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# Oxovanadium(v)-induced diastereoselective oxidative homocoupling of boron enolates†

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Oxovanadium(v)-induced *dl*-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)$_2$Cl at −30 °C.
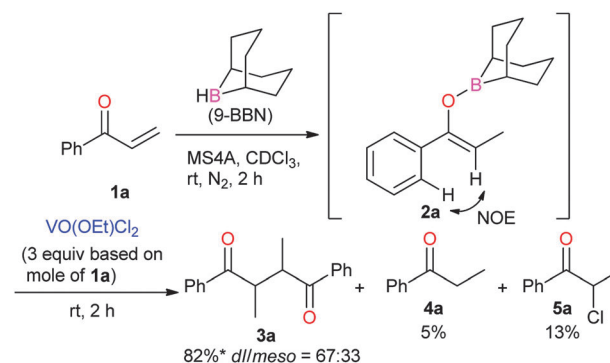
Oxidative coupling of enolates can directly afford a 1,4-dicarbonyl skeleton. This is one of the most straightforward approaches to construct such a skeleton, which is often found in natural products, medicinal compounds, organic materials, and their synthetic intermediates. So far, a lot of research 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.[3c] Recently, chiral cyclohexenones were revealed to be oxidatively coupled to afford the corresponding 1,4-diketones diastereoselectively.[3e] 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,[3a] 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,d]

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(v) compounds,[6] including the oxidative homo- and cross-coupling of silyl enol ethers to form the corresponding 1,4-diketones.[2j] Here, we report the oxidative homocoupling of boron enolates using oxovanadium(v) 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 ^{1}H NMR spectroscopy to check the conversion and geometric configuration. To a CDCl$_3$ 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 ^{1}H 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.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, and compounds characterization, including ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic analysis for *dl*-**3d** and *dl*-**3e**. CCDC 969200 and 969201. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc49624d



Scheme 1   Formation of boron enolate **2a** and the oxidative homocoupling with VO(OEt)Cl$_2$. * Yield of **3a** = (mole of **3a**) × 2/(mole of **1a**) × 100.

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)Cl$_2$ 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.[8] 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)Cl$_2$ 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 oxidation capability usually decreases with the increasing number of alkoxy groups in the complex. Reversely, it increases with the increasing number of the chlorides. The reaction with

**Table 1** Investigation of equivalents of VO(OEt)Cl$_2$ and reaction time in the oxidative homocoupling reaction[a]

$$\mathbf{1a} \xrightarrow[\text{MS4A, CDCl}_3\text{, rt, N}_2\text{, 2 h}]{\text{9-BBN}} [\mathbf{2a}] \xrightarrow[\text{rt, time}]{\text{VO(OEt)Cl}_2\text{ (equiv)}} 0.5\ \mathbf{3a}$$

| Entry | Molar equiv. of VO(OEt)Cl$_2$[b] | Time | Yield of **3a**[c,d] (%), *dl/meso* ratio |
|---|---|---|---|
| 1[e] | 3 | 2 h | 82, 67:33 |
| 2 | 3 | 5 min | 83, 67:33 |
| 3 | 1 | 2 h | 76, 67:33 |
| 4 | 0.5 | 2 h | 47, 67:33 |

[a] NMR tube experiments. [b] Based on mole of **1a**. [c] $^1$H NMR yield. [d] Yield = (mole of **3a**) × 2/(mole of **1a**) × 100. [e] Same as the result in Scheme 1.
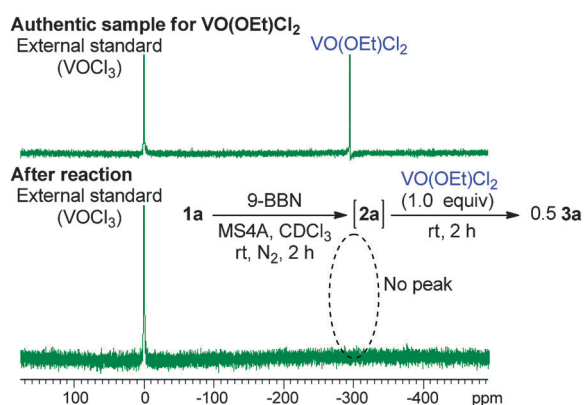


