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An efficient direct-aldol addition of methyl ketones with aldehydes promoted by MgI_2 etherate

Abstract: Direct aldol addition of ketones with aromatic aldehydes and vinyl aldehyde was carried out efficiently in the presence of MgI_2 etherate and Et_3N using untreated reagent grade CH_2Cl_2 under atmospheric conditions in a mild, efficient and highly chemoselective manner. Iodide counterion and non-coordinating reaction media (i.e., CH_2Cl_2) are among the critical factors for the unique reactivity of this reaction system.

Keywords: aldehydes; direct-aldol; ketones; MgI_2 etherate.

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Introduction

The aldol reaction is considered to be one of the most powerful methods for preparing β-hydrxoy carbonyl compounds. Substantial effort has gone into its development using preformed enolates, resulting in a remarkable level of regio- and stereochemical control (Carreira, 1999; Mahrwald, 2004). Recently, considerable effort has been applied to the development of direct-aldol reaction. The development of direct-aldol reaction from unactivated ketones and aldehydes does not require the preconversion of a ketone or an ester to a more reactive species (e.g., a silyl enol ether or a silyl ketene acetal) and has attracted a great deal of attention from synthetic organic chemists (Evans et al., 2002a,b, 2003; Lalic et al., 2003; Magdziak et al., 2005). Evans and co-workers have demonstrated that magnesium halide catalyzed aldol reactions of chiral N-acyloxazolidinones and N-acylthiazolidinethiones (Evans et al., 2002a,b). Magnesium is an abundant, cheap and benign element which exists in nature, and many reactions using magnesium salts have been developed recently in organic synthesis (Zhang and Li, 2003). In our previous paper, we have demonstrated that MgI_2 etherate could efficiently catalyze Mukaiyama-type aldol reaction of aldehydes with trimethylsilyl enolates and allylation of aldehydes with allylstannane (Li and Zhang, 2002; Zhang, 2008). We have also found that MgI_2 etherate promoted halo-aldol addition of cyclopropyl methyl ketone with aldehydes under mild reaction conditions via ring opening of cyclopropane (Zhang, 2009). Herein, we report unique chemoselective direct-aldol promoted by MgI_2 etherate under atmospheric conditions.

Results and discussion

At the onset of this work, we investigated a variety of conditions with a model reaction of acetophenone with 3-nitrobenzaldehyde using MgI_2 etherate as promoter in the presence of Et_3N. When 1.0 equiv. of acetophenone, 3-nitrobenzaldehyde and Et_3N were added at room temperature in untreated reagent grade dichloromethane, the aldol product was generated within 30 min with a good yield of 92%. This yield was optimized to a quantitative yield of 99% by using 1.2 equiv. of acetophenone, 1.2 equiv. of Et_3N and 1.0 equiv. of 3-nitrobenzaldehyde. Of various untreated solvents screened, excellent yield was obtained in non-coordinating reaction media CH_2Cl_2. Low yields were provided in non-polar solvent, such as benzene or toluene. The reaction was carried out very sluggishly in the coordinative polar solvents, such as Et_2O, dimethylformamide and tetrahydrofuran. To examine the halide anion effect, halogen analogs of MgI_2 etherate, $MgBr_2$ etherate and $MgCl_2$ etherate, were compared under parallel reaction conditions (1.0 equiv. of promoters). $MgCl_2$ etherate was almost inactive. $MgBr_2$ etherate is less effective in terms of substrate conversion and yield.

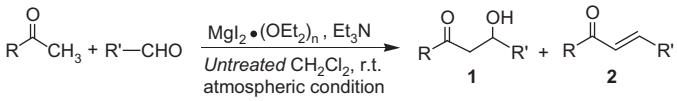
With these optimal conditions in hand, we explored the scope and limitation of this simple process by the reaction of electronically and functionally diverse aldehydes under the same conditions. There is no need to exclude

