcohols containing electron-withdrawing groups on the C=C double bond are not capable. [4] The residue of transition metal (especially heavy metal) is one of the most serious problems of drug safety, developing transition metal free strategy in drug synthesis tends to be one of the greatest challenges for chemists. However, only very limited transition metal free protocols for the allylic isomerization has been reported.[5] γ-keto esters are also important building blocks and versatile synthetic intermediates in the synthesis of natural products and drug leads. [6] However, unlike in the field of α/β-keto esters synthesis, few facile methodologies have been reported for γ-keto esters synthesis. [7]



Scheme 1. Overview of allylic alcohol isomerization.

Allylic isomerization of γ-hydroxy-α, β-alkenoic esters is one simple strategy for easily obtaining their corresponding γ-keto esters (Scheme 2). Unfortunately, electro deficient allylic alcohols, such as γ-hydroxy-α, β-alkenoic esters, were not suitable substrates for most of the developed transition metal catalytic systems. So far, only highly toxic $Fe(CO)_5$ was reported to promote the allylic isomerization of (*E*)-γ-hydroxy-α,β-alkenoic esters but with very limited examples. [3g, 4b] Most importantly, because the toxic $Fe(CO)_5$ is a volatile reagent, the operation MUST be particularly careful with strict safety precautions. Thereby, highly stable and safely operated catalytic systems are urgently in demand. The allylic isomerization of more hindered but more easily accessible (*Z*)-γ-hydroxy-α, β-alkenoic esters is a rather challenging issue for transition metal catalysts. In addition, intramolecular lactonization of (*Z*)-γ-hydroxy-α, β-alkenoic esters to γ-butyrolactone could readily take place either in a relative basic or acidic condition. To the best of our knowledge, methodologies for the isomerization of (*Z*)-γ-hydroxy-α, β-alkenoic esters to γ-keto esters has rarely been reported. Thus, new practical protocols need be eagerly developed to deal with the intense demands of all these challenging issues.



Scheme 2. One-pot Synthesis of γ-keto esters *via* allylic alcohol isomerization.

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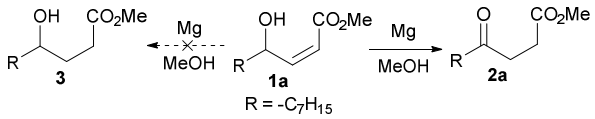
Although alkaline earth metal catalysis has received more and more attentions recently, [8] the applications of these catalysts are mainly focusing on the 1, 3-dicarbonyl compound addition [9] and activated esters-Aldol type reaction. [10] Catalytic applications of alkaline earth metals especially for magnesium to other novel transformations have been much less disclosed. [11] Herein we report a facile $Mg(OMe)_2$ promoted allylic isomerization to afford γ-keto esters involving an in-situ dienolate intermediate.

Results and discussion

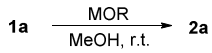
To expand the enantioselective synthesis of highly functionalized chiral γ-hydroxy-α, β-acetylenic esters to synthetic chemistry, [12] we intended to reduce **1a** with Mg/MeOH, which could be used for the conjugated reduction of γ-alkyl/aryl-α, β- alkenoic esters. [13] To our surprise, an isomerized product (**2a**) was afforded instead of a reduced product (**3**) (Scheme 3). Subsequent studies indicated that this process was essentially promoted by $Mg(OMe)_2$. [14] Other magnesium alkoxides were also examined in the model reaction but displayed much poorer catalytic activity. Then a series of reaction influences involving various alkali alkoxides, additives, as well as solvents has been well studied.



Scheme 3. Discovery of the present allylic isomerization.

Although similar transformation was carried out while using strong alkali KOH, [15] the corresponding γ-keto acid was afforded. Other alkali alkoxides showed poorer catalytic activity for this model transformation. The γ-keto ester **2a** was obtained in rather lower yields of 41.4% and 43% while using CH_3ONa and *t*-BuOK, respectively (entry 1-2, Table 1). A relatively higher yield (66.6%) was obtained when $Mg(OMe)_2$ was introduced into the reaction mixture (entry 3, Table 1). While using $Mg(Ot\text{-}Bu)_2$ in the model reaction, however, no **2a** was found. Complex byproducts was also observed via crude ^1H NMR.

