Lewis base-catalysed Mukaiyama–aldol reaction of trimethylsilyl enolates with aldehydes

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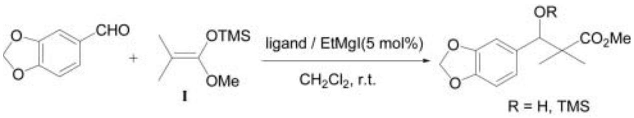
An efficient Mukaiyama-type aldol reaction of three typical silyl enolates, such as 1-(trimethylsiloxy)-1-methoxy-2-methyl-2-propene, 1-phenyl-1-trimethylsilyloxyethene and 1, 2-bis(trimethylsiloxy)cyclobutene, with aryl aldehydes and α,β–unsaturated aldehydes catalysed by 5 mol% of Lewis base catalyst 4-O_2NPhOMgI in dichloromethane is described. The reaction proceeds under mild reaction conditions in good to excellent yields.

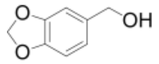
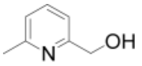
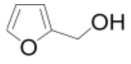
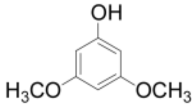
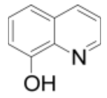
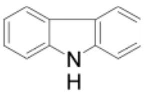
Keywords: aldehydes, trimethylsilyl enolates, Mukaiyama aldol, Lewis base

The aldol reaction is one of the most important methods for the formation of C–C bonds and is frequently employed in synthetic organic chemistry.[1–5] The Lewis acid-promoted Mukaiyama–aldol reaction has become very popular in the construction of carbon skeletons.[6–8] Recently, a Lewis base-catalysed aldol reaction of trichlorosilyl enolates with aldehydes by using phosphoramides was described by Denmark and Stavenger.[9] Hosomi and co-workers reported reactions using silyl enolates with an enhanced Lewis acidic silicon atom which reacted more readily with Lewis bases.[10] Another new method for the activation of silyl enolates was recently reported by Mukaiyama's group, which is the simple, mild, efficient and environmentally friendly aldol reaction of trimethylsilyl enolates with aldehydes in the presence of Lewis bases catalyst, such as lithium diphenylamide, lithium pyrrolidone, lithium alkoxides and lithium carboxylates in DMF or pyrridine.[11–13] We now describe a new catalytic aldol reaction of trimethylsilyl enolates with aldehydes by using 4-O_2NPhOMgI as Lewis base catalyst in dichloromethane.

Aminomagnesium halides or alkoxymagnesium halides prepared *in situ* by the reaction of a Grignard reagent with an amine or alcohol can efficiently promote Diels–Alder reactions in high yield and good enantioselectivity.[14,15] To the best of our knowledge, there are no prior descriptions of aldol reactions catalysed by alkoxymagnesium iodides. We now report the aldol reaction of aryl aldehydes with trimethylsilyl enolates in the presence of catalytic amounts of alkoxymagnesium iodide. Conventionally, such alkoxides were regarded as Brønsted bases and have never been used as the Lewis bases to activate the trimethylsilyl enolates having a hypervalent silicate. The Mukaiyama–aldol addition of a trimethylsilyl enolate (**I**) derived from methyl isobutyrate with piperonal was tested in CH_2Cl_2 by using 5 mol% catalytic amount of alkoxymagnesium iodide at room temperature. The reaction proceeded smoothly to provide the aldol adducts in good to excellent yields. Of all the alkoxymagnesium iodides screened, many species showed very efficient catalytic reactivity except for the bulkier tertiary alcohol (Table 1, entry 1). Amongst the alkoxymagnesium iodides prepared from the primary alcohols (Table 1, entries 2–4), the catalytic reactivity of entry 2 was better than that of entries 3 and 4. This is possibly due to the less Lewis acidity of magnesium(II) by the chelation with nitrogen atom or oxygen atom. In addition, the greater the acidity of the hydroxyl group of a substituted phenol, the better the catalytic reactivity that its aryloxymagnesium iodide possessed (Table 1, entries 5–7). However, due to coordination of the nitrogen atom with magnesium (II) the reaction proceeded sluggishly in entry 8. Interestingly, amino magnesium iodide and the thiomagnesium iodide showed the excellent catalytic character, respectively (Table 1, entries 9 and 10).

Table 1 The study of various alkoxymagnesium iodide on Mukaiyama–aldol reaction of silyl enolate **I** with piperonal



Entry	Ligand	Time/h	Yield/%[a]
1	^tBuOH	3	75
2		2	95
3		3	80
4		3	85
5	PhOH	1	93
6		**1**	94
7	4-O_2NPhOH	0.5	**98**
8		3	91
9	PhSH	2	96
10		**2**	95

[a]Isolated overall yield.

