Stereoselective Vinylogous Mukaiyama Aldol Reaction of \( \alpha \)-Haloenals

Yoichi Iwasaki, Ryosuke Matsui, Takahiro Suzuki, Atsuo Nakazaki, and Susumu Kobayashi*

Faculty of Pharmaceutical Sciences, Tokyo University of Science; 2641 Yamazaki, Noda, Chiba 278-8510, Japan.

Received January 11, 2011; accepted January 27, 2011; published online January 31, 2011

We have developed a high-yielding and stereoselective vinylogous Mukaiyama aldol reaction (VMAR) of \( \alpha \)-haloenals. Contrary to the simple \( \alpha,\beta \)-unsaturated aldehyde, \( \alpha \)-haloenals were found to be reactive affording the corresponding VMAR adducts in excellent yields. Some transformations of VMAR adducts by Pd-mediated cross-coupling were also examined in order to demonstrate the synthetic utility of VMAR of \( \alpha \)-haloenals.

Key words \( \alpha \)-vinylogous Mukaiyama aldol reaction; \( \alpha \)-haloenal; stereoselectivity; cross-coupling

We previously reported a highly stereoselective vinylogous Mukaiyama aldol reaction (VMAR) using vinylketene silyl \( N,O \)-acetal 1 and 2, which provides a unique and remarkable entry to a remote asymmetric induction (Chart 1).

From a synthetic point of view, this method can directly afford the anti-\( \delta \)-hydroxy-\( \alpha,\gamma \)-dimethyl-\( \alpha,\beta \)-unsaturated carbonyl unit which is seen in many naturally occurring products. Indeed, VMAR has successfully been utilized in natural product syntheses by many groups including ourselves. However, \( \alpha,\beta \)-unsaturated aldehyde is not generally a good substrate for VMAR in terms of yield (i.e., low to moderate). High yield could be achieved by the addition of a catalytic amount of water, or by carrying out the reaction for a prolonged period of time. In this context, we became interested in the employment of \( \alpha \)-haloenals as substrates which are considered to be much more reactive compared to simple enals. We also reasoned that the VMAR products from \( \alpha \)-haloenals could serve as versatile intermediates for introducing a variety of substituents using well-established Pd-mediated methodologies. Herein, we report a high-yielding and stereoselective VMAR of \( \alpha \)-haloenals achieved under standard conditions (TiCl\(_4\) in CH\(_2\)Cl\(_2\), 2.0 eq of aldehyde). Some transformations of VMAR products from \( \alpha \)-haloenals by Pd-catalyzed cross-coupling are also described.

In this study, we examined VMAR of \( \alpha \)-iodoenal 3a, \( \alpha \)-bromoenal 3b, and \( \alpha \)-chloroenal 3c as substrates which are considered to be much more reactive compared to simple enals. We also reasoned that the VMAR products from \( \alpha \)-haloenals could serve as versatile intermediates for introducing a variety of substituents using well-established Pd-mediated methodologies. Herein, we report a high-yielding and stereoselective VMAR of \( \alpha \)-haloenals achieved under standard conditions (TiCl\(_4\) in CH\(_2\)Cl\(_2\), 2.0 eq of aldehyde). Some transformations of VMAR products from \( \alpha \)-haloenals by Pd-catalyzed cross-coupling are also described.

In this study, we examined VMAR of \( \alpha \)-iodoenal 3a, \( \alpha \)-bromoenal 3b, and \( \alpha \)-chloroenal 3c as substrates which are considered to be much more reactive compared to simple enals. We also reasoned that the VMAR products from \( \alpha \)-haloenals could serve as versatile intermediates for introducing a variety of substituents using well-established Pd-mediated methodologies. Herein, we report a high-yielding and stereoselective VMAR of \( \alpha \)-haloenals achieved under standard conditions (TiCl\(_4\) in CH\(_2\)Cl\(_2\), 2.0 eq of aldehyde). Some transformations of VMAR products from \( \alpha \)-haloenals by Pd-catalyzed cross-coupling are also described.

Table 1. VMAR of \( \alpha \)-Haloenals

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>12</td>
<td>88</td>
<td>20 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>4</td>
<td>93</td>
<td>20 : 1</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>14</td>
<td>76</td>
<td>20 : 1</td>
</tr>
</tbody>
</table>

a) Diastereomeric ratio was determined by \(^1\)H-NMR analysis.