Table 1. Preliminary studies of the model reaction.[a]

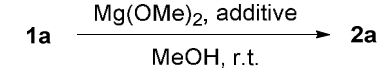


Entry	**1a** (mmol)	MOR	equivalent	Isolated yield (%)
1	0.1	CH_3ONa	0.8	41.4 [b]
2	0.1	t-BuOK	0.8	43 [b]
3	0.1	$Mg(OMe)_2$	0.8	66.6
4	0.1	$Mg(Ot\text{-}Bu)_2$	0.6	N. D.[b][c]

[a] Method A. [b] Complex byproducts were observed.[c] No **2a** was found.

Loadings of $Mg(OMe)_2$ and different kind of additives were examined to improve the isomerization of **1a** (Table 2). The isomerization was not completed in very long time (over 24h) while using low loadings of $Mg(OMe)_2$ (entry 1-2). It was interesting to find that 67 mol% of $Mg(OMe)_2$ afforded the corresponding γ-keto ester **2a** with the highest yield of 74.8% without using any additive (entry 7). Either increasing or decreasing the amount of $Mg(OMe)_2$ caused lower yield (entry 1-6 and 8-9). The isomerization yield was not improved but with longer reaction time while using DME or TEA as an additive (entry 10-11). When TMEDA was introduced into the reaction mixture as the bidentate ligand, it was found that the yield of the isomerization was well improved. Isolated yields varied from 86% to 91% via changing the loadings of TMEDA between 10-100 mol% (entry 12-17). A 91% yield of **2o** was obtained while using 67 mol% of $Mg(OMe)_2$ in combination with 50 mol% of TMEDA (entry 15).

Table 2. Optimization of reaction conditions.[a]



Entry	Mg(OMe)2 (mol %)[b]	Additive (mol %)[c]	Isolated yield (%)
1	10 %	None	40.7 %
2	20 %	...	47.2 %
3	40 %	...	51.5 %
4	60 %	...	56.6 %
5	63 %	...	63.9 %
6	65 %	...	73.6 %
7	67 %	...	74.8 %
8	70 %	...	63.1 %
9	80 %	...	66.6 %
10	67 %	DME (50 %)	73.0 %
11	...	TEA (50 %)	75.4 %
12	...	TMEDA (10 %)	86.0 %
13	...	TMEDA (20 %)	84.1 %
14	...	TMEDA (30 %)	85.5 %
15	...	TMEDA (50 %)	91 %
16	...	TMEDA (80 %)	87.9 %
17	...	TMEDA (100 %)	87.9 %

[a] Method B: 0.1mol of **1a** was used. [b] $Mg(OMe)_2$ was used as *in-situ* prepared in MeOH solution (0.033 M) and without additional MeOH. [c] The additives were freshly distilled before use.

To our delight, $Mg(OMe)_2$ (67mol%) in combination of TMEDA (50 mol%) can readily promote the isomerization of γ-hydroxy-α,β-alkenoic esters in a wide range (Table 3). Different γ-substituted **1** involving with aryl, alkenyl as well as alkyl substitutes was tolerated. The corresponding γ-keto esters (**2**) were afforded favourably with high to excellent yields under room temperature within 2h. With γ-aryl substitutes, (*Z*)-γ-keto esters **2b-e** (entry 1-4) and **2g-h** (entry 6-7) were obtained with 84%-96% yields. Lower yields of 79% and 75% were observed while using **2f** and **2i** with large steric ortho-subtitutes, respectively (entry 5 and 8). Hetero-aromatic substituted **2j** and γ-styryl **2k** were also favourably obtained with excellent yields (95% and 92%) (entry 9-10). The isomerization of alkyl substituted **1l-n** proceeded well and gave moderate to high yields (66-80%) of the corresponding γ-keto esters **2** (entry 11-13). It is noteworthy that **2o** could also be generated from (*E*)-**1o** with 67% yield, but much longer time (48h) was required (entry 15).