We examined the aldol addition of a trimethylsilyl enolate derived from methyl isobutyrate with piperonal in CH_2Cl_2 by using 5 mol% of 4-O_2NPhOMgI as a promoter at room temperature. The reaction proceeded efficiently to provide the aldol adducts in excellent yield (98%). Encouraged by these results, we explored the reaction of various aldehydes with 1-(trimethylsiloxy)-1-methoxy-2-methyl-2-propene (**I**), 1-phenyl-1-trimethylsilyloxyethene(**II**) and 1, 2-bis(trimethyl siloxy)cyclobutene (**III**) catalysed by 4-O_2NPhOMgI, respectively. The results were listed in Table 2. As shown in Table 2, the three typical trimethylsilyl enolates reacted smoothly with various aromatic aldehydes to afford the corresponding aldol adducts, such as β-hydroxy ester **1**, β-hydroxy ketone **2** and

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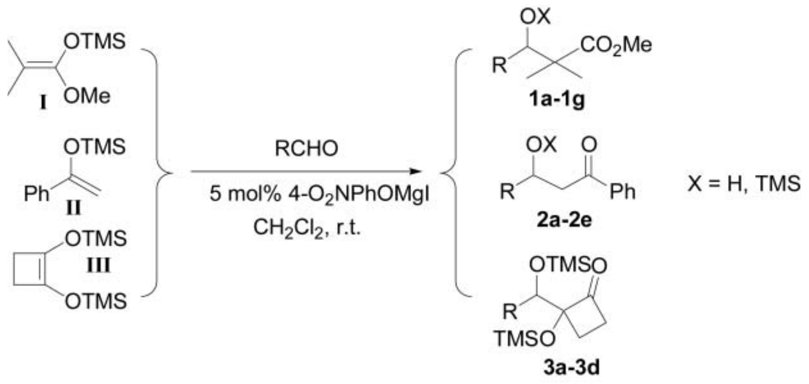
Table 2 4-$O_2NPhOMgI$-catalysed Mukaiyama–aldol reaction of various aldehydes with silyl enolates **I–III**



Entry	RCHO	Silyl enolates	Time/h	Product	Yield/%[a]
1	Piperonal	I	0.5	**1a**	98
2	2-$CH_3OC_6H_4CHO$	I	0.5	**1b**[b]	98
3	4-$(Me_2N)C_6H_4CHO$	I	0.5	**1c**[b]	96
4	C_6H_5CHO	I	4	**1d**	90
5	2-$CF_3C_6H_4CHO$	I	8	**1e**[b]	75
6	3-NCC_6H_4CHO	I	8	**1f**[b]	78
7	Geranial	I	4.	**1g**	75
8	C_6H_5CHO	II	4	**2a**	84
9	2-$MeOC_6H_4CHO$	II	1	**2b**	96
10	4-BrC_6H_4CHO	II	8	**2c**[b]	70
11	4-ClC_6H_4CHO	II	8	**2d**[b]	72
12	(*E*)-PhCH=CHCHO	II	3	**2e**[b]	75
13	C_6H_5CHO	III	7	**3a**	80 (*dr* 3:2)
14	2,5-$(MeO)_2C_6H_3$	III	1	**3b**	93 (*dr* 1:1)
15	2-$CH_3OC_6H_4CHO$	III	0.5	**3c**	95 (*dr* 7:2)[c]
16	4-$O_2NPhCHO$	III	10	**3d**	65 (*dr* 2:1)

[a] Isolated overall yield, ratio of diastereoselectivity of aldol product was determined by ^1H NMR analysis.
[b] The product was subjected to deprotection of TMS group.
[c] *dr* value was determined by the ratio of its corresponding diol acetonide using ^1H NMR analysis.

α-hydroxy cyclobutanone **3**, in good to excellent yields, respectively. Aromatic bearing an electron-donating group (i.e. *o*- or *p*-OMe, NMe_2) could give the desired aldol adducts in excellent yields (Table 2, entries 2–4, 9 and 14–15). Otherwise, aromatice aldehydes, which have an electron-withdrawing group (*i.e.* Cl, Br, CN, NO_2, CF_3), provided the products in moderate yields (Table 2, entries 5, 6, 10, 11, 16). Additionally, aliphatic aldehydes and ketones were unreactive under these conditions. When the conjugate aldehydes were used, only 1, 2-aldol adducts were generated in high yield without the accompanying 1, 4-adduct (Table 2, entries 7 and 12).