**Fig. 1** $^{51}$V NMR spectra of the authentic sample of VO(OEt)Cl$_2$ and after the reaction.

**Table 2** Investigation of oxidant in the oxidative homocoupling reaction[a]

$$\mathbf{1a} \xrightarrow[\text{MS4A, CDCl}_3\text{, rt, N}_2\text{, 2 h}]{\text{9-BBN}} [\mathbf{2a}] \xrightarrow[\text{temperature, time}]{\text{oxidant} \atop \text{(3 equiv based on mole of 1a)}} 0.5\ \mathbf{3a}$$

| Entry | Oxidant | Time (h) | Temperature (°C) | Yield of **3a**[b,c] (%), *dl/meso* ratio |
|---|---|---|---|---|
| 1[d] | VO(OEt)Cl$_2$ | 0.5 | rt | 88, 67:33 |
| 2 | VO(OPr-i)$_2$Cl | 0.5 | rt | 78, 80:20 |
| 3 | VO(OPr-i)$_2$Cl | 0.5 | −30 | 76, 92:8 |
| 4 | VO(OPr-i)$_2$Cl | 19 | −30 | 96, 94:6 |
| 5[e] | VO(OPr-i)$_2$Cl | 24 | −40 | 93,[f] 86:14 |
| 6 | VO(OPr-i)$_3$ | 0.5 | rt | Trace |
| 7 | FeCl$_3$ | 19 | −30 | 0 |
| 8 | CuCl$_2$ | 19 | −30 | 0 |
| 9 | CAN | 19 | −30 | 53, 53:47 |

[a] NMR tube experiments. [b] $^1$H NMR yield. [c] Yield = (mole of **3a**) × 2/(mole of **1a**) × 100. [d] Same as the result in Scheme 1. [e] 100 mg scale reaction. [f] Isolated yield.

VO(OPr-i)$_2$Cl resulted in **3a** in 78% yield with a *dl/meso* ratio of 80:20 (Table 2, entry 2), where the diastereoselectivity is higher as compared to that of VO(OEt)Cl$_2$ although the yield is a little lower than that of VO(OEt)Cl$_2$. 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 6). Other oxidants such as FeCl$_3$ and CuCl$_2$ did not induce the oxidative homocoupling (Table 2, entries 7 and 8). In the case of [Ce(NO$_3$)$_6$](NH$_4$)$_2$ (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)$_2$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-, TBSO-, F-, Cl-, and CF$_3$-groups were tolerated without the substitution effect to give the corresponding homocoupling products in high yields with high *dl*-selectivity (Table 3, entries 1–5).[9a–e] 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).[9e] In the case of (E)-chalcone (**1h**), the diastereoselectivity was lower although the yield was high (Table 3, entry 7).[8]

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 Schmittel and co-workers also discussed the related reaction mechanism in the intramolecular oxidative homo-coupling reaction of ketone enolates.[3b] Oxovanadium alkoxide compounds are known to self-assemble to form a dimer,[10] so that the observed *dl*-selectivity may be accounted for by the intra-molecular coupling in the dimer *via* the formation of the vanadium enolate species. A similar chelation model was also

**Table 3**  Substrate scope in the oxidative homocoupling reaction[a]



| Entry | Substrate | R$^1$ | R$^2$ | Yield of **3**[b,c] (%), dl/meso ratio |
|-------|-----------|-------|-------|----------------------------------------|
| 1 | **1b** | (4-methylphenyl) | H | 96, 94 : 6 |
| 2 | **1c** | TBSO—C$_6$H$_4$— | H | 98, 90 : 10 |
| 3 | **1d** | F—C$_6$H$_4$— | H | 92, 91 : 9 |
| 4 | **1e** | Cl—C$_6$H$_4$— | H | 94, 87 : 13 |
| 5 | **1f** | F$_3$C—C$_6$H$_4$— | H | 93, 85 : 15 |
| 6 | **1g** | cyclohexyl | H | 97, 77 : 23 |
| 7 | **1h** | Ph | Ph | 95, 76 : 24 |

[a] NMR tube experiments. [b] $^1$H NMR yield. [c] Yield = (mole of **3**) × 2/(mole of **1**) × 100.

presented in the oxidative homocoupling of ester enolates using TiCl$_4$ 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-hydroboration 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)$_2$Cl at −30 °C. The mechanistic study and synthetic application are now underway.

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