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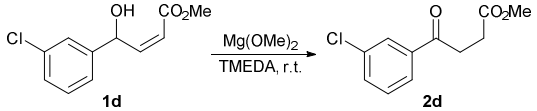
Table 3. Allylic isomerization **1** to γ-Keto Esters. [a]

Entry	Substrate	γ-Keto Esters	Yield (%) [b]
1	(*Z*)-**1b**	**2b**	88%
2	(*Z*)-**1c**	**2c**	92%
3	(*Z*)-**1d**	**2d**	84%
4	(*Z*)-**1e**	**2e**	94%
5	(*Z*)-**1f**	**2f**	79%
6	(*Z*)-**1g**	**2g**	94%
7	(*Z*)-**1h**	**2h**	96%
8	(*Z*)-**1i**	**2i**	75%
9	(*Z*)-**1j**	**2j**	92%
10	(*Z*)-**1k**	**2k**	95%
11	(*Z*)-**1l**	**2l**	80%
12	(*Z*)-**1m**	**2m**	78%
13	(*Z*)-**1n**	**2n**	66%
14	(*Z*)-**1o**	**2o**	91%
15[c]	(*E*)-**1o**	**2o**	67%

[a] All cases precedded in 0.1 mmol scale for 2h in 2 mL of MeOH, **1**:TMEDA:$Mg(OMe)_2$ = 1:0.67:0.5. [b] Isolated yields. [c] Reacted for 48h.

Exploring the isomerization of **1d** to **2d** as a model reaction, solvent influence was subsequently studied (Table 4). It was found that the solvent played an important role: the reaction proceeded favourably in MeOH and gave 83% of **2d** within 2h (entry 1). Although similar yield of 81% was obtained while using toluene as the solvent (entry 2), much longer reaction time (24h) was necessary for the completion of this process. Complex byproducts were observed after stirring for long time in CH_2Cl_2 (entry 3). Other non-protic solvents were far more unsuitable for this reaction due to the poorer solubility of $Mg(OMe)_2$ (entry 4-5). The isomerization of **1d** was not completed even after 24h neither in THF nor in Et_2O.

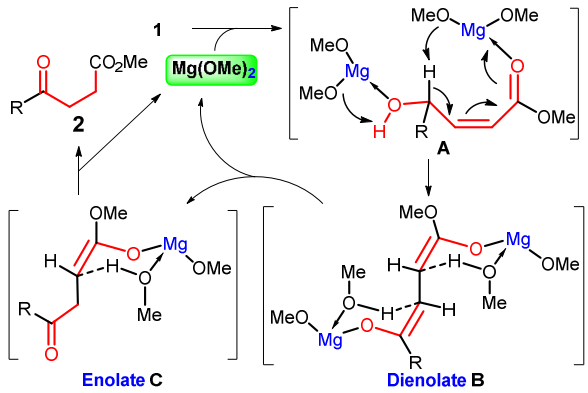
Table 4. Solvent effect for the allylic isomerization.[a]



1d **2d**

Entry	Solvent [b]	Time	Isolated yield (%)
1	MeOH	2h	84
2	Toluene	8h	81
3	CH_2Cl_2	24h	47
4 [c]	THF	24h	48
5 [c]	Et_2O	24h	44

[a] Method C: **1d** : $Mg(OMe)_2$ (solid) : TMEDA = 1: 0.67 : 0.5. [b] All of the reaction was performed in 2 mL of the corresponding solvent. [c] The reaction was not completed detected by TLC.



Scheme 4. Proposed mechanism.

In general, two classes of mechanisms, the metal hydride addition-elimination pathway and the π-allyl intermediate pathway were widely recognized to explain the transition metal catalyzed allylic isomerization.[16] However, the proposed dienolate[17] pathway mechanism is more preferred to illustrate this work (Scheme 4). Firstly, dienolate **B** was generated via deprotonating complex **A** in combination of **1** with $Mg(OMe)_2$. According to the poorer stability of the dienolate compared with ester enolate, a fast semi-protonation step was followed by. Meanwhile, one molecular $Mg(OMe)_2$ was generated along with the formation of enolate **C**. Then, γ-keto ester **2** as well as another molecular $Mg(OMe)_2$ were then afforded during the second protonation step. For the isomerisation of (*E*)-**1**, intermediate **A** was hardly afforded according to the *trans*-geometry of the C=C bond. Thus, the formation of dienolate **B** may undergo an intermolecular deprotonation pathway, and this

