800 Chinese Chemical Letters Vol. 14, No. 8, pp 800 – 803, 2003
http://www.imm.ac.cn/journal/ccl.html

Regioselective Addition of Silyl Enolates to α, β-Unsaturated Aldehyde and its Acetal Catalyzed by MgI_2 Etherate

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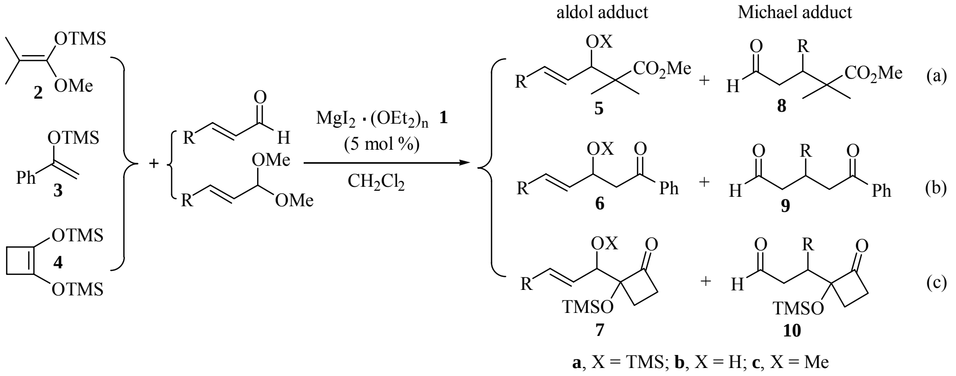
Abstract: Regioselective addition reactions of silyl enolates to α, β-unsaturated aldehyde and its acetal catalyzed by MgI_2 etherate give aldol adducts (1, 2-addition) preferentially over Michael adducts (1, 4-addition). This unique regioselectivity is distinctly different with other Lewis acidic promoters and may be attributed to the high oxyphilicity of IMg^+.

Keywords: MgI_2 etherate, silyl enolate addition, regioselective.

In our previous letter[1], we have reported the unique catalytic reactivity of MgI_2 etherate **1** in the chemoselective Mukaiyama-type aldol reactions of aryl or vinyl aldehyde and aldehyde acetals with silyl enolates. Aryl or alkyl α, β-unsaturated aldehydes (and their acetals) are particularly reactive in this catalytic addition reaction due to possibly the effective activation of the electron-rich carbonyl by highly oxyphilic Lewis acidic species, *i.e.* IMg^+, in non-coordinative media (*i.e.* CH_2Cl_2). Herein, we report the unique regioselectivity in the addition reaction of α, β-unsaturated aldehyde (and its acetal) with typical silyl enolates **2–4** catalyzed by MgI_2 etherate **1** (**Scheme 1**).

Scheme 1



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As shown in **Table 1**, the silyl enolate addition (Mukaiyama-type) reactions of α, β-unsaturated aldehydes[2] were performed in CH_2Cl_2 in the presence of a catalytic amount (5 mol %) of freshly prepared[3] **1** (0.2 mol/L in Et_2O/benzene 1:2) at –78°C or room temperature over a period of hours under argon. The crude products (**5**–**7**) were purified by chromatography on silica gel eluting with petroleum ether / ethyl acetate (v/v = 30:1~10:1).

Table 1 MgI_2 etherate–catalyzed Mukaiyama aldol coupling of vinyl aldehydes with silyl enolates

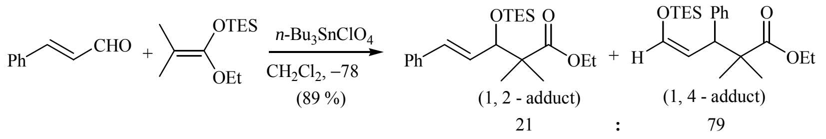
$$\text{RCHO} + \mathbf{2\text{–}4} \xrightarrow[\text{CH}_2\text{Cl}_2]{\mathbf{1}\ (5\ \text{mol}\ \%)} \mathbf{5\text{–}7}\ (\mathbf{a}, \mathbf{b}) + \mathbf{8\text{–}10}$$

entry	R[a]	enolate / T °C / t h	products[4] / ratio[b] / yield (%)[c]
1	PhCH=CH	2 / –78 / 3	5 (a+b) + 8 / 72 : 28 / 85
2	PhCH=CH	3 / r.t. / 2	6 (a+b) only // 75
3	PhCH=CH	4 / r.t. / 0.5	7a only // 98 (dr 3 : 2)
4	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CH$	2 / –78 / 4	5a only // 78
5	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CH$	4 / r.t. / 4	7a only // 40[d]
6	$CH_3CH{=}CH$	4 / r.t. / 4	7a + 10 / 80 : 20 / 60[e]