moisture and oxygen from the reaction system. The experimental results are summarized in Table 1. As shown in Table 1, MgI_2 etherate-Et_3N could promote direct-aldol coupling of acetophenone and substituted acetophenone with aromatic aldehydes in good to excellent yields in a short period (Table 1, entries 1–5). Interestingly enough, the nucleophilic addition of cyclopropyl methyl ketone with benzaldehyde in the presence of MgI_2 etherate and Et_3N was also processed efficiently without ring opening reaction of cyclopropane (Table 1, entry 6). Moreover, the aromatic aldehydes bearing electron-donating and electron-withdrawing groups in the aromatic ring were reacted smoothly to afford the desired aldol adducts in good to excellent yields (Table 1, entries 6–13). Furthermore, we observed the following delicate electronic effects: (1) aromatic aldehydes with an electron-donating substituent (i.e., OMe) afforded the corresponding adducts in lower yields than benzaldehyde (Table 1, entries 6–9). (2) Aromatic aldehydes with an electron-withdrawing substituent (i.e., Cl, F, NO_2) reacted much faster than benzaldehyde and provided the corresponding adducts in excellent yields (Table 1, entries 11–13). It is noteworthy that 3-anisaldehyde is more reactive than 4-anisaldehyde (Table 1, entries 9 and 10). Seemingly, this reactivity of aromatic aldehydes is principally dependent on the inherent electrophilicity of the carbonyl group. Heteroaromatic aldehyde, such as 2-thiophenealdehyde, was also a good substrate (Table 1, entry 14). Acid-sensitive aldehyde, such as cinnamaldehyde, reacted with cyclopropyl methyl ketone to afford a good yield of the 1,2-adduct without any decomposition or polymerization under the present reaction conditions (Table 1, entry 15). In general, both aromatic, heteroaromatic and α,β-unsaturated aldehydes underwent the conversion efficiently in a short period, whereas ketones did not yield any product even prolonging the reaction times in the presence of MgI_2 etherate and Et_3N.

This interesting chemoselectivity was further evaluated by crossover experiments of various aromatic aldehydes with ketones, respectively. MgI_2 etherate shows high levels of aromatic aldehydes discrimination in the competitive reactions with ketone. MgI_2 etherate can effectively recognize the delicate difference in electronic effect involved in benzaldehyde (Table 2). Expectedly, 4-anisaldehyde is much less reactive than benzaldehyde, 4-nitrobenzaldehyde and 3-nitrobenzaldehyde in the MgI_2 etherate-promoted process. Only the aldol adduct of benzaldehyde, 4-nitrobenzaldehyde and 3-nitrobenzaldehyde was obtained, respectively (Table 2, entries 1–3). In crossover-aldol addition of benzaldehyde with 4-nitrobenzaldehyde or 3-nitrobenzaldehyde, the former shows less

Entry	R	R'	Room temperature (h)	Ratio 1/2[b]	Overall yield (%)[c]
1	C_6H_5	3-$NO_2C_6H_4$	0.5	82:18	99
2	C_6H_5	3-$CH_3OC_6H_4$	2	54:46	95
3	C_6H_5	C_6H_5	2	>99:<1	84
4	4-$CH_3OC_6H_4$	C_6H_5	2	>99:<1	85
5	4-FC_6H_4	C_6H_5	2	>99:<1	90
6	Cyclopropyl	C_6H_5	1	<1/>99	88
7	Cyclopropyl	Piperonal	4	55:45	83
8	Cyclopropyl	4-$CH_3COOC_6H_4$	5	60:40	85
9	Cyclopropyl	4-$CH_3OC_6H_4$	6	>99:<1	81
10	Cyclopropyl	3-$CH_3OC_6H_4$	1	>99:<1	94
11	Cyclopropyl	3-$NO_2C_6H_4$	0.5	>99:<1	98
12	Cyclopropyl	4-$NO_2C_6H_4$	0.5	>99:<1	99
13	Cyclopropyl	2-Cl-6-F-C_6H_3	1	73:27	91
14	Cyclopropyl	2-thiophenyl	1	>99:<1	87
15	Cyclopropyl	(E)-C_6H_5CH=CH	2	>99:<1	86

Table 1 MgI_2-promoted direct-aldol addition of ketones with various aldehydes.[a]



[a]Conducted under atmospheric conditions by combining 1.2 mmol of ketone, 1.0 mmol of aldehyde and 1.0 mmol of $MgI_2 \cdot (OEt_2)_n$ in untreated reagent grade CH_2Cl_2, followed by addition of 1.2 mmol of Et_3N.
[b]The ratio was determined by flash column chromatography.
[c]Overall isolatedyield.

reactivity than the latter (Table 2, entries 5–7) and the reaction exclusively gave the aldol adduct of 4-nitrobenzaldehyde and 3-nitrobenzaldehyde, respectively. Similarly, the reactivity of 4-nitrobenzaldehyde and 3-nitrobenzaldehyde is much better than that of 3-anisaldehyde (Table 2, entries 8–10). More significantly, MgI_2 etherate shows the remarkable preference for 3-anisaldehyde over 4-anisaldehyde (Table 2, entry 4). These results suggest that the relative reactivity of aromatic aldehydes in the MgI_2 etherate-promoted process is determined almost solely by electrophilicity of aromatic aldehydes themselves.