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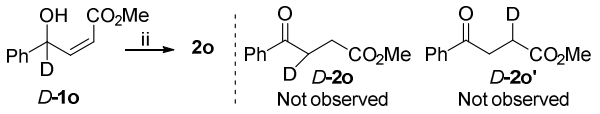
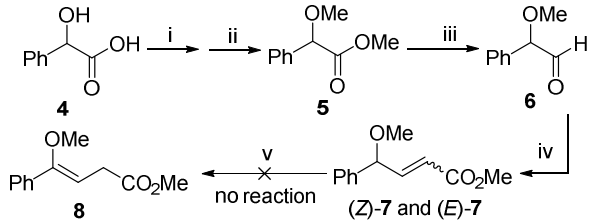
was undoubtedly the critical rate-limiting step as for (*E*)-**1** isomerization. From this point of view, it was no hard to understand why much longer reaction time was required for the isomerization of (*E*)-**1o** compared with (*Z*)-**1o** but with much lower yield (entry 14-15, Table 3). It was suggested that additive chelating with magnesium increased the stability of the intermediates and positively affected the reaction yield.

To further understand the mechanism, the deuteration experiment [5d] was carried out as shown in Scheme 5. Following the similar procedure, deuterated **1o** (*D*-**1o**) was readily obtained from a deuterated benzaldehyde**.** Under the standard conditions, the isomerization of *D*-**1o** proceeded smoothly and only afforded the γ-ketone ester **2o**. However, neither *D*-**2o** nor *D*-**2o'** was observed as the deuterated product. The result indicated the 1, 2-hydride shift mechanism was excluded in the present isomerization.



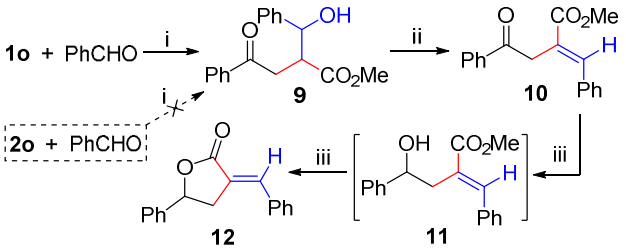
Scheme 5. Isomerization of γ-methoxy-α, β-alkenoic esters. i: Lindlar Pd, H_2, Et_2O. ii: $Mg(OMe)_2$ (67mol%), TMEDA (50mol%), MeOH.

To trap the enolate intermediate, two isomers of γ-methoxy-α, β-alkenoic ester **7** were synthesized using mandelic acid **4** as the starting material. Unfortunately, neither (*Z*)-**7** nor (*E*)-**7** did not afford the desired isomerized product **8** even after 48h under standard conditions (Scheme 6). In one hand, it was difficult to deprotonate the γ-CH of (*Z*/*E*)-**7** to form the dienolate intermediate due to the steric hindrance of the γ-methoxy group. In another point of view, it was supposed that the ketone-enolate protonation step might be blocked by the methylated γ-hydroxy group (**8**) for the isomerization of compound **7**. In other words, it was that the ketone-enolate protonation of dienolate **B** to afford enolate **C** definitively facilitate this isomerization. Thus, the subsequent experiment was carried out to conform whether the dienolate or ester enolate intermediate can be captured by an electrophile. If so, it would be of great significance for the application of this protocol.



Scheme 6. Isomerization of γ-methoxy-α, β-alkenoic esters. i: $SOCl_2$, MeOH, quantitative. ii: NaH, CH_3I, 51%. iii: DIBAL. iv: $Ph_3PCH_2CO_2CH_3$, 58% and 29% yields of (*Z*)-**7** and (*E*)-**7** for two steps, respectively. v: $Mg(OMe)_2$ (67mol%), TMEDA (50mol%), MeOH, 48h.

As we expected, a tandem allylic isomerization-Aldol [3g, 18] reaction was carried out while benzaldehyde was introduced as the electrophile under standard conditions (Scheme 7). When the reaction was performed on a 2 mmol scale, unlike the transition metal catalyzed allylic isomerization, a Reformatsky-like adduct **9** was obtained with a high yield of 89% instead of a ketone-Aldol adduct. [19] While combining γ-ketone ester **2o** with benezaldehyde under standard isomerization condication however, compound **9** was not afforded, but only with **2o** and benezaldehyde being remained. Although the relative stereochemistry of compound **9** and the diastereoselectivity of this tandem allylic isomerization-Aldol reaction were not well studied, it was noteworthy that only (*E*)-**10** was isolated via dehydrating compound **9** using TFA. [20] Converting (*E*)-**10** to (*E*)-**12** was readily carried out in one-pot with an overall yield of 70%.‡ Thus, the above proposed mechanism was reliably confirmed via the formation of Reformatsky-like adduct **9**. Additionally, this approach can be applied to the synthesis of α-alkenyl-γ-butyrolactone which is a significant class of natural product. [21]



Scheme 7. Tandem allylic isomerization-Aldol reaction for the synthesis of (*E*)-α-alkenyl-γ-butyrolactone. i: **1o**: $Mg(OMe)_2$: TMEDA: PhCHO= 1: 0.67: 0.5: 1, 89%. ii: TFA (30 equ.), CH_2Cl_2, 98%. iii: a) $NaBH_4$ (3 equ.), MeOH, then b) HCl (1M) in one-pot, 70% for the two steps.