Chart 1. Vinylogous Mukaiyama Aldol Reaction

Chart 2. Determination of the Stereochemistry of 4a, 4b, and 4c

Reagents and conditions: (a) Me\(_4\)Sn, Pd(dba)\(_2\), Ph\(_3\)As, HMPA, 60 °C, 92%; (b) Me\(_4\)Sn, Pd(dba)\(_2\), HMPA, 60 °C, 11% (br sm 72%); (c) TBSOTf, i-Pr\(_2\)NEt, CH\(_2\)Cl\(_2\), 0 °C, 100%; (d) NaBH\(_4\), THF–H\(_2\)O, RT, 99%; (e) O\(_3\), CH\(_3\)Cl–MeOH, −78 °C then NaBH\(_4\), RT, 38%; (f) p-TsOH, acetone, RT, quant.
from 4a and 4b agreed with those of the known ent-4d.31
(Synthetic 4d: [α]2525° = 17.3, c = 1.09 in CH2Cl2, reported ent-4d:
[α]2525° = 16.5, c = 1.16 in CH2Cl2).
Stereochemistry of the aldol adduct 4c was determined by
transforming to the known compound 6.31 After protection of
the secondary alcohol with TBSOTf, the chiral auxiliary
were recorded on a JASCO FT/IR-410 spectrometer using NaCl (neat) or
well-established Pd-catalyzed cross-coupling has been
ployed to vinyl iodide
ability of the present approach
of enals in VMAR by employing
General Procedure for Vinylogous Mukaiyama Aldol Reaction of
Vinylketene Silyl N,O-Acetal 2 with α-Haloenals
To a solution of aldehyde (1.41 mmol, 2.0 eq) in CH2Cl2 (3.5 ml), a 1.0 M TiCl4 solution in
CH2Cl2 (0.70 ml, 0.70 mmol, 1.0 eq) was added dropwise at –78 °C. Then a solution of 1 (239 mg, 0.705 mmol) in CH2Cl2 (3.5 ml) was added
drops of acetonitrile solution of saturated NaHCO3aq. and saturated Rochelle salt aq. (25 ml). The mixture was di-
used with Et2O (25 ml) and stirred vigorously at room temperature until the
white slurry was completely dissolved. The aqueous layer was separated times with Et2O. The combined organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt) to give the aldol adducts.
Aldol adduct 4a: TLC, Rf = 0.28 (hexane/AcOEt = 2: 1). mp 114 °C. H-NMR (600 MHz, CDCl3) δ: 0.86 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.9 Hz), 0.94 (3H, d, J = 7.0 Hz), 1.84 (3H, d, J = 6.4 Hz), 2.02 (3H, d, J = 1.3 Hz), 2.36 (1H, dq, J = 4.7, 7.0, 6.9 Hz), 2.94 (1H, ddq, J = 10.5, 9.0, 6.6 Hz), 3.30 (1H, dd, J = 9.0, 2.4 Hz), 3.64 (1H, dd, J = 9.1 Hz), 4.35 (1H, dd, J = 9.1, 9.1 Hz), 4.58 (1H, dd, J = 9.1, 5.6 Hz), 5.82 (1H, dq, J = 10.5, 1.3 Hz), 6.02 (1H, q, J = 6.4 Hz). 13C-NMR (150 MHz, CDCl3) δ: 14.3, 15.2, 16.0, 17.8, 21.4, 28.5, 40.0, 58.1, 63.5, 81.7, 113.9, 133.0, 135.3, 154.4, 171.3. [α]2525° = -26 (c = 1.0, CHCl3). IR (CHCl3, cm−1) 2664, 2465, 2769, 1769, 1676, 1368, 1301, 1209; high resolution (HR)-MS (electrospray ionization) (ESI) m/z: 444.0644 (Calcd for C22H23NO3Na+ [M+Na]+ 444.0642).
Aldol adduct 4b: TLC, Rf = 0.52 (hexane/AcOEt = 2: 1). IR (CHCl3, cm−1) 3078, 2965, 2875, 1770, 1655, 1445, 1367, 1301, 1209. HR-MS (ESI) m/z: 396.0786 (Calcd for C21H22NO3NaBr [M+Br]− 396.0780).
Aldol adduct 4c: TLC, Rf = 0.29 (hexane/AcOEt = 2: 1). IR (CHCl3, cm−1) 3005, 2965, 2925, 2870, 1770, 1639, 1367, 1315, 1209; HR-MS (ESI) m/z: 392.1281 (Calcd for C21H21NO3Na+ [M+Na]+ 392.1286).
Aldol adduct 4d: TLC, Rf = 0.34 (hexane/AcOEt = 2: 1). IR (CHCl3, cm−1) 3078, 2965, 2875, 1770, 1655, 1445, 1367, 1301, 1209. HR-MS (ESI) m/z: 332.1822 (Calcd for C19H19NO3Na+ [M+Na]+ 332.1823).
Alcohol 5: To a solution of 4c (385 mg, 0.171 mmol) in CH2Cl2 (1.2 ml), i-Pr2NEI (0.61 ml, 0.350 mmol) and TBSOTf (0.064 ml, 0.280 mmol) was added at 0 °C. After stirring for 40 min, the reaction was quenched with MeOH. After stirring further 10 min, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt = 8: 1) to give the corresponding TBS ether (51.8, 100% yield). To a solution of the corresponding TBS ether (49.7 mg, 0.112 mmol) in THF (2.8 ml), NaH1 (29.6 mg, 0.783 mmol) in water (0.6 ml) was added at 0 °C. After stirring for 3 h at r.t., the reaction was di-
used with water and Et2O. The aqueous layer was extracted twice with Et2O and the combined organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt = 8: 1) to give alcohol 5 (35.2 mg, 99% yield). Alcohol 5: colorless oil. TLC,
Alcohol 6: Alcohol 5 (12.1 mg, 0.0379 mmol) was distilled in 1:1 CHCl3/MeOH (2.0 mL) and cooled to −78 °C. Ozone was bubbled through the solution until a blue tint was observed (about 3 min), and then argon was passed through the solution for 15 min, after which NaBH4 (11.5 mg, 0.330 mmol) was added. After stirring for 8 h at rt, the reaction was quenched with saturated NH4Cl aq. The aqueous layer was extracted twice with Et2O. The combined organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt = 2:1) to give the corresponding diol (3.4 mg, 38% yield). To a solution of the corresponding diol (2.2 mg, 9.39 mmol) in acetone (0.5 mL), p-TsOH (0.9 mg, 4.69 mmol) was added at rt. After stirring for 16 h, the reaction was neutralized with saturated NaHCO3 aq. The aqueous layer was extracted twice with Et2O. The combined organic layer was dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The residue was purifed by column chromatography on silica gel (elution with hexane/MeOH = 95:5) to give the corresponding diol (7.0 mg, quantitative yield). Alcohol 7a: To a solution of iodide 4a (30.0 mg, 0.071 mmol) in degassed HMPA (0.8 mL), Me3Sn (0.04 mL, 0.285 mmol), Pd(dba)2 (4.1 mg, 0.007 mmol) and AsPh3 (8.7 mg, 0.028 mmol) were added respectively at rt. After stirring for 40 min at 60 °C, the reaction mixture was poured into H2O. The mixture was diluted with Et2O and the aqueous layer was extracted twice with Et2O. The combined organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt = 6:1) to give 4b (20.2 mg, 92% yield).

