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Auxiliary induced asymmetric Michael-aldol reaction under kinetic and thermodynamic conditions

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Abstract

Asymmetric intramolecular Michael-aldol reaction of (−)-phenylmenthyl enoates **1** affords tricyclic cyclobutanes **2** in excellent diastereoselectivity. It is made clear that Michael-aldol reaction is reversible under conditions using trimethylsilyl iodide (TMSI) in the presence of hexamethyldisilazane (HMDS) at ambient temperature. The difference of stereoselectivity under kinetic or thermodynamic conditions are reported.

Keywords: asymmetric reactions; isomerism; cyclobutanes; Michael-aldol reactions.

We have described the convenient construction of polycyclic cyclobutanes from α,β-unsaturated esters having ketocarbonyl group by intramolecular Michael-aldol reaction,[1] which can highly control the relative configuration of four or five stereogenic centers. The asymmetric modification of the reaction would provide an extremely potent synthetic methodology to obtain optically pure cyclobutanes.[2] Now, we report the asymmetric Michael-aldol reaction induced by chiral auxiliary. Since 8-arylmenthols had been utilized as effective chiral inducer in the conjugate addition and cycloaddition reactions,[3,4] we planned to use (−)-8-phenylmenthol for asymmetric Michael-aldol reaction.

The substrates **1a** and **1b** were easily prepared from the corresponding ketoaldehyde[1b] by Wittig reaction. Intramolecular Michael-aldol reaction was carried out under TMSI–HMDS conditions,[5,6] which have been established by us for non-asymmetric version.[1b,1d] The treatment of ketoesters **1a** and **1b** with TMSI–HMDS or TMSOTf–HMDS in CH_2Cl_2 afforded tricyclo[5.4.0.0^{3,7}]undecane and tricyclo[5.3.0.0^{3,7}]decane compounds, respectively (Scheme 1 and Table 1).[7] At ambient temperature, Michael-aldol reaction of **1a** afforded a mixture of diastereomers **2a** and **3a**, which were separable by column chromatography on silica gel (entries 1 and 2). After the elimination of auxiliary of **2a** and **3a** by DIBAL-H, the resulting diols were characterized as **5** and its antipode. The specific rotations,

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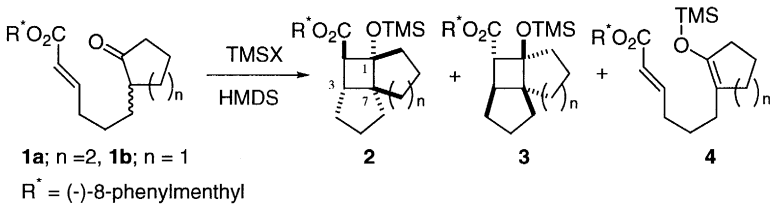
$[\alpha]_D^{26}$ (c 1.0, $CHCl_3$), of the diols derived from **2a** and **3a** were −26.6 and +26.1, respectively. The relative stereochemistry was identical with the known diol.[1b] The absolute configuration of **2a** was determined by circular dichroism of the spiro cyclohexanone **6**[8] ($[\theta]$=+886, λ=308.6 nm). The application of the octant rule suggested (*R*)-configuration of the spiro carbon. Accordingly, **2a** has (1*S*,2*R*,3*R*,7*R*)-tricyclo[5.4.0.0^{3,7}]undecane structure. At the lower temperature, the diastereoselectivity of **2a** remarkably improved and the yield of the silyl enol ether **4** decreased (entries 3–5). Especially, the reaction, carried out at −78°C, resulted in 85% yield of **2a** with perfect selectivity. When **1a** was treated with TMSOTf–HMDS, although the diastereoselectivity was not different, the reaction rate was remarkably slow at lower temperature (entries 6 and 7). The cyclopentanone **1b** also furnished the Michael-aldol adducts **2b** and **3b** and excellent selectivity was achieved at −78°C (entries 8 and 9).

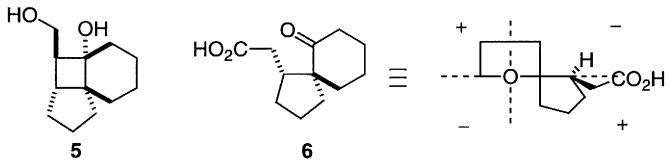


Scheme 1.

Table 1
Asymmetric Michael-aldol reactions of **1**

entry	substrate	reagent	temp (°C)	time (h)	yield (%) 2	3	4	de (%)[f]
1[a]	**1a**	TMSI–HMDS	rt	1	44	6	38	76
2[a]	**1a**	TMSI–HMDS	rt	11	30	15	33	33
3[a]	**1a**	TMSI–HMDS	0	9	55	6	23	80
4[a]	**1a**	TMSI–HMDS	–30	9	76	3	15	92
5[a]	**1a**	TMSI–HMDS	–78	11	85	0	0	100
6[b]	**1a**	TMSOTf–HMDS	rt	14	29	15	30	32
7[c]	**1a**	TMSOTf–HMDS	–30	15	35	trace	7	~95
8[d]	**1b**	TMSI–HMDS	rt	8	70[e]	9[e]	0	77
9[d]	**1b**	TMSI–HMDS	–78	20	73[e]	0	0	100

[a] TMSI (1.2 eq)–HMDS (1.5 eq) [b] TMSOTf (1.2 eq)–HMDS (1.5 eq) [c] TMSOTf (3.0 eq)–HMDS (3.0 eq) [d] TMSI (1.5 eq)–HMDS (1.5 eq) [e] The configuration was determined based on the reaction mechanism. [f] The diastereomeric excess (de) was determined based on isolated yield. de = (**2** – **3**) / (**2** + **3**).



