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# Oxazaborolidinone-Promoted Vinylogous Mukaiyama Aldol Reactions

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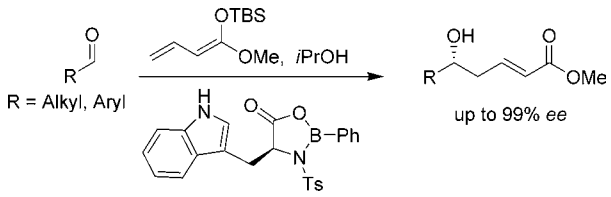
## ABSTRACT

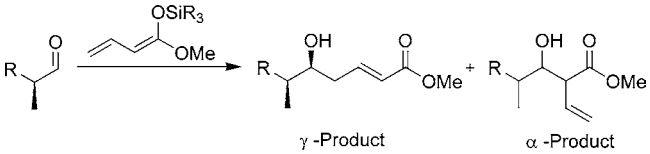



***δ*-Hydroxy-α,*β*-unsaturated carbonyl compounds were prepared in one step via the vinylogous Mukaiyama aldol reactions with *O*,*O*-silyl ketene acetals. Isopropyl alcohol as additive and tryptophane-based *B*-phenyloxazaborolidinone were required for obtaining the *γ*-alkylated product in high enantioselectivities.**

The increasing demand for new antibiotics and antitumor compounds led to a growing interest in biologically active compounds. In particular, polyketides proved to be attractive targets for biology-driven research. In this context, the rapid and efficient total synthesis of these natural products becomes increasingly important. Standard strategies for the construction of the polyketide framework parallel the biosynthesis of these compounds where acetate or propionate unites are joined.[1] Despite the reliable predictability and broad applicability of aldol or aldol-like reactions, new methods for the rapid access of larger polyketide frameworks could speed up the synthesis of new compounds.

With this background, different approaches to install stereoselective variations of the vinylogous Mukaiyama aldol reaction (VMAR) or vinylogous aldol reactions in general have been put forward, providing access to *δ*-hydroxy-α,*β*-unsaturated esters or lactones.[2−4] The vinylogous extension of the aldol reactions is associated with regioselectivity issues since addition to the ketene acetal can proceed in the α- or *γ*-position (Scheme 1).[5] We previously reported the tri-

**Scheme 1.** Regioselectivity in the VMAR




arylborane-catalyzed VMAR with unsubstituted silyl ketene acetals in high regio- and Felkin selectivities.[6]

Based on the wide range of applications for the vinylogous Mukaiyama aldol reaction, enantioselective variations became increasingly important, and we envisioned that amino

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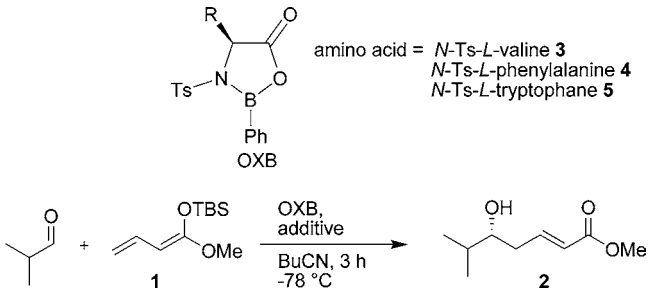
**Table 1.** Enantioselective VMAR with Isobutyraldehyde and Ketene Acetal **1** Catalyzed by OXB[a]




| | | | | γ-product **2** | |
|---|---|---|---|---|---|
| entry[a] | OXB (mol %) | additive | γ/α | yield[c,d] (%) | ee[e] (%) |
| 1 | **3** (20/100) | | 99:<1 | 38 | 0 |
| 2 | **4** (20/100) | | 99:<1 | 44 | 72 |
| 3 | **5** (20/100) | | 99:<1 | 32 | 74 |
| 4[b] | **3** (20) | *i*-PrOH | 99:<1 | 31 | 0 |
| 5[b] | **4** (20) | *i*-PrOH | 99:<1 | 46 | 83 |
| 6[b] | **5** (20) | *i*-PrOH | 99:<1 | 32 | 96 |
| 7[b,f] | **5** (20) | *i*-PrOH | 99:<1 | 44 | 96 |
| 8[b,f] | **5** (50) | *i*-PrOH | 99:<1 | 63 | 97 |
| 9[b,f] | **5** (100) | *i*-PrOH | 99:<1 | 75 | 98[e,g] |