Experimental

Method A (Table 1). Alkaline earth metal alkoxides screening in the allylic isomerization of 1a: To a round-bottom flask was added MOR, ROH (2 mL), and γ-hydroxy-α, β-alkenoic esters (0.1 mmol). After stirring at room temperature for 2 h, the resulting solution was concentrated under vacuum, The residue was purified by chromatography on silica gel (PE / EA = 9:1 to 7:1) to afford the compound.

Method B (Table 2 and 3). To a round-bottom flask that was added γ-hydroxy-α, β-alkenoic esters (0.1 mmol), additive and $Mg(OMe)_2$ (0.033M in MeOH and without additional solvent). After stirring the mixture at room temperature for 2 h, the resulting solution was concentrated directly under vacuum, The residue was purified by chromatography on silica gel (PE / EA = 9:1 to 7:1) to afford the compound.

Method C (Table 4). Solvent effect examination for the allylic isomerization of 1d: To a round-bottom flask that was added γ-hydroxy-α, β-alkenoic esters (0.1 mmol), TMEDA (7.5 μl, 0.05 mmol, 50 mol %), $Mg(OMe)_2$ (5.75 mg, 0.067 mmol, 67 %) and solvent. After stirring at room temperature for 2 h (24h while using CH_2Cl_2, THF or Et_2O as solvent), the resulting solution was concentrated directly under vacuum. The residue was then purified by chromatography on silica gel (PE / EA = 9:1 to 7:1) to afford the compound.

Conclusions

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In conclusion, we have developed a $Mg(OMe)_2$ promoted allylic isomerization of γ-hydroxy-α,β-alkenoic esters using TMEDA as an additive. A series of γ-keto esters were readily afforded in high yield (up to 96%) under very mild conditions. In addition, an in-situ dienolate pathway mechanism was proposed and verified by a tandem allylic isomerization-Aldol reaction, which can be applied to the synthesis of α-alkenyl-γ-butyrolactones. Applications and extensions of this protocol are under investigating in our group.

Acknowledgements

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Notes and references

‡ Un-optimized conditions.

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Mg(OMe)2 Promoted Allylic Isomerization of γ-Hydroxy-α,β-Alkenoic Esters to The Synthesis of γ-Ketone Esters

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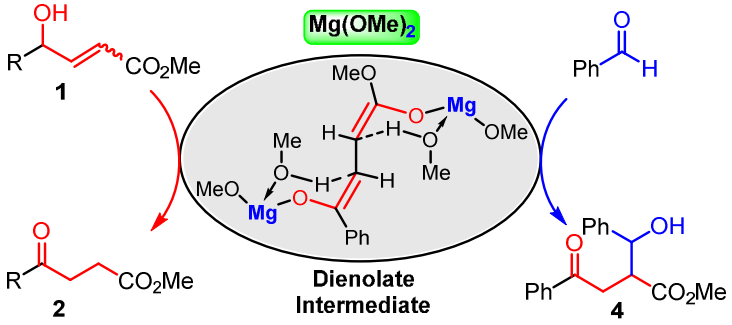

This work concerns the Mg $(OMe)_2$ promoted allylic isomerization of γ-hydroxy-α, β-alkenoic esters with TMEDA as an additive. The isomerization proceeded under mild condition and afforded in high yield of γ-keto esters (up to 96%) within 2h. Both (Z)- and (E)-γ-hydroxy-α,β-alkenoic ester were tolerated under the reaction conditions. This transformation involves an in-situ formation of dienolate intermediate from easily accessible γ-hydroxy-α, β-alkenoic ester. The in-situ generated dienolate can reacted with benzaldehyde and provide a practical useful tandem allylic isomerization-Aldol reaction to more functionalized compounds.