Ethyl derivative 7a: To a solution of iodide 4a (10.7 mg, 0.025 mmol) in degassed HMPA (0.5 mL), Pd(dba)2 (1.5 mg, 0.0025 mmol) and AsPh3 (3.1 mg, 0.010 mmol) were added respectively at rt. Then a 1.08 mL Et3Zn solution in hexane (0.994 mL, 0.0102 mmol) was added dropwise at 0 °C. After stirring for 1 h at rt, reaction mixture was quenched with saturated NH4Cl aq. The aqueous layer was extracted twice with Et2O. The combined organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with hexane/AcOEt = 1:1) to give 7a (5.9 mg, 72% yield). Ethyl derivative 7a: TLC: Rf = 0.38 (hexane/AcOEt = 2:1). H-NMR (600 MHz, CDCl3, δ = 0.01 (3H, s), 0.86 (9H, s), 0.88 (3H, d, J = 6.9 Hz), 1.16 (1H, t, J = 6.2 Hz), 1.67 (3H, d, J = 1.3 Hz), 1.73 (3H, d, J = 6.6 Hz), 2.80 (1H, dqq, J = 9.7, 6.5, 6.9 Hz), 3.88 (1H, d, J = 6.5 Hz), 3.99 (2H, d, J = 6.2 Hz), 5.23 (1H, dq, J = 9.7, 13.3 Hz), 5.71 (1H, q, J = 6.6 Hz). 13C-NMR (150 MHz, CDCl3, δ = −5.1, −4.8, 13.4, 14.1, 17.4, 18.1, 25.7, 36.4, 69.1, 80.5, 121.5, 128.3, 135.4, 136.8. [M+Na]+ 3328, 2958, 2929, 2857, 1660, 1255, 1095, 1006. HR-MS (ESI) m/z: 341.1658 (Calcd for C16H31O2NaSiCl [M+Na]+ 341.1674).

Acknowledgement This research was supported in part by a Grant-in-Aid for Scientific Research (B) (KAKENHI No. 18390010) from the Japan Society for the Promotion of Science.

References and Notes
26) Especially, the electron-withdrawing ability of chloro group probably shortened the reaction time in the VMAR of α-chloroanil 3c.