In summary, we have demonstrated the unique reactivity of MgI_2 etherate in the chemoselective direct-aldol coupling of aromatic aldehydes with ketones. This magnesium-promoted direct-aldol addition is mild, efficient and operationally simple. Iodide counterion and non-coordinating reaction media are critical factors for the unique reactivity of this reaction system. Further investigation on the reactivity of MgI_2 etherate in other C-C bond constructing reactions is underway.

Experimental section

General methods

For product purification by flash column chromatography, silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90°C) were used. ^{1}H NMR spectra were taken on a Bruker Avance III 500 MHz spectrometer (Switzerland) with TMS (tetramethylsilane) as an internal standard and $CDCl_3$ as solvent. The reactions monitoring was accomplished by thin layer chromatography on silica gel polygram SILG/UV 254 plates. Elemental analysis was performed on a VarioEL-3 instrument (Elementar, Germany).

Representative experimental procedure of MgI_2 etherate-promoted direct-aldol reaction

To a stirred mixture solution of 3-nitrobenzaldehyde (151 mg, 1 mmol) and acetophenone (144 mg, 1.2 mmol) in CH_2Cl_2 (10 ml) was added a freshly prepared MgI_2 etherate (Arkley et al., 1962) (1 mmol) at room temperature, followed by addition of Et_3N (121 mg, 1.2 mmol). The resulting reaction mixture was stirred at room temperature for 30 min and quenched with saturated aqueous Na_2SO_3. Extractive workup with ether and chromatographic purification of the crude product on silica gel gave the desired aldol adduct in 99% yield.

3-Hydroxy-1,3-diphenyl-propan-1-one (Diana et al., 1977): colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ = 3.31–3.36 (m, 2H), 3.65–3.66 (m, 1H), 5.31–5.34 (m, 1H), 7.26–7.29 (m, 1H), 7.34–7.37(m, 2H), 7.41–7.45 (m, 4H), 7.55–7.58 (m, 1H), 7.92–7.93 (m, 2H).

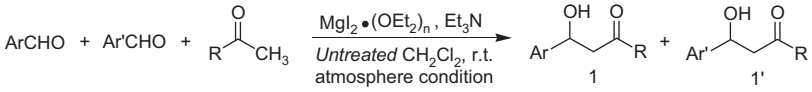
3-Hydroxy-3-(3-methoxy-phenyl)-1-phenyl-propan-1-one (Yutaka et al., 1995): colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ = 3.35 (s, 1H), 3.36 (d, *J* = 2.5 Hz, 1H), 3.63 (d, *J* = 2.5 Hz, 1H), 3.81 (s, 3H), 5.30–5.33 (m, 1H), 6.83 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.98–7.01 (m, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.9–7.95 (m, 2H).

(*E*)-3-(3-Methoxy-phenyl)-1-phenyl-propenone (Rao et al., 2008): colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ = 3.82 (s, 3H), 6.94 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.14 (t, *J* = 1.5 Hz, 1H), 7.21–7.24 (m, 1H), 7.29–7.32 (m, 1H), 7.46–7.49 (m, 3H), 7.51–7.57 (m, 1H), 7.76 (d, *J* = 15.5 Hz, 1H), 8.00–8.01 (m, 2H).

