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# One-pot Mukaiyama–Mannich reaction of aldehydes, amines and silyl enol diazoacetate catalyzed by Mgl<sub>2</sub> etherate

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# ABSTRACT

Three-component Mukaiyama–Mannich reaction of aldehydes, amines, and silyl enol diazoacetoacetate was efficiently carried out to afford  $\delta$ -amino substituted- $\alpha$ -diazoacetoacetate derivatives catalyzed by 5 mol% of Mgl<sub>2</sub> etherate (Mgl<sub>2</sub>•(OEt<sub>2</sub>)<sub>n</sub>) under mild and neutral reaction conditions in good to excellent yields.

#### **GRAPHICAL ABSTRACT**



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# KEYWORDS

Three-component; silyl enol diazoacetoacetate; Mukaiyama–Mannich reaction; Mgl<sub>2</sub> etherate

#### Introduction

Diazoacetoacetates are widely used reactants for metal carbene transformations in the synthesis of natural products and compounds of pharmaceutical interest.<sup>[1-3]</sup> Diazoacetoacetates exhibit higher thermal and acid stability than do their diazoacetate counterparts, and they often offer greater reaction control in transformations following diazo decomposition.<sup>[4]</sup> Catalytic reactions of diazoacetoacetate involving addition, insertion and association that produce cyclopropanes, cycloalkanone structures and  $\beta$ -lactams are well documented.<sup>[5–8]</sup> Chemical modifications with diazocarbonyl compounds have been of long-standing interest and both acid or base promoted aldol reactions have been developed for this purpose. However, these reactions generally result in the loss of the diazo functionality.<sup>[9]</sup> Typically, the addition product was obtained by nucleophilic addition of the diazoacetoacetate enolate with imine in the presence of a strong base LiHMDS [lithium bis(trimethylsilyl)-amide] in good yields.<sup>[14]</sup> Although the anionic species thus generated can efficiently add to carbonyl compounds and imines, some of these methods clearly require stoichiometric strong bases or Lewis acids, low temperature and anhydrous conditions. Silyl enol ether, as an equivalent of the corresponding enolate anion, has been well applied in organic synthesis due to its good stability and group<sup>[10]</sup> firstly high selectivity, Doyle's reported scandium(III) triflate-catalyzed Mukaiyama-Mannich addition of methyl 3-(tert-butyldimethylsilanoxy)-2-diazobut-3enoate with imines catalyzed by. Wang et al.<sup>[11]</sup> reported TiCl<sub>4</sub>-promoted Mukaiyama–Mannich addition of α-diazoβ-ketoester or α-diazo-β-ketoketone and aromatic and aliphatic *N*-tosylaldimines to give δ-*N*-tosylamino-substituted β-keto diazocarbonyl compounds. In addition, the asymmetric Mukaiyama–Mannich type reaction of silyl enol diazoacetoacetate with chiral *N*-(benzylidene)-*p*-toluene was investigated in the presence of Lewis acids, such as BF<sub>3</sub>•Et<sub>2</sub>O, TiCl<sub>4</sub>, Cu(OTf)<sub>2</sub>, La(OTf)<sub>3</sub> and TBSOTf. However, only TBSOTf provided a low yield of the desired adduct.<sup>[12,13]</sup> To the best of our knowledge, few reports of one-pot Mukaiyama–Mannich addition of aldehydes, amines and silyl enol ether of diazo compounds were reported.<sup>[15]</sup>

We have recently reported an efficient and facile method for the synthesis of  $\alpha$ -diazo- $\beta$ - hydroxy esters by the coupling of aldehydes with ethyl diazoacetate (EDA) promoted by MgI<sub>2</sub> etherate (MgI<sub>2</sub>•(OEt<sub>2</sub>)<sub>n</sub>) in the presence of DIPEA (diisopropyl ethyl amine) at room temperature.<sup>[16]</sup> In continuation of our interest on the catalytic applications of MgI<sub>2</sub> etherate for various organic transformation, we herein wish to describe a facile and efficient protocol for one-pot Mukaiyama–Mannich addition of ethyl 3-(*tert*-butyldimethylsilanoxy)-2-diazobut-3-enoate **1a** with aldehydes, amines catalyzed by MgI<sub>2</sub> etherate under mild reaction conditions.