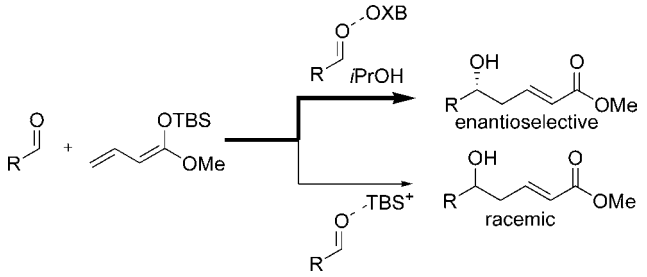
[a] 1.0 equiv of aldehyde and 1.2 equiv of ketene acetal **1**. [b] 1.2 equiv of additive. [c] Isolated yield after chromatography. [d] Additionally 3% racemic TBS-protected γ-product. [e] Determined by (+)-Eu(hfc)$_3$.[11] [f] By simultaneous addition of the starting materials and the additive via syringe pump. [g] Determined by chiral GC on TBS-protected compound.

acid based oxazaborolidinones[7] should promote the VMAR of ester-derived ketene acetals with high enantioselectivities. One of the major advantages of oxazaborolidinones compared to other chiral Lewis acids is their readily available access from sulfonamides of α-amino acids and boranes. Their valuable contribution to asymmetric synthesis was demonstrated by applications of the Yamamoto[8a] and Kiyooka[8b] protocol in Lewis acid catalyzed Mukaiyama aldol reactions. In particular, applications with *B*-phenyloxazaborolidinones were very effective in obtaining high yields and selectivities.

Herein, we report the enantioselective vinylogous Mukaiyama aldol reaction of *O*,*O*-silyl ketene acetals promoted by *B*-phenyloxazaborolidinones (OXB). Our initial studies to optimize the reaction conditions were performed using isobutyraldehyde and ketene acetal **1**[9] (Table 1). For the construction of the OXB catalysts, the amino acids valine, phenylalanine, and tryptophane were used. In initial experiments, only the γ-addition products were isolated in 32−44% yield (entries 1−3). While the use of OXB **3** only generated racemic mixtures of **2**, the OXBs **4** and **5** gave enantioselectivities between 72 and 74%, independent of the catalyst concentration.

In order to suppress the competing pathway of carbonyl activation through cationic silicon species,[10] which would result in racemic products (Scheme 2), isopropyl alcohol was used as a nucleophile. When the reaction was carried out with isopropyl alcohol and 20 mol % of **5** (entries 5 and 6, Table 1) an increase in enantioselectivity up to 96% was observed, albeit in moderate chemical yields.

**Scheme 2.** OXB-Activated Aldehyde vs $Si^+$-Activated Aldehyde




To improve the unexpected low yields, careful optimization of the reaction conditions was required. Higher yields were observed by simultaneous addition of the starting materials and the additive via syringe pump. The use of stoichiometric amounts of OXB **5** further improved the yield up to 75% with concomitant increase of the enantioselectivity to 98% ee (entry 9). On the other hand, changing the solvent to EtCN or $CH_2Cl_2$ did not improve the yields.

