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Asymmetric Vinylogous Mukaiyama Aldol Reaction of Aldehyde-Derived Dienolates

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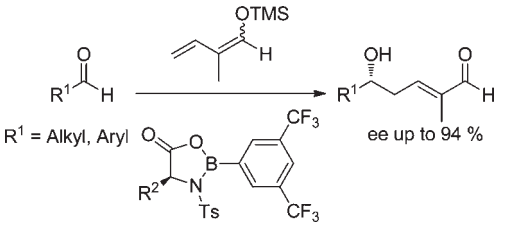
ABSTRACT



Unsaturated aldehydes are exquisite building blocks for further transformations in polyketide synthesis. Besides standard transformations that take advantage of the aldehyde functionality, the conjugate addition of hydrides followed by internal protonation allows access to alpha chiral aldehydes. Even though vinylogous Mukaiyama aldol reactions have been used in natural product syntheses before, the first enantioselective Mukaiyama aldol reaction of aldehyde-derived dienolates is described.

The vinylogous Mukaiyama aldol reaction (VMAR) has been proven as a useful tool for the construction of larger polyketide fragments.[1] Its potential in the total syntheses of natural products was significantly extended by the development of asymmetric variations.[2] So far, enantioselective vinylogous Mukaiyama aldol reactions were developed only for ester-, amide-, or ketone-derived dienolates. On the other hand, aldehyde-derived dienolates stand out as redox economic reagents[3] and would be preferentially employed if enantioselective protocols were available.[4,5]

We recently used unsaturated aldehydes as precursors for asymmetric protonations of aldehyde-derived enolates. This process involves the directing effect of a δ-hydroxyl group, which in turn is introduced through a vinylogous aldol reaction. Since this asymmetric protonation is a diastereoselective process, the synthesis of enantiomers relies on the stereoselectivity of the upstream aldol reaction.[6] The combination of these two transformations could provide an efficient strategy for the rapid assembly of complex polyketide fragments (Scheme 1). Previously, we demonstrated that amino acid-derived oxazaborolidinones (OXB)[7] promote the VMAR with ester-derived ketene acetals in excellent selectivities.[1e,f] Consequently, we used these chiral

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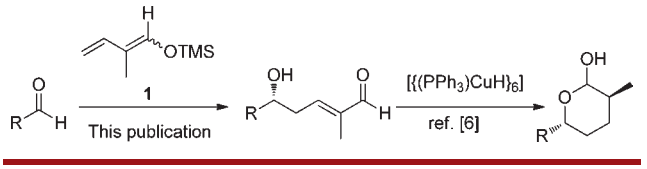
Scheme 1. VMAR Followed by Stereoselective Protonation



Lewis acids in order to establish an enantioselective protocol for the addition of aldehyde-derived dienolates.

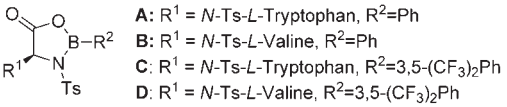
First results were obtained using silyl dienol ether **1** and aldehyde **2**, which originates from our synthetic endeavors toward the total synthesis of angiolam[6,8] (Table 1). The valine- and tryptophane-based OXB **A** and **B** in propionitrile gave the desired product in only moderate yields and selectivites.

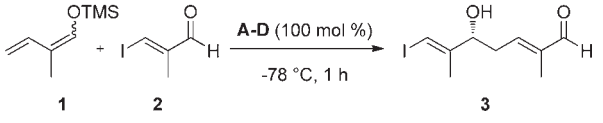
However, changing the Lewis acidity at boron by introducing the 3,5-bis(trifluoromethyl)benzene substituent led to improved selectivities and yields (Table 1, entry 4, 5).

As shown by Yamamoto et al., these modified OXBs are highly active in Mukaiyama aldol reactions of ketone-derived silyl enol ethers.[9] By using modified OXB **C** we were able to increase the yield from 62% to 82%, while the enantioselectivity remained 74% (entries 1 and 3). By changing the solvent from propionitrile to butyronitrile we could increase the enantioselectivity up to 91% ee, while the yield slightly dropped (entries 4 and 5). When reducing the stoichiometry of Lewis acid[10] **C**, we realized that the yield significantly dropped when less than 80 mol % was used. On the other hand, the selectivity was obviously not affected by the concentration of the Lewis acid (entries 6–8). Nevertheless, best results were obtained when a stoichiometric concentration of OXB was used.