# **Results and discussion**

We investigated one-pot Mukaiyama-Mannich addition of a variety of aldehydes, such as aromatic, heteroaromatic, and

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silyl enol diazoacetoacetate <b>1a-1c</b> catalyzed by Mgl <sub>2</sub> •(OEt <sub>2</sub> )n <sup>a</sup> .							
Entry	R <sup>1</sup>	R <sup>2</sup>	R	Time(h)	Product	Yield(%) <sup>b</sup>	
	C <sub>6</sub> H₅	C <sub>6</sub> H₅	OEt	2	2a	90	
	2-MeOC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	OEt	10	2b	73	
	4-MeOC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	OEt	1	2c	94	
	4-MeC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	OEt	2	2d	93	
	$4-NO_2C_6H_4$	C <sub>6</sub> H <sub>5</sub>	OEt	1	2e	95	
	4-CIC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H₅	OEt	1	2f	91	
	$4-NO_2C_6H_4$	4-MeOC <sub>6</sub> H <sub>4</sub>	OEt	0.5	2g	97	
	C <sub>6</sub> H <sub>5</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	OEt	1	2ĥ	94	
	C <sub>6</sub> H <sub>5</sub>	$4-MeC_6H_4$	OEt	1	2i	93	
	C <sub>6</sub> H <sub>5</sub>	4-CIC <sub>6</sub> H <sub>4</sub>	OEt	5	2j	89	
	C <sub>6</sub> H <sub>5</sub>	$4-NO_2C_6H_4$	OEt	5	2k	87	
	4-MeOC <sub>6</sub> H <sub>4</sub>	$4-NO_2C_6H_4$	OEt	5	21	88	
	C <sub>6</sub> H <sub>5</sub>	2-MeOC <sub>6</sub> H <sub>4</sub>	OEt	10	2m	77	
	trans-PhCH = CH	C <sub>6</sub> H <sub>5</sub>	OEt	1	2n	90	
	2-thienyl	C <sub>6</sub> H <sub>5</sub>	OEt	2	20	88	
	2-furyl	C <sub>6</sub> H <sub>5</sub>	OEt	2	2р	87	
	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	OMe	2	2q	90	
	4-CIC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	OMe	2	2r	92	
	2-thienyl	C <sub>6</sub> H <sub>5</sub>	OMe	2	2s	90	
	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	O <sup>t</sup> Bu	4	2t	89	
	2-thienyl	C <sub>6</sub> H <sub>5</sub>	O <sup>t</sup> Bu	4	2u	88	

Table 1. One-pot Mukaiyama-Mannich addition of aldehydes, amines with

<sup>a</sup>The reaction was carried out by addition of aldehyde (1.0 mmol), amine (1.0 mmol) in CH<sub>3</sub>CN, followed by addition of silyl enol diazoacetoacetate 1a-1c (1.2 mmol) and 5 mol% of Mgl<sub>2</sub>•(Et<sub>2</sub>O)<sub>n</sub>. The reaction mixture was stirred at room temperature for various time.

OEt

12

NAc

NR<sup>c</sup>

 $C_6H_5$ 

PhCH-

<sup>b</sup>lsolated yields on silica gel column chromatography.

 $^{c}NA = not$  available, NR = no reaction.

CeHe

 $\alpha$ , $\beta$ -unsaturated aldehydes, with aniline, 4-methoxyaniline, 4-toluidine, 4-nitroaniline, 4-chloroaniline. The results were summarized in Table 1. The good to excellent yields strongly suggest that  $MgI_2 \bullet (OEt_2)_n$  is an efficient Lewis acid catalyst for the three-component Mukaiyama-Mannich addition of aldehydes, amines and silyl enol α-diazoacetoacetate 1a-1c. The reaction proved to be general and proceeded smoothly under very mild conditions at room temperature in a short period.

