Oxovanadium(ν)-induced di-selective oxidative homocoupling of boron enolates†

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Oxovanadium(ν)-induced di-selective oxidative coupling of (Z)-boron enolate was demonstrated to give the corresponding 2,3-disubstituted 1,4-diketone in a good yield. High selectivity (up to 94 : 6) was attained when the reaction was performed with VO(OPr-i)2Cl at –30 °C.

Oxidative coupling of enolates can directly afford a 1,4-dicarbonyl skeleton. This is one of the most straightforward approaches to construct such a skeleton, which is often found in natural products, medicinal compounds, organic materials, and their synthetic intermediates. So far, a lot of research has been conducted to develop this type of oxidative coupling reaction.1

The reaction focused on here is intermolecular oxidative homocoupling of ketone enolates. This kind of coupling reaction has been investigated since 1974, and the combination of various oxidants and enolates have been investigated to date.2 However, there is only limited information on the diastereoselective coupling reaction.3 This contrasts sharply with the oxidative homocoupling reaction of acyl enolates, in which the chiral auxiliaries can be utilized.4 As a special case, the enolate of (1R)-camphor was exhibited to undergo the stereoselective oxidative homocoupling.5 Recently, chiral cyclohexenones were revealed to be oxidatively coupled to afford the corresponding 1,4-diketones diastereoselectively.5e As a general strategy, the diastereoselective oxidative coupling of the metalated (S)-(-)-1-amino-2-methoxymethylpyrrolidine (SAMP) or its (R)-isomer, RAMP hydrazone, with iodine was reported,5d where the oxidative cleavage of the N–N bond of the hydrazone using ozone is required to obtain the corresponding ketones, and the overall yields remain low to moderate. Another approach for the diastereoselective synthesis includes the intramolecular oxidative coupling using a traceless tether such as titanium and silicon for two ketone enolates, although the tethered enolate intermediate requires a synthetic step for its preparation.1b,3b,4d

Boron enolates have been utilized in a variety of organic syntheses that include a stereoselective aldol reaction.5 Nevertheless, boron enolates have not been used for the oxidative homocoupling reaction to the best of our knowledge. In the present study, boron enolates are focused on from this point of view. So far, we have studied the oxidative carbon–carbon bond formation induced by oxovanadium(ν) compounds6 including the oxidative homo- and cross-coupling of silyl enol ethers to form the corresponding 1,4-diketones.5b Here, we report the oxidative homocoupling of boron enolates using oxovanadium(ν) compounds. Notably, a high yield with high dl-selectivity was exhibited.

Boron enolates were prepared via 1,4-hydroboration of enones (Scheme 1).7 This reaction was monitored by 1H NMR spectroscopy to check the conversion and geometric configuration. To a CDCl3 solution of enone 1a the THF solution of 9-borabicyclo[3.3.1]nonane(9-BBN) was added in the presence of MS4A at room temperature. After 2 h, the peaks for enone 1a disappeared in the 1H NMR spectrum. Instead, a characteristic quartet peak appeared at 5.55 ppm, assignable to the vinyl proton in boron enolate 2a. This enolate was formed as a sole diastereomer almost quantitatively.

† Electronic supplementary information (ESI) available: Details of the experimental procedures, and compounds characterization, including 1H and 13C NMR spectra, and X-ray crystallographic analysis for dl-3d and dl-3e. CCDC 969200 and 969201.

Scheme 1 Formation of boron enolate 2a and the oxidative homocoupling with VO(OEt)Cl2. * Yield of 3a = (mole of 3a) × 2/(mole of 1a) × 100.

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Its stereo-configuration was determined to be (Z)-form based on the observation of a NOE between the ortho-protons of the phenyl group and vinyl proton. To the thus-obtained boron enolate three molar equivalents of VO(OEt)Cl₂ were added at room temperature (Scheme 1). After 2 h, the mixture was subjected to aqueous work-up. The desired homocoupled product 3a was obtained in 82% yield, where the diastereomeric ratio (dl/meso) was 67 : 33. Propiophenone (4a) and 2-chloropropiophenone (5a) were observed as side products in this reaction (5% and 13% yields, respectively). The yield of 3a after a 5-minute reaction was comparable to that after 2 h (83%, Table 1, entry 2), indicating that the reaction proceeded fast. Lowering the amount of the oxidant to one molar equivalent caused the yield of 3a to decrease a little (76%, Table 1, entry 3). In this entry, $^{51}$V NMR was measured after the reaction. Consequently, the characteristic peak at −294 ppm for VO(OEt)Cl₂ disappeared to lead to a vanadium(IV) species (Fig. 1). Further decreasing the amount of the oxidant (0.5 molar equivalents) yielded 3a in 47% yield. These results show that the oxovanadium(V) oxidant formally works as a one-electron oxidant toward the boron enolate.

Various oxovanadium(V) oxidants were investigated, as summarised in Table 2. The alkoxy ligands in oxovanadium(V) compounds are known to affect the oxidation reaction. Their oxidizing capability was lower than that of VO(OEt)Cl₂. A lower temperature (−30 °C) increased diastereoselectivity (Table 2, entry 3). Finally, a satisfactory yield and diastereoselectivity was obtained at −30 °C for 19 h (96%, dl/meso = 94 : 6, Table 2, entry 4), although a scale-up reaction (100 mg scale) slightly decreased the selectivity even at −40 °C (Table 2, entry 5). These reaction conditions were used for the following investigation as optimized conditions. On the other hand, VO(OPr-i)₃ did not induce the oxidative coupling due to the lower oxidation capability (Table 2, entry 7). Other oxidants such as FeCl₃ and CuCl₂ did not induce the oxidative homocoupling (Table 2, entries 2 and 8). In the case of $\text{[Ce(NO₃)₆]₄[NH₄]₃}$ (CAN) as an oxidant, 3a was obtained in 53% yield with a low dl/meso selectivity.

