In situ halo-aldol reaction of aldehydes with cyclopropyl ketone promoted by MgI_2 etherate

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A facile synthesis of α-iodoethyl-β-hydroxyketones via the MgI_2 etherate-mediated ring opening of cyclopropyl ketones was reported using mild condition.

Keywords: halo-aldol reaction, cyclopropyl ketone, MgI_2 etherate

Ring expansion reactions of highly strained rings such as cyclopropanes constitute an efficient method for the construction of cyclic compounds.[1-3] One useful approach to ring expansion involves the ring opening of an activated cyclopropane, which can act as a homo-Michael acceptor, where the enolate or enol intermediate generated *in situ* acts as a nucleophile in a cyclisation.[4-5] Sequential nucleophilic reaction of the resulting enolate with electrophiles provides an extremely effective methodology for construction of the carbon framework of organic molecules. Among them, ring opening of cyclopropyl ketones is an attractive method to prepare enolates and this has been explored extensively in carbon-carbon bond formation.[4-8] Oshima *et al.*[9] have demonstrated that $TiCl_4$-n-Bu_4NI is a mixed reagent which efficiently provides titanium enolates by ring opening of cyclopropyl ketones. These subsequently react with various aldehydes to afford a variety of α-iodethyl-β-hydroxy ketones. Recently, Li and co-workers[10,11] have reported an asymmetric halo-aldol addition and halo-Mannich reaction by reacting chiral cyclopropyl carbonyl derived enolates with aldehydes or aldimines catalysed by Et_2AlI. However reactions using Lewis acids such as $TiCl_4$ and Et_2AlI must be carried out under strictly anhydrous conditions, and they are difficult to handle especially on a large scale. Consequently, the development of less expensive, environmentally benign, and easily handled promoters to mediate halo-aldol addition of cyclopropyl ketones with aldehydes is still highly desirable.

Due to their abundant, inexpensive and nontoxic character, Lewis acidic Mg(II) catalysts have been widely utilised in various organic reactions.[12] In our previous paper,[13] we have demonstrated that MgI_2 etherate could efficiently catalyse a Mukaiyama-type aldol reaction of aldehydes with trimethylsilyl enolates and the allylation of aldehydes with allylstannanes. Here we report that MgI_2 etherate can mediate enolate formation from cyclopropyl ketones, and the sequential trapping of the resulting Mg-enolates with aldehydes to afford α-iodethyl-β-hydroxyketones.

Recently several reports have been published in which MgI_2 etherate ($MgI_2{\bullet}(OEt_2)_n$) was used as a Lewis acid/halogen donor.[15-17] We began our studies by carrying out the halo-aldol addition of benzaldehyde to cyclopropyl methyl ketone in the presence of MgI_2 etherate. Cyclopropyl methyl ketone was added under argon at room temperature to the freshly prepared MgI_2 etherate (0.2 M in Et_2O/benzene 1 : 2)[18] anhydrous CH_2Cl_2 solution. After stirring for 1 h, addition of benzaldehyde afforded an inseparable mixture of the aldol adduct **1a** in 70% yield (Table 1, entry 1).

Encouraged by this result, we turned our attention to the various aromatic aldehydes, and α,β−unsaturated aldehydes. The experimental results are summarised in Table 1. As the data in Table 1 indicate, the halo-aldol adducts were usually obtained in high yield as inseparable diastereomers after the usual aqueous workup and flash chromatography on silica gel.

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We have observed the following electronic effects: (1) aryl aldehydes with electron-donating substituent (i.e. *o*- or *p*-OMe) reacted much faster than benzaldehyde (Table 1, entries 2–4) and (2) electron-withdrawing substituent (*i.e.* –Br, $–NO_2$) deactivated aryl aldehyde remarkably (Table 1, entries 6 and 7). For example, *o*- and *p*-anisaldehyde are much more reactive than *m*-anisaldehyde and benzaldehyde (Table 1, entries 1, 3, 4 and 5). Furthermore, (*E*)-cinnamaldehyde is a highly reactive substrate and gave the 1, 2-aldol adducts with exclusive regioselectivity and stereoselectivity (Table 1, entry 8). The Mg-enolate **2** is also reacted with aliphatic aldehydes. For example, acetaldehyde afforded the aldol adduct **1i** in 88% yield (Table 1, entry 9).