The resulting configuration is consistent with the proposed transition state for OXB-catalyzed aldol-type reactions (Figure 1),[8a,12] for which the observed configuration is based on shielding of the aldehyde's *si*-face through the indole moiety. In our case, the initial theory based configurational assignment was independently confirmed by the Mosher method.[13]

Next, we investigated the scope and limitations using different aldehydes (Table 2). At this point, it should be

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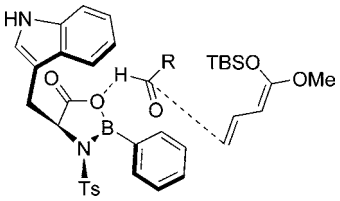


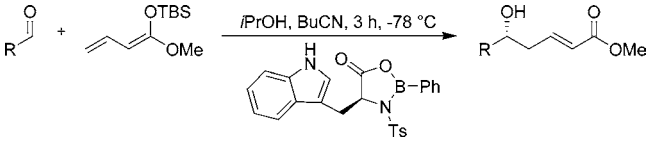
**Figure 1.** Proposed transition state for the VMAR using *N*-Ts-L-tryptophane.

pointed out that for many transformations aliphatics are the more challenging substrates.

Here, very good yields and selectivities were observed for aliphatic as well as for aromatic or unsaturated aldehydes. As observed previously, the $\gamma$-product was again obtained in high enantiomeric excess with only a small amount of the α-product observed for unsaturated aldehydes.

In order to evaluate the practicability of the vinylogous Mukaiyama aldol reaction in total syntheses, α-chiral aldehydes were additionally used as substrates. We observed that the appropriate choice of protecting groups for high selectivities (Scheme 3). Here, the TBS ethers provided useful selectivities in contrast to PMB-protected substrates. For aldehydes obtained from the Roche ester, the matched and mismatched case gave similar selectivities and yields, indicating that the chiral Lewis acid overrides the inherent Felkin selectivity. Aldehydes obtained from lactic acid on the other hand did show a distinct different selectivity for the matched and mismatched case. Here only on the matched case provided useful results.

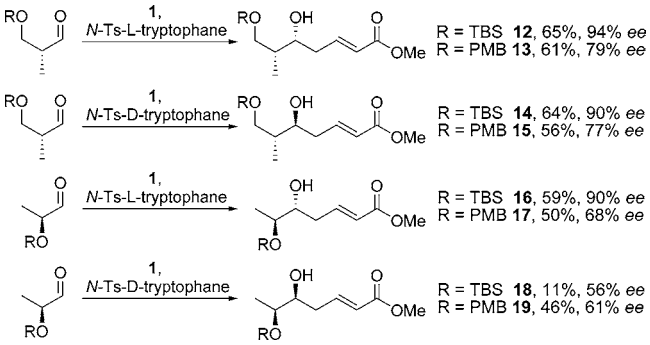
**Table 2.** VMAR on Different Aldehydes




| | | α-product | γ-product | |
|---|---|---|---|---|
| entry | aldehyde | yield[a,b] (%) | yield[a,b] (%) | ee (%) |
| 1 | pivalaldehyde | <1 | **6** (65) | 99[c,d] |
| 2 | valeraldehyde | 4 | **7** (70) | 94[c,e] |
| 3 | cyclohexylaldehyde | <1 | **8** (80) | 96[c,e] |
| 4 | 2-furylaldehyde | 9 | **9** (66) | 83[e] |
| 5 | benzaldehyde | 11 | **10** (60) | 80[c,e] |
| 6 | *E*-cinnamaldehyde | 13 | **11** (63) | 76[c,e] |

[a] Isolated yield after chromatography. [b] Additional 4% of racemic TBS-protected product. [c] Determined by (+)-Eu(hfc)$_3$.[11] [d] Determined by chiral GC on the TBS-protected compound. [e] Determined by the Mosher method.

**Scheme 3.** Vinylogous Mukaiyama Aldol Reaction with α-Chiral Aldehydes




In summary, the use of tryptophane-derived *B*-phenyloxazaborolidinone for the enantioselective vinylogous Mukaiyama aldol reaction of *O*,*O*-silyl ketene acetal **1** provided an efficient access to chiral building blocks for polyketide synthesis. These studies additionally add to the general picture that isopropyl alcohol is required as an additive for suppressing the racemic TBS-catalyzed pathway and enhances the enantioselectivity. In cases of α-chiral aldehydes it could be shown that the appropriate choice of protecting groups is essential for high selectivities.

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**Supporting Information Available:** Spectroscopic data and experimental procedures for compounds **1**, **2**, **5**−**12**, **14**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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