There is no need to exclude moisture and oxygen from the reaction system. The aromatic aldehydes bearing electron-donating and electron-withdrawing groups in para-substituted aromatic ring reacted smoothly to afford the desired  $\delta$ -amino substituted- $\alpha$ -diazoacetoacetate derivatives in excellent yields (Table 1, entries 3-6). Anilines bearing an electron-donating group in para-substituted aromatic ring (i.e. OMe, Me) reacted faster than anilines bearing an electronwithdrawing group (i.e. NO<sub>2</sub>, Cl) and afforded the corresponding Mannich adduct in better yields (Table 1, entries 7-12). Due to the steric hindrance, Mukaiyama-Mannich addition of o-methoxybenzlaldehyde or o-methoxyaniline with ethyl silyl enol diazoacetoacetate 1a proceeded sluggishly and gave a mild yield, respectively (Table 1, entries 2 and 13). Vinyl aldehydes such as cinnamaldehyde reacted with aniline to afford the Mannich adduct in good yield under the similar reaction conditions (Table 1, entry 14). Especially, MgI<sub>2</sub> etherate worked well with acid sensitive electron-rich heterocyclic aldehydes such as furfural, thiophene-2-carbaldehyde, which provided the corresponding products in high yields. (Table 1, entries 15 and 16). As well, MgI<sub>2</sub> etherate could efficiently catalyze one-pot Mukaiyama-Mannich addition of silyl enol α-diazoacetoacetate derived from methyl  $\alpha$ -diazoacetoacetate (1b) and tertbutyl  $\alpha$ -diazoacetoacetate (1c), respectively (Table 1, entries 17-21). We have observed that the use of an aromatic amine gave, in general, good results whereas an aliphatic amine did not yield any product even prolonging the reaction time in the presence of  $MgI_2$  etherate. (Table 1, entry 20).

Compound 21 was obtained as a yellow powder with a molecular formula of C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub> as established by the HR-ESI-TOF-MS m/z at 435.1286  $[M + Na]^+$  (calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>NaO<sub>6</sub>: 435.1275). The IR spectrum indicated the presence of an amino group (3375 cm<sup>-1</sup>), a diazo group  $(2137 \text{ cm}^{-1})$ , an ester group  $(1714 \text{ cm}^{-1})$  and a carbonyl group  $(1645 \text{ cm}^{-1})$ . The <sup>1</sup>H-NMR (see Supplemental Materials) of compound 2l showed eight aromatic proton signals at  $\delta_{\rm H}$  6.46 (dd, J = 1.9, 7.4 Hz, 2H), 6.88 (dd, J = 2.0, 6.8 Hz, 2H), 7.30 (dd, J = 1.8, 6.8 Hz, 2H) and 7.99 (dd, J = 1.7, 7.4 Hz, 2H), which were characteristic of a 1,4-substituted phenyl ring; an amino proton signal at  $\delta_{\rm H}$  5.72 (d, J = 6.3 Hz, 1H), a benzyl proton signal at  $\delta_{\rm H}$  4.91-4.95 (m, 1H), a methylene signal at  $\delta_{\rm H}$  4.35 (q, J = 7.2 Hz, 2H), a methoxy group at  $\delta_{\rm H}$  3.79 (s, 3H), a methylene signal at  $\delta_{\rm H}$ 3.35 (dd, J=4.7, 14.6 Hz, 1H) and 3.40 (dd, J=8.8, 14.6 Hz, 1H), and a typical methyl signal at  $\delta_{\rm H}$  1.35 (t, J = 7.2 Hz, 3H). The <sup>13</sup>C NMR spectroscopic data (see Supplemental Materials) revealed that compound 2l contained 16 carbon resonances. Among them, signals at  $\delta c$  161.49 and 190.36 indicated that there was a ketone carbonyl and an ester carbonyl group. Signals at  $\delta c$  14.31 was assignable to a methyl group. Signals at  $\delta c$  29.67 was assignable to a tertiary carbon of CN<sub>2</sub> group. Signals at  $\delta c$  55.25, 61.90 and 46.88 were assignable to an oxygenated methylene, a methoxy, and a methylene group, respectively. Signals at  $\delta c$  54.31 was assignable to a benzyl carbon. Signals at  $\delta c$  112.10 (2C), 114.36 (2C), 126.12 (2C), 127.24 (2C), 132.72, 138.30, 152.12, 159.15 were sp2 carbons on aromatic ring.