We assumed that the activation of cyclopropyl ketone arose from the coordination of the Lewis basic oxygen atom of the carbonyl function with the Lewis acidic magnesium (II) species, like $[MgI]^+$.[15] The dissociated iodide ion then attacks cyclopropyl ring to form the Mg-enolate **2**, which subsequently reacted with aldehydes to afford the desired product α-iodoethyl-β-hydroxyketone (Scheme 1). The unique catalytic reactivity of the MgI_2 etherate is attributed to the dissociative character of iodide counterion and a more Lewis acidic cationic $[MgI]^+$ species as a result of a Lewis base activation of Lewis acid.[19]

In conclusion, we have demonstrated that MgI_2 etherate can efficiently promote *in situ* halo-aldol addition of cyclopropyl ketone with aldehydes under mild reaction conditions. It has some advantages over previous methods[9-11] such as low cost, simplicity of operation, and good yields. Further investigations on MgI_2 etherate-catalysed other bond formation reactions are being actively pursued in our laboratory.

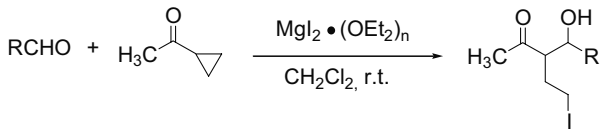
Experimental

Silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90 °C) were used for product purification by flash column chromatography, ^{1}H NMR spectra were obtained on a Bruker Avance-400 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. Reactions were monitored by TLC on silica gel polygram SILG/UV 254 plates. All mixtures were identified by ^{1}H NMR and FT-IR spectroscopy.

Typical experimental procedure of MgI_2 etherate-promoted halo-aldol reaction of cyclopropyl ketone with aldehydes.
Cyclopropyl methyl ketone (2.0 mmol) was added dropwise to a stirred solution of freshly prepared MgI_2 etherate (2.0 mmol) in CH_2Cl_2 (5 mL) at room temperature under argon. After the addition, the reaction mixture was stirred for 1 h. Then a solution of benzaldehyde in CH_2Cl_2 (5 mL) was added. The resulting reaction mixture was stirred at room temperature for 12 h and quenched with an aqueous saturated Na_2SO_3 solution. Extraction with dichloromethane and flash chromatographic purification of the crude product on silica gel gave the product **1a** in 70% yield as a mixture of unseparated diastereomers (*dr* : 93 : 7) from ^{1}H NMR analysis.

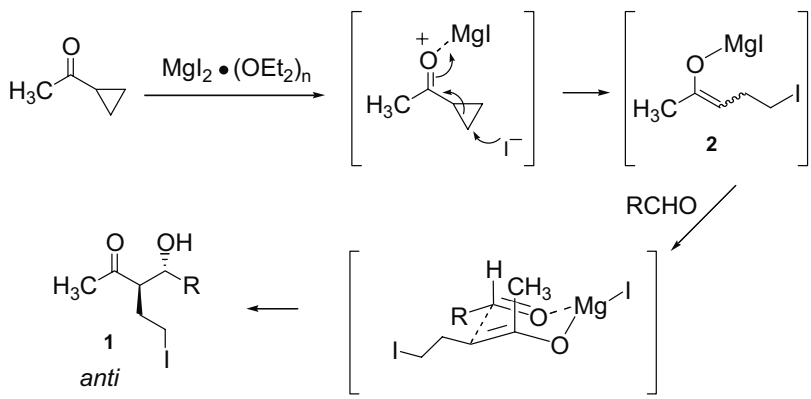
Spectroscopic data of diastereometric mixtures **1a** to **1i**
1a[9] IR (film) υ (cm^{-1}) 3598 (OH), 1710 (C=O). δ_H 1.62–1.74 (m, 1H), 1.82–2.08 (m, 1H), 2.19 (s, 3H), 2.45 (br s, 1H), 2.94–2.96 (m, 1H), 2.98–3.04 (m, 1H), 3.17–3.21 (m, 1H), 4.75 (d, *J* = 7.4 Hz, 0.93H), 4.94 (d, *J* = 5.8 Hz, 0.07H), 7.30–7.36 (m, 5H).