In conclusion, we have demonstrated the unique catalytic reactivity of alkoxymagnesium iodide as Lewis base in Mukaiyama–aldol condensation under mild reaction condition. Further investigations on other alkoxymagnesium iodide-catalysed bond formation reactions are being actively pursued in our lab.

Experimental

Silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90 ºC) were used for product purification by flash column chromatography. All solvents were purified and dried by standard techniques, and distilled prior to use. EtMgI etherate solution was prepared using standard procedures. ^1H NMR spectra were taken on a Bruker AM-500 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. All compounds were identified by ^1H NMR and are in good agreement with those reported.

Representative experimental procedure of 4-$O_2NPhOMgI$-catalysed Mukaiyama–aldol reaction

To a solution of piperonal (750 mg, 5 mmol) and 4-$O_2NPhOMgI$ (73 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was added dropwise 1-(trimethylsiloxy)-1-methoxy-2-methyl-2-propene (**I**) (1.04 g,6 mmol) under argon. After stirring for 30 min at that temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (5.0 mL). The resultant solution was extracted three times with Et_2O. The combined organic layers were successively washed with water and brine. The extract was dried over anhydrous $MgSO_4$ and evaporated under atmosphere pressure. Flash silica gel chromatography provided the desired aldol adducts in 98% yield.

Methyl 3-(benzo[d][1,3]dioxol-5-yl)-2,2-dimethyl-3-(trimethylsilyloxy) propanoate (**1a**):[16] IR (film) υ (cm^{-1}) 1737 (C=O), 1501, 1488, 1442, 1250. δ_H 0.01 (s, 9H), 1.01 (s, 3H), 1.14 (s, 3H), 3.69 (s, 3H), 4.91 (s, 1H), 5.97 (s, 2H), 6.73–6.82 (m, 3H).

Methyl 3-hydroxy-3-(2-methoxyphenyl)-2,2-dimethylpropanoate (**1b**):[17] IR (film) υ (cm^{-1}) 3432 (OH), 1722 (C=O), 1612, 1513, 1465, 1248. δ_H 1.11 (s, 3H), 1.21 (s, 3H), 3.60 (br s, 1H), 3.70 (s, 3H), 3.79 (s, 3H), 5.28 (s, 1H), 6.83–7.32 (m, 4H).

Methyl methyl 3-(4-(dimethylamino)phenyl)-3-hydroxy-2,2-dimethylpropanoate (**1c**):[18] IR (film) υ (cm^{-1}) 3405 (OH), 1727 (C=O), 1612, 1458, 1249. δ_H 1.11 (s, 3H), 1.16 (s, 3H), 2.96 (s, 6H), 3.73 (s, 3H), 4.84 (s, 1H), 6.73 (d, 2H, J = 8.8 Hz), 7.20 (d, 2H, J = 8.8 Hz).

Methyl 2,2-dimethyl-3-phenyl-3-(trimethylsilyloxy)propanoate (**1d**):[19] IR (film) υ (cm^{-1}) 1741 (C=O), 1586, 1452, 1434, 1251. δ_H 0.01 (s, 9H), 1.01 (s, 3H), 1.14 (s, 3H), 3.69 (s, 3H), 5.00 (s, 1H), 7.30 (s, 5H).

Methyl methyl 3-hydroxy-2,2-dimethyl-3-(2-(trifluoromethyl)phenyl) propanoate (**1e**): IR (film) υ (cm^{-1}) 3445 (OH), 1740 (C=O), 1561, 1453, 1252. δ_H 1.16 (s, 3H), 1.23 (s, 3H), 3.72 (d, 1H, J = 5.2 Hz), 3.8 (s, 3H), 5.34 (d, 1H, J = 5.0 Hz), 7.40-7.55 (m, 4H). HRMS (EI) Calcd for $C_{13}H_{15}F_3O_3$: 276.0973, Found for $[M]^+$: 276.0967.

Methyl 3-(3-cyanophenyl)-3-hydroxy-2,2-dimethylpropanoate (**1f**): IR (film) υ (cm^{-1}) 3433 (OH), 2250 (CN), 1738 (C=O), 1501, 1488, 1442, 1250. δ_H 1.15 (s, 3H), 1.17 (s, 3H), 3.38 (s, 1H), 3.77 (s, 3H), 4.97 (s, 1H), 7.30-7.66 (m, 4H). HRMS (EI) Calcd for $C_{13}H_{15}NO_3$: 233.1052, Found for $[M]^+$: 233.1045.