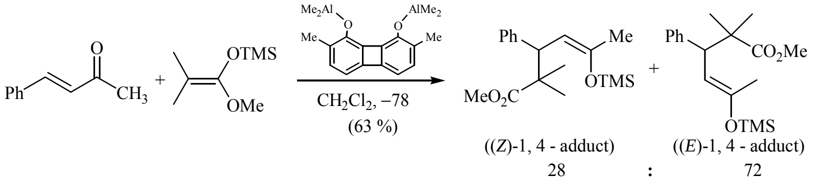
[a] All aldehydes are *trans*-configurated. [b] Ratio refers to 1, 2-adduct *vs.* 1, 4-adduct. [c] Isolated overall yield, *dr* was determined by ^1H NMR analysis. [d] *dr* was not determined. [e] *dr* values were *ca*. 2:1 for **7a** and **10**.

We observed that the regioselectivity of silyl enolate addition catalyzed by MgI_2 etherate **1** was depended on the electronic and steric factors of carbonyl substrates, as well as the nucleophilic reactivity of silyl enolates. Cinnamaldehyde reacted with silyl ketene acetal **2** in the presence of 5 mol % of **1** at –78°C to give aldol product (1, 2-addition) preferentially (72%) along with 28% of Michael adduct in an overall yield of 85% (entry 1), while reacting with less reactive enol silanes **3** or **4** resulted in aldol product exclusively (entries 2 and 3). For sterically more congested vinyl aldehyde, for example geranial, the catalytic addition with silyl nucleophiles **2** or **4** afforded solely the corresponding silylated aldol adduct (entries 4 and 5). The sterically less demanding enal, such as crotonaldehyde, reacted with cyclic enol silane **4** to yield aldol product predominantly over Michael adduct (entry 6). It is apparent that the aldol addition is favored over 1, 4-addition in the MgI_2 etherate–catalyzed Mukaiyama-type condensation of enals with silyl enolates.

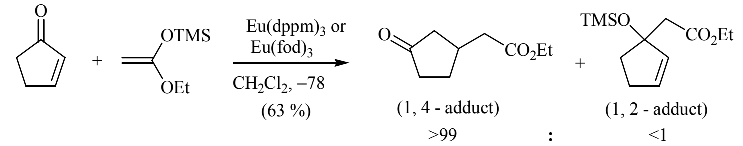
The above regioselectivity are in sharp contrast to other Lewis acidic catalysts in the silyl enolate addition reactions of α, β-unsaturated carbonyl substrates reported in the literature. For examples, the organotin Lewis acid[5], bis(organoaluminum) complex[6], europium complexes[7], and Lewis acidic titanium species[8] exhibited remarkable preference for Michael addition over aldol addition as illustrated in Equations **1–4** respectively. We reasoned that the conjugated carbonyl coordination with highly oxyphilic Lewis acidic species IMg^+ might account for the kinetically favored regioselective electrophilic activation of the carbonyl carbon.



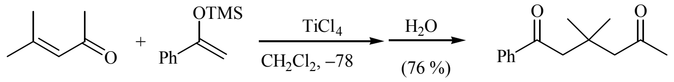
(1)



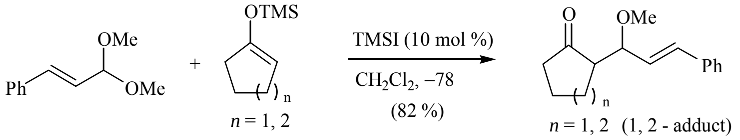
(2)



(3)



(4)