3-Hydroxy-3-(3-nitro-phenyl)-1-phenyl-propan-1-one (Wang et al., 2004): pale yellowish oil. ^{1}H-NMR (500 MHz, $CDC1_3$) δ: 3.34–3.46 (m, 2H), 3.87 (s, 1H), 5.46 (dd, *J* = 2.5, 9.0 Hz, 1H), 7.47–7.50 (m, 2H), 7.56

Entry	R	Ar	Ar'	Ratio (1/1')[b]	Overall yield (%)[c]
1	Cyclopropyl	C_6H_5	4-$CH_3OC_6H_4$	>99/<1	85
2	Cyclopropyl	4-$NO_2C_6H_4$	4-$CH_3OC_6H_4$	>99/<1	96
3	Cyclopropyl	3-$NO_2C_6H_4$	4-$CH_3OC_6H_4$	>99/<1	94
4	Cyclopropyl	3-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	80:20	96
5	Cyclopropyl	3-$NO_2C_6H_4$	C_6H_5	>99/<1	92
6	Ph	3-$NO_2C_6H_4$	C_6H_5	>99/<1	91
7	Cyclopropyl	4-$NO_2C_6H_4$	C_6H_5	>99/<1	95
8	Cyclopropyl	3-$NO_2C_6H_4$	3-$CH_3OC_6H_4$	92:8	93
9	Cyclopropyl	4-$NO_2C_6H_4$	3-$CH_3OC_6H_4$	>99/<1	94
10	Ph	3-$NO_2C_6H_4$	3-$CH_3OC_6H_4$	>99/<1	94

Table 2 $MgI_2{\cdot}(OEt_2)_n$-promoted crossover direct-aldol reaction.[a]



[a]Reactions were run with a mixture of 1.0 mmol of each aromatic aldehyde, 1.0 mmol of ketone and 1.0 mmol of $MgI_2{\cdot}(OEt_2)_n$ in untreated CH_2Cl_2, followed by addition of 1.2 mmol of Et_3N at room temperature under atmospheric condition.
[b]The ratio was determined by flash column chromatography.
[c]Overall isolated yield.

(t, *J* = 8.0 Hz, 1H), 7.60–7.63 (m, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.95–7.97 (m, 2H), 8.15–8.17 (m, 1H), 8.33 (t, *J* = 1.5 Hz, 1H).

(*E*)-3-(3-Nitro-phenyl)-1-phenyl-propenone (Giancarlo et al., 2003): pale yellowish oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 7.54–7.57 (t, *J* = 8.0 Hz, 2H), 7.62–7.65 (m, 2H), 7.68 (d, *J* = 16.0 Hz, 1H), 7.86 (d, *J* = 15.5 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 2H), 8.28 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.53 (s, 1H).

3-Hydroxy-3-phenyl-1-(4-fluorophenyl)-propan-1-one (Wei et al., 2004): colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 7.92–7.96 (m, 2H), 7.38–7.44 (m, 2H), 7.33–7.36 (m, 2H), 7.28–7.31 (m, 1H), 7.09–7.12 (m, 1H), 5.31–5.34 (m, 1H), 3.31–3.34 (m, 2H).

(*E*)-1-Cyclopropyl-3-phenyl-propenone (Galina et al., 2005): colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.96–0.99 (m, 2H), 1.15–1.18 (m, 2H), 2.23–2.28 (m, 1H), 6.88 (d, *J* = 16.0 Hz, 1H), 7.38–7.40 (m, 3H), 7.55–7.63 (m, 3H).

3-Benzo[1,3]dioxol-5-yl-1-cyclopropyl-3-hydroxy-propan-1-one (Diana et al., 1977): colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.92 (dd, *J* = 3.5, 8.0 Hz, 2H), 1.08 (dd, *J* = 5.0, 8.5 Hz, 2H), 1.90–1.93 (m, 1H), 2.88–2.98 (m, 2H), 3.53 (d, *J* = 3.0 Hz, 1H), 5.04–5.06 (m, 1H), 5.93 (d, *J* = 1.0 Hz, 2H), 6.75–6.81 (m, 2H), 6.88 (d, *J* = 1.0 Hz, 1H).

(*E*)-3-Benzo[1,3]dioxol-5-yl-1-cyclopropyl-propenone (Diana et al., 1977): colorless oil. ^{1}H-MR (500 MHz, $CDC1_3$): δ: 1.12–1.15 (m, 2H), 1.25 (s, 2 H), 2.18–2.22 (m, 1H), 5.96 (d, *J* = 1.0Hz, 2H), 6.70 (d, *J* = 16.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.06 (d, *J* = 1.5Hz, 1H), 7.51 (d, *J* = 16.0 Hz, 1H).