(E)-Methyl 2,2,5,9-tetramethyl-3-(trimethylsilyloxy)deca-4,8-dienoate (**1g**):[16] IR (film) υ (cm^{-1}) 1739 (C=O), 1456, 1383, 1254. δ_H 0.01 (s, 9H), 0.93 (s, 3H), 1.12 (s, 3H), 1.54–1.72 (m, 9H), 1.97–2.10 (m, 4H), 3.63 (s, 3H), 4.59 (d, 1H, J = 9.4 Hz), 5.06–5.11 (m, 2H).

1-Phenyl-3-phenyl-3-(trimethylsilyloxy)propan-1-on (**2a**):[20] IR (film) υ (cm^{-1}) 1789 (C=O), 1494, 1452, 1253. δ_H 0.01 (s, 18H), 1.76–2.81 (m, 4H), 4.71 (s, 0.4H) and 4.75 (s, 0.6H), 7.29–7.36 (m, 5H).

1-(2-Methoxyphenyl)-3-phenyl-3-(trimethylsilyloxy)propan-1-on (**2b**):[16] IR (film) υ (cm^{-1}) 1686 (C=O), 1598, 1489, 1247. δ_H 0.01 (s, 9H), 3.18–3.30 (m, 2H), 3.86 (s, 3H), 5.73 (dd, 1H, J = 8.2, 3.6 Hz), 6.85–8.06 (m, 9H).

3-(4-Bromo-phenyl)-3-hydroxy-1-phenyl-propan-1-one (**2c**): IR (film) υ (cm^{-1}) 3464 (OH), 1665 (C=O), 1592, 1577, 1490, 1446, 1212. δ_H 3.32 (d, 2H, J = 6.0 Hz), 3.76 (br s, 1H), 5.30 (t, 1H, J = 6.0 Hz), 7.26–7.96 (m, 9H). HRMS (EI) Calcd for $C_{15}H_{13}BrO_2$: 304.0099, Found for [M]$^+$: 304.0089.

3-(4-Chloro-phenyl)-3-hydroxy-1-phenyl-propan-1-one (**2d**):[21] IR (film) υ (cm^{-1}) 3466 (OH), 1667 (C=O), 1593, 1578, 1493, 1446, 1213. δ_H 3.34 (d, 2H, J = 6.0 Hz), 3.75 (br s, 1H), 5.32 (t, 1H, J = 6.0 Hz), 7.26–7.96 (m, 9H).

(E)-3-Hydroxy-1,5-diphenylpent-4-en-1-one (**2e**):[21] IR (film) υ (cm^{-1}) 3447 (OH), 1681 (C=O), 1597, 1097, 1211. δ_H 3.30 (d, 2H, J = 6.0 Hz), 3.52 (br s, 1H), 4.98 (dd, 1H, J = 7.4, 6.0 Hz), 6.34 (dd, 1H, J = 16.2, 6.0 Hz), 6.73 (d, 1H, J = 16.2 Hz), 7.24–8.05 (m, 10H).

2-(Phenyl(trimethylsilyloxy)methyl)-2-(trimethylsilyloxy)cyclobutanone (**3a**):[22] IR (film) υ (cm^{-1}) 1789 (C=O), 1494, 1452, 1253. δ_H 0.01 (s, 18H), 1.76–2.81 (m, 4H), 4.71 (s, 0.4H) and 4.75 (s, 0.6H), 7.29–7.36 (m, 5H).

2-((2,5-Dimethoxyphenyl)(trimethylsilyloxy)methyl)-2-(trimethylsilyloxy)cyclobutanone (**3b**):[16] IR (film) υ (cm^{-1}) 1785 (C=O), 1497, 1462, 1252. δ_H 0.02 (s, 9H), 0.05 (s, 9H), 1.80–2.83 (m, 4H), 3.71 (s, 3H), 3.77 (s, 3H), 5.29 (s, 1H), 6.75–7.88 (m, 3H).

2-((2-Methoxyphenyl)(trimethylsilyloxy)methyl)-2-(trimethylsilyloxy) cyclobutanone (**3c**):[16] IR (film) υ (cm^{-1}) 1786 (C=O), 1612, 1512, 1250. δ_H 0.01 (s, 9H), 0.02 (s, 9H), 1.65–2.80 (m, 4H), 3.80 (s, 3H), 4.66 (s, 0.5 H) and 4.70 (s, 0.5 H), 6.80–7.31 (m, 4H).

2-((4-Nitrophenyl)(trimethylsilyloxy)methyl)-2-(trimethylsilyloxy) cyclobutanone (**3d**):[16] IR (film) υ (cm^{-1}) 1788 (C=O), 1607, 1532, 1253. δ_H 0.01–0.21 (m, 18H), 1.62–2.91 (m, 4H), 5.81 (s, 0.6 H) and 5.86 (s, 0.4 H), 7.35–7.91 (m, 4H).

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