The results of the experiments at room temperature (Table 1, entries 1 and 2) indicated that TMSI–HMDS conditions afforded thermodynamic equilibrium between **2a** and **3a**. The correlation between the diastereomeric proportion and the reaction time at room temperature was investigated to throw light on the thermodynamic behavior of the reaction (Fig. 1). After 1 h, **2a** was populated by about seven times more than **3a**. As the reaction time was longer, the ratio of **3a** increased, and finally the diastereomeric ratio equilibrated (**2a**:**3a** 11:9).

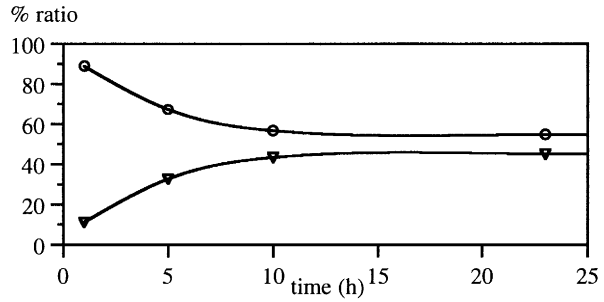


Fig. 1. Time course for the diastereomeric proportion of **2a** (◯) and **3a** (▽)

The reaction mechanism and the stereoselectivities can be explained as follows. Initially the thermodynamically stable silyl enol ether **4** was generated from **1** under TMSI–HMDS conditions.[5] Then, Mukaiyama-type Michael addition and successive aldol reaction were promoted to give **2** and/or **3**. At low temperatures the diastereofacial selection was controlled by π-stacking effect of phenylmenthol,[9] as expected, to give **2** (Fig. 2). Even at ambient temperature, the kinetic product **2** was initially preferred. However, retro-Michael-aldol reaction was gradually promoted by TMSI–HMDS, and consequently the isomerization of Michael-aldol adducts occurred via the silyl enol ether **4** to provide a mixture of **2** and **3**. Actually, the treatment of isolated **2a** with TMSI and HMDS at room temperature afforded a mixture of **2a**, **3a** and **4a**.

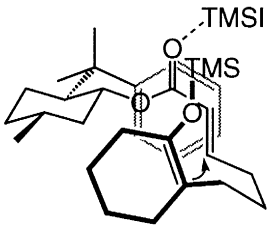
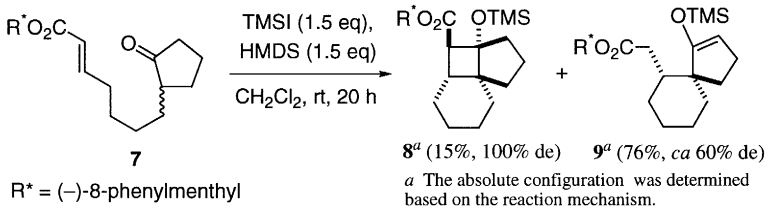


Fig. 2. Diastereofacial selection of **1a**

Exposure of cyclopentanone **7** to TMSI–HMDS at room temperature gave tricyclo-undecane **8** and the mono-Michael adduct **9** in 15% and 76% yield, respectively (Scheme 2). Though the yield of **8** was unsatisfactory, the pseudo-antipode of **8** was not detected. The formation of **9** provides supporting evidence that the cyclization is promoted through a stepwise mechanism.



Scheme 2.

In summary, we have developed an effective method for the construction of optically pure tricyclic cyclobutanes via asymmetric Michael-aldol reaction. We found that Michael-aldol reaction is reversible under TMSI–HMDS conditions at ambient temperature; the stereoselectivities are dependent on the reaction temperature and time. It is noteworthy that the four stereogenic centers can be entirely controlled by 8-phenylmenthol chiral auxiliary at −78°C.

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7. The asymmetric Michael-aldol reaction was performed by the procedure in Ref. 1b. Selected data for the Michael-aldol adduct **2a**: colorless oil; $[\alpha]_D^{27}$ (c 1.1, $CHCl_3$) −23.4; IR (neat) ν 2950, 1715, 1250, 1200, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.23 (m, 4H), 7.19–7.12 (m, 1H), 4.85 (ddd, 1H, *J*=10.8, 10.8, 4.4 Hz), 2.36 (d, 1H, *J*=7.7 Hz), 2.26 (dd, 1H, *J*=8.0, 4.0 Hz), 2.22 (m, 1H), 2.00–1.85 (m, 3H), 1.78–0.72 (m, 18H), 1.33 (s, 3H), 1.23 (s, 3H), 0.86 (d, 3H, *J*=6.6 Hz), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 151.1, 128.0, 125.6, 125.3, 75.1, 74.2, 52.7, 52.6, 50.3, 41.9, 40.1, 39.4, 34.7, 34.5, 34.3, 31.7, 31.3, 30.3, 28.5, 27.0, 25.1, 25.0, 22.5, 21.7, 19.8, 1.7. HRMS calcd for $C_{31}H_{48}O_3Si$ (M^+): 496.3370, found 496.3369.
8. Cyclohexanone **6** was obtained by the treatment of **2a** with TBAF, followed by hydrolysis with NaOMe.
9. For a review of π-stacking effects in asymmetric synthesis, see: Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475–497.