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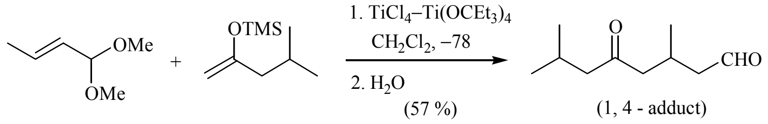
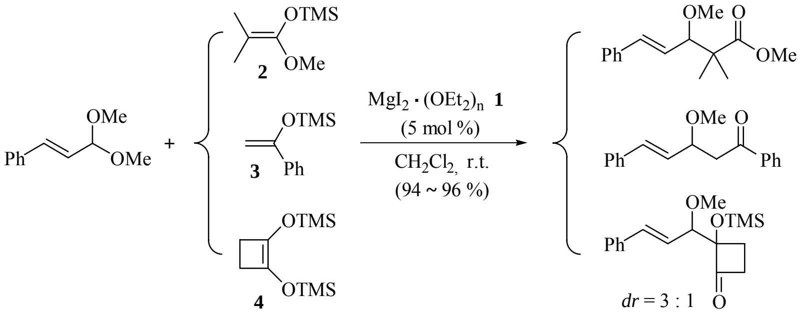


(6)

Furthermore, Mukaiyama-type coupling of acetal of α, β-unsaturated aldehyde (*i. e.* cinnamaldehyde) with silyl enolates **2**–**4** catalyzed by MgI_2 etherate **1** afforded the aldol adducts[4] exclusively (**Scheme 2**). Similar regioselectivity was observed in the iodotrimethylsilane (TMSI)–catalyzed reaction (Equation **5**)[9]. However, the use of titanium tetrachloride–alkoxy titanium led to the Michael addition only (Equation **6**)[8].

Scheme 2 MgI_2 etherate–catalyzed silyl enolates addition to vinyl aldehyde acetal



In summary, regioselective Mukaiyama-type coupling of silyl enolates to α, β-unsaturated aldehyde and its acetal is available with remarkable 1, 2-addition preference by using MgI$_2$ etherate **1** as Lewis acid catalyst, which may be complementary to other Lewis acid systems. Further investigation of the catalytic reactivity of **1** in the other C–C bond forming reactions is in progress.

Acknowledgments

We are grateful for the financial supports from the National Outstanding Youth Fund (No. 29925204), the Foundation for University Key Teacher by the Ministry of Education of China, and a Visiting Fund of the National Laboratory of Applied Organic Chemistry.

References and Notes

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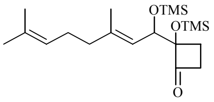
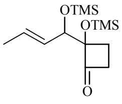
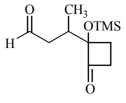
4. Cf. ref. 1 for spectral data of products, except for the following adducts:



A



B



C

A: colorless oil, IR (film) ν 1789(s), 1668, 1443, 1252, 1075, 843 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$, *ppm*) δ 0.01 (s, 9 H), 0.09 (s, 9 H), 1.59–1.73 (m, 9 H, CH$_3$), 1.86–2.78 (m, 8 H, CH$_2$), 4.34–4.46 (m, 1 H), 5.10–5.18 (m, 2 H); EIMS: *m/z* 382 (M$^+$, 0.01), 354 (0.3), 257 (4.4), 217 (13.4), 73 (100).

B: colorless oil, IR(film) ν 1789(s), 1653, 1445, 1251, 1096, 844 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$, *ppm*) δ 0.10 (s, 9 H), 0.16 (s, 9 H), 1.63–1.77 (m, 3 H, CH$_3$), 1.83–2.79 (m, 4 H, CH$_2$), 4.08 (d, 0.33 H, J = 5.6 Hz), 4.16 (d, 0.67 H, J = 5.6 Hz), 5.40–5.58 (m, 1H), 5.60–5.80 (m, 1 H); EIMS: *m/z* 272 (M$^+$–28, 0.3), 257 (0.5), 244 (0.3), 217 (6.7), 147 (17.0), 129 (14.6), 73 (100).

C: colorless oil, IR (film) ν 1787(s), 1725(s), 1398, 1253, 1064, 845 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$, *ppm*) δ 0.14 (s, 9 H), 1.00 (d, 1 H, J = 6.6 Hz, CH$_3$), 1.02 (d, 2 H, J = 6.6 Hz, CH$_3$), 1.93–2.87 (m, 7 H), 9.73 (s, 0.33 H, CHO) and 9.82 (s, 0.67 H, CHO); EIMS: *m/z* 228 (M$^+$, 0.06), 200 (0.8), 171 (6.9), 143 (6.8), 73 (100).

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Received 4 November, 2002