Table 1 MgI_2•$(OEt_2)_n$-promoted halo-aldol reaction of cyclopropyl methyl ketone



Entry	Aldehyde	Time/h	Products	Yield/%[a](*anti*/*syn*)
1		12	**1a**	70 (93:7)
2		12	**1b**	74 (60:40)
3		6	**1c**	92 (>99:1)
4		8	**1d**	82 (>99:1)
5		12	**1e**	45 (50:50)
6		24	**1f**	50 (63:37)
7		24	**1g**	35 (91:9)
8		12	**1h**	96 (>99:1)
9		12	**1i**	88 (70:30)

[a]Isolated overall yield and ratio of *anti*/*syn* isomers determined by ^{1}H NMR analysis.



Scheme 1 The proposed mechanism of halo-aldol addition promoted by MgI_2•$(OEt_2)_n$.

1b: IR (film) υ (cm^{-1}) 3599 (OH), 1711 (C=O). δ_H 2.03–2.08 (m, 2H), 2.15 (s, 1.2H) and 2.21 (s, 1.8H), 2.35 (s, 3H), 2.96–3.24 (m, 3H), 4.71 (d, *J* = 7.6 Hz, 0.6H) and 4.89 (d, *J* = 6.0 Hz, 0.4H), 7.14–7.34 (m, 4H).

1c: IR (film) υ (cm^{-1}) 3599 (OH), 1710 (C=O). δ_H 1.50–1.70 (m, 1H), 1.96–2.04 (m, 1H), 2.21 (s, 3H), 2.96–3.24 (m, 3H), 3.77 (s, 3H), 4.65 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 6.6 Hz, 2H), 7.20 (d, *J* = 6.6 Hz, 2H).

1d: IR (film) υ (cm^{-1}) 3599 (OH), 1710 (C=O). δ_H 1.75–1.90 (m, 1H), 2.05–2.11 (m, 1H), 2.13 (s, 3H), 2.97–3.02 (m, 1H), 3.06–3.11 (m, 1H), 3.31–3.34 (m, 1H), 3.87 (s, 3H), 5.01 (d, *J* = 6.8 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.94–6.98 (m,1H), 7.24–7.29 (m, 2H).

1e: IR (film) υ (cm^{-1}) 3598 (OH), 1710 (C=O). δ_H 1.62–1.75 (m, 1H), 1.96–2.12 (m, 1H), 2.07 (s, 1.5H) and 2.20 (s, 1.5H), 2.61 (br s, 1H, OH), 2.90–3.20 (m, 3H), 3.81 (s, 3H), 4.71 (d, *J* = 7.6 Hz, 0.5H) and 4.91 (d, *J* = 5.6 Hz, 0.5H), 6.80–6.89 (m, 3H), 7.23–7.27 (m, 1H).

1f: IR (film) υ (cm^{-1}) 3595 (OH), 1712 (C=O). δ_H 1.70–1.75 (m, 1H), 2.04–2.11 (m, 1H), 2.10 (s, 1.2H) and 2.18 (s, 1.8H), 2.95–3.10 (m, 3H), 4.69 (d, *J* = 7.2 Hz, 0.6H) and 4.91 (d, *J* = 5.2 Hz, 0.4H), 7.19 (dd, *J* = 2.0, 8.4 Hz, 2H), 7.44–7.50 (m, 2H).

1g: IR (film) υ (cm^{-1}) 3594 (OH), 1713 (C=O). δ_H 1.83–1.91 (m, 1H), 2.03–2.24 (m, 1H), 2.16 (s, 3H), 3.08–3.28 (m, 3H), 4.89 (d, *J* = 6.0 Hz, 1H), 7.55 (d, *J* = 5.4 Hz, 2H), 8.23 (d, *J* = 5.4 Hz, 2H).

1h: IR (film) υ (cm^{-1}) 3596 (OH), 1712 (C=O). δ_H 1.94–2.05 (m, 1H), 2.13–2.19 (m, 1H), 2.30 (s, 3H), 2.55 (br s, 1H, OH), 3.01–3.14 (m, 2H), 3.18–3.23 (m, 1H), 4.30–4.40 (m, 1H), 6.17 (dd, *J* = 7.0, 16.0 Hz, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 7.25–7.40 (m, 5H).

1i [9] IR (film) υ (cm^{-1}) 3599 (OH), 1711 (C=O). δ_H 1.13–1.21 (m, 3H), 1.86–2.22 (m, 2H), 2.25 (s, 3H), 2.74–2.77 (m, 1H), 2.79 (br s, 1H, OH), 2.91–3.16 (m, 2H), 3.87–3.91 (m,.0.7H) and 4.99–5.02 (m, 0.3H).

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