The interesting chemoselectivity was evaluated by crossover experiments (Table 2) of silvl enol diazoacetoacetate 1a with aldimines and parent aldehydes. its Mukaiyama-Mannich addition of aldimines with silyl enol diazoacetoacetate la was carried out prior to its parent aromatic aldehydes in the competitive reactions. The reactivity of aldimines is better than that of aldehydes in this MgI<sub>2</sub> etherate catalysis. No Mukaiyama aldol adduct was observed in the one-pot Mukaiyama-Mannich addition of aldehydes, amines and silyl enol diazoacetoacetate 1a under the same reaction conditions, which is attributed to the rapid formation and activation of imines in the presence of MgI<sub>2</sub> etherate. The unique reactivity of MgI<sub>2</sub> etherate is attributed to the dissociative character of iodide counterion.<sup>[17,18]</sup>

#### **Experimental**

## General

For product purification by flash column chromatography, silica gel ( $200 \sim 300$  mesh) and light petroleum ether (PE, b.p.  $60 \sim 90^{\circ}$ C) were used. <sup>1</sup>H NMR spectra were taken on a Bruker AM-500 spectrometer with TMS as an internal standard and CDCl<sub>3</sub> as solvent. <sup>13</sup>C NMR spectral measurements were performed at 125 MHz using TMS as an internal





<sup>a</sup>The reaction was carried out by addition of aldehyde (1.0 mmol), imine (1.0 mmol) with silyl enol diazoacetoacetate 1a (1.0 mmol) catalyzed by 5 mol %  $Mgl_2 \bullet (OEt_2)_n$  in untreated CH<sub>3</sub>CN at room temperature.

<sup>b</sup>Ratio was determined by isolated yields on silica gel column chromatography.

standard. IR spectroscopy was performed on a Nicolet 6700 infrared spectrometer. HRMS were determined on a GCT Premier spectrometer. The reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. The Supplemental Materials contains sample <sup>1</sup>H and <sup>13</sup>C NMR spectra of products 2 (Figures S1–S35).

The representative one-pot Mukaiyama-Mannich reaction—To a stirred solution of benzaldehyde (1.0 mmol) and aniline (1.0 mmol) in CH<sub>3</sub>CN (5 mL) was added a freshly prepared MgI<sub>2</sub> etherate (0.05 mmol) at room temperature, followed by addition of ethyl 3-(*tert*-butyldimethylsilanoxy)-2-diazobut-3-enoate **1a** (1.2 mmol). The resulting homogeneous mixture was stirred at room temperature for 2.0 h and quenched by saturated NaHCO<sub>3</sub> aqueous solution. Extractive workup with ethyl acetate and chromatographic purification of the crude product on silica gel gave *ethyl 2-diazo-3-oxo-5phenyl-5-(phenylamino)pentanoate* **2a** in 90% yield.

Spectroscopic data for the products (Table 1, entries 2a-2s) was list in Supplemental Materials file. Among them, compounds 2b, 2e, 2g, 2k-2p, 2s-2u are unknown compounds.

#### Conclusions

We have demonstrated that the unique catalytic reactivity of MgI<sub>2</sub> etherate in the one-pot Mukaiyama–Mannich addition

of various aldehydes including aromatic aldehydes, heteroaromatic aldehydes, vinyl aldehydes, and amines with silyl enol diazoacetoacetate. In this context, MgI<sub>2</sub> etherate, as a mild Lewis acid, demonstrates a remarkable catalytic performance. This magnesium-catalyzed Mukaiyama–Mannich addition has some advantages of simplicity, efficiency, mild reaction conditions and high yields. Further investigation on the asymmetric Mukaiyama–Mannich coupling catalyzed by chiral Mg(II)-complex is ongoing in our lab.

#### References

- Doyle, M. P.; Ratnikov, M.; Liu, Y. Intramolecular Catalytic Asymmetric Carbon-Hydrogen Insertion Reactions. Synthetic Advantages in Total Synthesis in Comparison with Alternative Approaches. Org. Biomol. Chem. 2011, 9, 4007–4016. DOI: 10. 1039/c0ob00698j.
- [2] Fang, C.; Shanahan, C. S.; Paull, D. H.; Martin, S. F. Enantioselective Formal Total Syntheses of Didehydrostemofoline and Isodidehydrostemofoline through a Catalytic Dipolar Cycloaddition Cascade. *Angew. Chem. Int. Ed.* 2012, 51, 10596–10599. DOI: 10.1002/anie.201205274.
- [3] Doyle, M. P.; McKervey, M. A.; Ye, T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides; John Wiley & Sons: New York, 1998.
- [4] Doyle, M. P. In *Comprehensive Organometallic Chemistry II*, H. L. S, Ed.; Pergamon Press: New York, **1995**; Vol. 12, Chapter 5.2.