1-Cyclopropyl-3-hydroxy-3-(4-methoxy-phenyl)-propan-1-one colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.88–0.91 (m, 2H), 1.05 (dd, *J* = 4.0, 8.0 Hz, 2H), 1.87–1.92 (m, 1H), 2.88 (dd, *J* = 3.5, 17.0 Hz, 1H), 2.96 (dd, *J* = 9.0, 17.5 Hz, 1H), 3.66 (d, *J* = 3.0 Hz, 1H), 3.76 (s, 3H), 5.05–5.08 (m, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H). Elemental analyses: calculated (%) for $C_{13}H_{16}O_3$ (220.11 g/mol): C 70.89, H 7.32, found: C 70.98, H 7.26.

1-Cyclopropyl-3-hydroxy-3-(3-methoxy-phenyl)-propan-1-one colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.88–0.92 (m, 2H), 1.03–1.09 (m, 2H), 1.87–1.92 (m, 1H), 2.90 (dd, *J* = 3.5, 17.5 Hz, 1H), 2.96 (dd, *J* = 8.5, 17.5 Hz, 1H), 3.77 (d, *J* = 6.5 Hz, 3H), 4.58 (s, 1H), 5.10 (dd, *J* = 3.5, 8.5 Hz, 1H), 6.80 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.88–6.92 (m, 2H), 7.21–7.25 (m, 1H). Elemental analyses: calculated (%) for $C_{13}H_{16}O_3$ (220.11 g/mol): C 70.89, H 7.32, found: C 70.96, H 7.25.

Acetic acid 4-(3-cyclopropyl-1-hydroxy-3-oxo-propyl)-phenyl ester colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.91–0.93 (m, 2H), 1.06–1.09 (m, 2H), 1.89–1.93 (m, 1H), 2.28 (d, *J* = 2.0 Hz, 3H), 2.93 (dd, *J* = 0.5, 8.0 Hz, 2H), 3.67 (d, *J* = 3.0 Hz, 1H), 5.12–5.15 (m, 1H), 7.04–7.07 (m, 2H), 7.33–7.38 (m, 2H). Elemental analyses: calculated (%) for $C_{14}H_{16}O_4$ (248.10 g/mol): C 67.73, H 6.50, found: C 67.85, H 6.56.

(*E*)-Acetic acid 4-(3-cyclopropyl-3-oxo-propenyl)-phenyl ester colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.96–1.00 (m, 2H), 1.15–1.18 (m, 2H), 2.22–2.25 (m, 1H), 2.32 (d, *J* = 3.5 Hz, 3H), 6.83 (d, *J* = 16.0 Hz, 1H), 7.12–7.15 (m, 2H), 7.57–7.60 (m, 3H). Elemental analyses: calculated (%) for $C_{14}H_{14}O_3$ (230.09 g/mol): C 73.03, H 6.13, found: C 73.16, H 6.21.

1-Cyclopropyl-3-hydroxy-3-(4-nitro-phenyl)-propan-1-one (Siyutkin et al., 2010): pale yellowish oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.96–1.01(m, 2H), 1.08–1.16 (m, 2H), 1.91–1.96 (m, 1H), 2.95 (dd, *J* = 9.0, 18.0 Hz, 1H), 3.03 (dd, *J* = 3.0, 15.0 Hz, 1H), 3.82 (d, *J* = 3.0 Hz, 1H), 5.25–5.28 (m, 1H), 7.54–7.57 (m, 2H), 8.20–8.23 (m, 2H).

(*E*)-1-Cyclopropyl-3-(4-nitro-phenyl)-propenone (Hercouet and Le Corre, 1977): pale yellowish oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 1.03–1.06 (m, 2H), 1.20–1.25 (m, 2H), 2.23–2.28 (m, 1H), 6.98 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 16.0 Hz, 1H), 7.71–7.73 (m, 2H), 8.25–8.28 (m, 2H).

1-Cyclopropyl-3-hydroxy-3-(3-nitro-phenyl)-propan-1-one (Siyutkin et al., 2010): pale yellowish oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.96–1.00 (m, 2H), 1.01–1.15 (m, 2H), 1.92–1.97 (m, 1H), 2.98 (dd, *J* = 9.0, 18.0 Hz,1H), 3.06 (dd, *J* = 3.5, 17.5 Hz, 1H), 3.87 (d, *J* = 3.0 Hz, 1H), 5.24–5.27 (m, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 8.12–8.14 (m, 1H), 8.26 (t, *J* = 1.5 Hz, 1H).