Unfortunately, reaction conditions optimized for aldehyde **2** (method I) did not provide the same satisfying results for aliphatic aldehydes. When aldehyde **4** was subjected to the previously optimized reaction conditions,

Table 1. OXB-Induced Enantioselective VMAR of Silyl Dienol Ether **1** and Aldehyde **2**

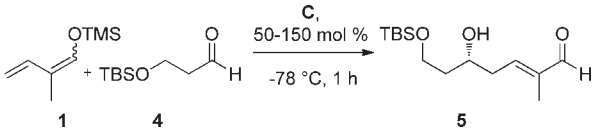




entry	OXB (mol %)	yield (%)[a,b]	ee (%)[c]
1[d]	**A** (100)	62	74
2[d]	**B** (100)	67	70
3[d]	**C** (100)	82	74
4[e]	**C** (100)	71	81
5[e]	**D** (100)	67	91[c,f]
6[e]	**C** (50)	18	80
7[e]	**C** (80)	65	80
8[e]	**C** (150)	68	78

[a] After treatment of the crude product with HCl (1 M) in THF. [b] Isolated yield after chromatography. [c] Determined by chiral GC. [d] Reaction in propionitrile (0.125 M). [e] Reaction in butyronitrile (0.125 M). [f] Determined by Mosher method.

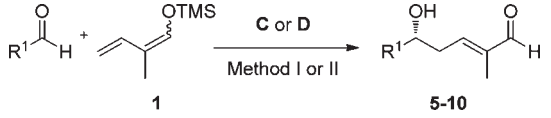
Table 2. Optimization of the Reaction Conditions for Aliphatic Aldehydes



entry	method[a]	OXB (equiv)	yield (%)[d,e]	ee (%)[f]
1[b]	I	1.0	15	n.d.
2[b]	II	0.5	26	88
3[b]	II	1.0	33	88
4[b]	II	1.4	56	86
5[b]	II	2.0	60	88
6[c]	II	1.4	68	84

[a] Method I: Solution of the dienol ether added to a solution of the aldehyde (1.0 equiv) and Lewis acid. Method II: Solution of the aldehyde (1.0 equiv) added to a solution of the dienol ether and Lewis acid. [b] Reaction in butyronitrile (0.125 M). [c] Reaction in propionitrile (0.125 M). [d] Isolated yield after chromatography. [e] After treatment of the crude product with HCl (1 M) in THF. [f] Determined by chiral GC.

Table 3. Substrate Screening with OXBs **C** and **D**



entry	R^1	OXB	Method	yield (%)[a,b]	ee (%)[c]
1	cyclohexyl	**C**	II	**6** (67)	94[c]
2		**D**	II	**6** (49)	rac.[c]
3	TIPSO	**C**	II	**7** (61)	92
4		**D**	II	**7** (47)	13
5	TBSO	**C**	II	**5** (68)	84
6		**D**	II	**5** (44)	21
7	*n*-butyl	**C**	II	**8** (68)	88
8		**D**	II	**8** (47)	20
9		**C**	II	**9** (52)	87
10		**D**	II	**9** (47)	20
11		**C**	I	**3** (71)	81
12		**C**	II	**3** (66)	74
13		**D**	I	**3** (67)	91
14		**D**	II	**3** (55)	89
15	phenyl	**C**	I	**10** (89)	50
16		**D**	I	**10** (68)	45

[a] Isolated yield after chromatography. [b] After treatment of the crude product with HCl (1 M) in THF. [c] Determined by chiral GC unless otherwise noted. [d] Determined by the Mosher method.

decomposition and only small amounts of the desired VMAR product could be detected. However, by changing the order of addition and optimization of the concentration, good yields could be re-established (Table 2, entries 1−5). In the course of this optimization the same trends concerning solvent and Lewis acid concentration became apparent as mentioned above. For method II 1.4 equiv of the Lewis acid in propionitrile turned out to be ideal.

Next we investigated the substrate scope using OXBs **C** and **D** (Table 3). Good yields and excellent selectivities of up to 94% ee in the case of cyclohexane carbaldehyde were observed for aliphatic aldehydes when Lewis acid **C** was used.

In contrast to our observations with aldehyde **2**, Lewis acid **D** gave only moderate yields and poor selectivites with aliphatic aldehydes. In the case of aromatic aldehydes both OXBs showed good yields and moderate selectivites. Furthermore our studies pointed out that method I provides slightly higher selectivites and yields than method II.

Highly active oxazaborlidinones **C** and **D** gave the best results for the substrates that originate in our synthetic approach toward the natural product angiolam. Lewis acid **C** showed the broadest substrate spectrum, tolerating aliphatic, unsaturated, and aromatic aldehydes.

In summary we introduced the first asymmetric vinylogous Mukaiyama aldol reaction with aldehyde-derived silyl dienol ethers. This methodology offers a highly redox economic access to α-substituted δ-hydroxy-α,β-unsaturated aldeyhdes that are the precursors for the asymmetric protonation recently described by our group.

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Supporting Information Available. Spectroscopic data and experimental procedures for compounds **1**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For the determination of chiral induction see the Supporting Information.