- [5] Doyle, M. P.; Duffy, R.; Ratnikov, M. O.; Zhou, L. Catalytic Carbene Insertion into C-H Bonds. *Chem. Rev.* 2010, 110, 704–724. DOI: 10.1021/cr900239n.
- [6] Merlic, C. A.; Zechman, A. L. Selectivity in Rhodium(II) Catalyzed Reactions of Diazo Compounds: Effects of Catalyst Electrophilicity, Diazo Substitution, and Substrate Substitution. From Chemoselectivity to Enantioselectivity. *Synthesis* 2003, 2003, 1137–1156. DOI: 10.1055/s-2003-39389.
- [7] Davies, H. M. L.; Beckwith, R. E. J. Catalytic Enantioselective C-H Activation by Means of Metal-Carbenoid-Induced C-H Insertion. *Chem. Rev.* 2003, 103, 2861–2903. DOI: 10.1021/ cr0200217.
- [8] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. Catalytic Enantioselective Rearrangements and Cycloadditions Involving Ylides from Diazo Compounds. *Chem. Soc. Rev.* 2001, 30, 50–61. DOI: 10.1039/b000708k.
- [9] Holmquist, C. R.; Roskamp, E. J. A Selective Method for the Direct Conversion of Aldehydes into β-Keto Esters with Ethyl Diazoacetate Catalyzed by Tin(II) Chloride. J. Org. Chem. 1989, 54, 3258–3260. DOI: 10.1021/jo00275a006.
- [10] Liu, Y.; Zhang, Y.; Jee, N.; Doyle, M. P. Catalytic Addition Methods for the Synthesis of Functionalized Diazoacetoacetates and Application to the Construction of Highly Substituted Cyclobutanones. Org. Lett. 2005, 7, 5171–5174. DOI: 10.1021/ ol052003s.
- [11] Dong, C.; Deng, G.; Wang, J. New Approaches to Polysubstituted Pyrroles and  $\gamma$ -Lactams Based on Nucleophilic Addition of Ti(IV) Enolates Derived from  $\alpha$ -Diazo- $\beta$ -Keto Carbonyl Compounds to N-Tosylimines. J. Org. Chem. 2006, 71, 5560–5564. DOI: 10.1021/j00605039.

- [12] Kundu, K.; Doyle, M. P. Constructing Chiral Diazoacetoacetates by Enantioselective Catalytic Mukaiyama Aldol Reactions. *Tetrahedron Asymmetry* 2006, 17, 574–577. 2005. 12. 030. DOI: 10.1016/j.tetasy.
- [13] Doyle, M. P.; Kundu, K.; Russell, A. E. Catalytic Addition Methods for the Synthesis of Functionalized Diazoacetoacetates and Application to the Construction of Highly Substituted Cyclobutanones. Org. Lett. 2005, 7, 3131–3134. DOI: 10.1021/ ol052003s.
- [14] Dong, C.; Mo, F.; Wang, J. Highly Diastereoselective Addition of the Lithium Enolate of α-Diazoacetoacetate to N-Sulfinyl Imines: Enantioselective Synthesis of 2-Oxo and 3-Oxo Pyrrolidines. J. Org. Chem. 2008, 73, 1971–1974. DOI: 10.1021/ jo702275a.
- [15] For a review, see: Zhang, Y.; Wang, J. Recent Development of Reactions with a-Diazocarbonyl Compounds as Nucleophiles. *Chem. Commun.* 2009, 5350–5361. DOI: 10.1039/b908378b.
- [16] Qi, W. P.; Xie, X. Q.; Zhong, T. J.; Zhang, X. X. Highly Efficient and Chemoselective Direct Aldol Reaction of Acyldiazomethane with Aldehydes Promoted by MgI<sub>2</sub> Etherate. *Chin. Chem. Lett.* **2018**, *29*, 194–196. 2017.04.019. DOI: 10. 1016/j.cclet.
- [17] Corey, E. J.; Ishihara, K. Highly Enantioselective Catalytic Diels-Alder Addition Promoted by a Chiral Bis(Oxazoline)-Magnesium Complex. *Tetrahedron Lett.* **1992**, *33*, 6807–6810. DOI: 10.1016/S0040-4039(00)61781-1.
- [18] Corey, E. J.; Imai, N.; Zhang, H.-Y. Designed Catalyst for Enantioselective Diels-Alder Addition from a C2-Symmetric Chiral Bis(Oxazoline)-Iron(III) Complex. J. Am. Chem. Soc. 1991, 113, 728–729. DOI: 10.1021/ja00002a081.