3-(2-Chloro-6-fluoro-phenyl)-1-cyclopropyl-3-hydroxy-propan-1-one colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.92–0.95 (m, 2H), 1.10 (t, *J* = 4.5 Hz, 2H), 1.94–1.99 (m, 1H), 2.97 (dd, *J* = 3.5, 17.0 Hz, 1H), 3.37 (s, 1H), 3.44 (dd, *J* = 9.5, 17.5 Hz, 1H), 5.76 (d, *J* = 9.5 Hz, 1H), 6.98–7.02 (m, 1H), 7.16–7.28 (m, 2H). Elemental analyses: calculated (%) for $C_{12}H_{12}ClFO_2$ (242.05 g/mol): C 59.39, H 4.98, found: C 59.46, H 4.91.

(*E*)-3-(2-Chloro-6-fluoro-phenyl)-1-cyclopropyl-propenone colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.99–1.03 (m, 2H), 1.18–1.21 (m, 2H), 2.22–2.27 (m, 1H), 7.03–7.07 (m, 1H), 7.14 (d, *J* = 1.0 Hz, 1H), 7.25–7.27 (m, 2H), 7.81 (d, *J* = 16.5 Hz, 1H). Elemental analyses: calculated (%) for $C_{12}H_{10}ClFO$ (224.04 g/mol): C 64.15, H 4.49, found: C 64.28, H 4.43.

1-Cyclopropyl-3-hydroxy-3-thiophen-2-yl-propan-1-one (Downey and Johnson, 2007): colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.92 (dd, *J* = 3.5, 8.0 Hz, 2H), 1.04–1.09 (m, 2H), 1.91–1.95 (m, 1H), 3.02–3.12 (m, 2H), 3.88 (d, *J* = 3.5 Hz, 1H), 5.35–5.38 (m, 1H), 6.94 (d, *J* = 3.0 Hz, 2H), 7.22 (t, *J* = 3.0 Hz, 1H).

(*E*)-1-Cyclopropyl-3-hydroxy-5-phenyl-pent-4-en-1-one colorless oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 0.92–0.97 (m, 2H), 1.07–1.14 (m, 2H), 1.93–1.98 (m, 1H), 2.86 (dd, *J* = 8.5, 17.0 Hz, 1H), 2.90 (dd, *J* = 3.5, 17.5 Hz, 1H), 3.32 (d, *J* = 2.0 Hz, 1H), 4.76 (s, 1H), 6.22 (dd, *J* = 6.0, 16.0 Hz,1H), 6.65 (dd, *J* = 0.5, 16.0 Hz, 1H), 7.22–7.26 (m, 1H), 7.30–7.37(m, 2H), 7.39 (d, *J* = 1.5 Hz, 2H). Elemental analyses: calculated (%) for $C_{14}H_{16}O_2$ (216.12 g/mol): C 77.75, H 7.46, found: C 77.83, H 7.40.

3-Hydroxy-3-phenyl-1-(4-methoxy-phenyl)-propan-1-one (Wei et al., 2004): pale yellowish oil. ^{1}H-NMR (500 MHz, $CDC1_3$): δ: 7.90–7.92 (m, 2H), 7.40–7.43 (m, 2H), 7.33–7.35 (m, 2H), 7.27–7.30 (m, 1H), 6.90–6.92 (m, 2H), 5.29–5.31 (m, 1H), 3.83 (s, 3H), 3.27–3.30 (m, 2H).

Typical experimental procedure of the MgI_2 etherate-promoted crossover direct-aldol of various aromatic aldehydes

A freshly prepared MgI_2 etherate (1 mmol) was added to a solution of 4-nitrobenzaldehyde (151 mg, 1 mmol), 4-anisaldehyde (136 mg, 1 mmol) and cyclopropyl methyl ketone (84 mg, 1.0 mmol) in CH_2Cl_2 (10 ml) at room temperature, followed by addition of Et_3N (121 mg, 1.2 mmol). After stirring for 30 min at room temperature, the reaction mixture was poured into saturated aqueous Na_2SO_3 solution. The resulting mixture was extracted with Et_2O and combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel eluting with PE/EtOAc to provide aldol adduct (R = 4-$NO_2C_6H_4$) in 96% yield.

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