Table 3 shows the scope of the substrates in the oxidative homocoupling using VO(OPr-i)₃, Cl as an oxidant. All of enones 1 used here were transformed to the corresponding boron enolate stereoselectively. Various p-substitutions of the phenyl group in the boron enolates 1b-f were investigated. Me-, TBSCO-, F-, Cl-, and CF₃groups were tolerated without the substitution effect to give the corresponding homocoupling products in high yields with high dl-selectivity (Table 3, entries 1–5). Instead of the phenyl group, the cyclohexyl group as an example for an aliphatic substrate underwent the homocoupling in 97% yield with a dl/meso selectivity ratio of 77 : 23 (Table 3, entry 6). In the case of (E)-chalcone (1h), the diastereoselectivity was lower although the yield was high (Table 3, entry 7). Considering the stereoselectivity based on the steric repulsion between the enolates, the dl-product is favorable in a chelation model and unfavorable in the non-chelation model (see Scheme S1 in the ESI†) as Schmitt and co-workers also discussed the related reaction mechanism in the intramolecular oxidative homocoupling reaction of ketone enolates. Oxovanadium alkoxide compounds are known to self-assemble to form a dimer,² so that the observed dl-selectivity may be accounted for by the intramolecular coupling in the dimer via the formation of the vanadium enolate species. A similar chelation model was also

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**Table 2** Investigation of oxidant in the oxidative homocoupling reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Yield of 3a&lt;sup&gt;dl&lt;/sup&gt; (%)</th>
<th>dl/meso ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;cl&lt;/sup&gt;</td>
<td>VO(OEt)Cl₂</td>
<td>0.5</td>
<td>rt</td>
<td>88</td>
<td>67 : 33</td>
</tr>
<tr>
<td>2</td>
<td>VO(OPr-i)₃Cl</td>
<td>0.5</td>
<td>rt</td>
<td>78</td>
<td>80 : 20</td>
</tr>
<tr>
<td>3</td>
<td>VO(OPr-i)₃Cl</td>
<td>0.5</td>
<td>−30</td>
<td>76</td>
<td>92 : 8</td>
</tr>
<tr>
<td>4</td>
<td>VO(OPr-i)₃Cl</td>
<td>19</td>
<td>−30</td>
<td>96</td>
<td>94 : 6</td>
</tr>
<tr>
<td>5&lt;sup&gt;r&lt;/sup&gt;</td>
<td>VO(OPr-i)₃Cl</td>
<td>24</td>
<td>−40</td>
<td>93</td>
<td>86 : 14</td>
</tr>
<tr>
<td>6</td>
<td>VO(OPr-i)₃</td>
<td>0.5</td>
<td>rt</td>
<td>Trace</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>FeCl₃</td>
<td>19</td>
<td>−30</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CuCl₂</td>
<td>19</td>
<td>−30</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CAN</td>
<td>19</td>
<td>−30</td>
<td>53</td>
<td>53 : 47</td>
</tr>
</tbody>
</table>

<sup>a</sup> NMR tube experiments.  
<sup>b</sup> H NMR yield.  
<sup>c</sup> Yield = (mole of 3a) / (mole of 1a) × 100.  
<sup>d</sup> Same as the result in Scheme 1.  
<sup>e</sup> 100 mg scale reaction.  
<sup>f</sup> Isolated yield.

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**Fig. 1** $^{51}$V NMR spectra of the authentic sample of VO(OEt)Cl₂ and after the reaction.
presented in the oxidative homocoupling of ester enolates using TiCl₄ to explain the dl-selectivity.¹¹

In conclusion, dl-selective oxidative coupling of (Z)-boron enolate was demonstrated to give the corresponding 2,3-disubstituted 1,4-diketone in a high yield. (Z)-Boron enolate was prepared by 1,4-hydroxymethylation of the enone, and it was used for the oxidative coupling reaction in one pot. Stereoselectivity strongly depended on the oxovanadium(v) oxidant and reaction temperature. High selectivity (up to 94 : 6) was attained when the reaction took place with VO(OPr-i)Cl at −30 °C. The mechanistic study and synthetic application are now underway.

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Notes and references


8 The diastereometric ratio of meso compounds was determined by ¹H NMR. The assignment for dl and meso compounds was according to the following reference: S. E. Drewes, C. J. Hogan, P. T. Kaye and G. H. P. Roos, J. Chem. Soc. Perkin Trans. 1, 1989, 1585–1591.

9 The diastereometric ratio of (dl)/meso was determined by ¹H NMR. The assignment for dl and meso compounds was performed as follows: (a) For 3b: H. Ikeda, T. Takasaki, Y. Takahashi, A. Konno, M. Matsumoto, Y. Hoshii, T. Aoki, T. Suzuki, J. L. Goodman and T. Miyashio, J. Org. Chem., 1999, 64, 1640–1649; (b) For 3c: S. G. A. Moinuddin, S. Hishiyama, M.-H. Cho, L. B. Davin and N. G. Lewis, Org. Biomol. Chem., 2003, 1, 2307–2313; (c) For 3d: the dl-isomer was determined with X-ray crystallographic analysis (CCDC-969201), see ESi; (d) For 3e: the dl-isomer was determined with X-ray crystallographic analysis (CCDC-969200), see ESi; (e) For 3f and 3g: although the assignments could not be confirmed, they are predicted according to the tendency of ¹H NMR spectra for 3b–3e and 3h.
