

# Catalytic Asymmetric Synthesis of Hydroxy Enol Ethers: Approach to a Two-Carbon Homologation of Aldehydes

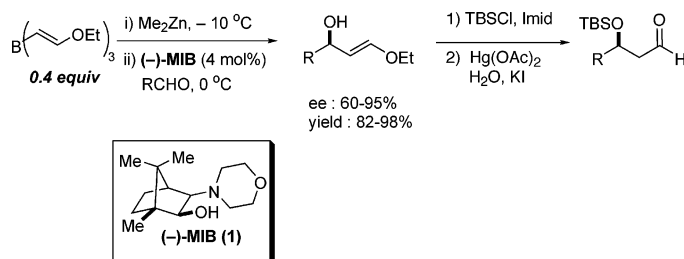
Sang-Jin Jeon, Young K. Chen, and Patrick J. Walsh\*

Department of Chemistry, P. Roy and Diana T. Vagelos Laboratories,  
University of Pennsylvania, Philadelphia, Pennsylvania 19104

pwalsh@sas.upenn.edu

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## ABSTRACT

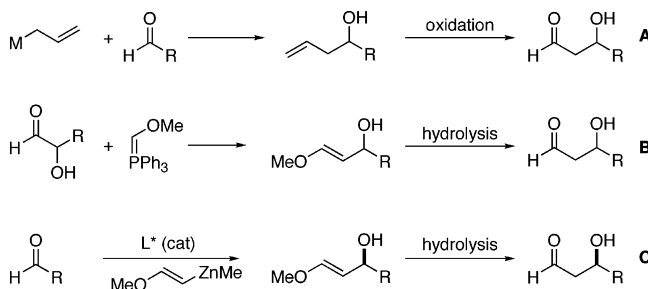


Hydroboration of ethoxy acetylene, transmetalation to zinc, and addition to aldehydes in the presence of a chiral amino alcohol ligand (MIB) affords hydroxy enol ethers with high ee. The resultant enantiomerically enriched hydroxy enol ethers were converted to protected hydroxy aldehydes, a useful synthetic building block for the construction of a variety of polyoxygenated natural products. In addition, diastereoselective formation of *syn*- and *anti*-1,3-diols was studied.

$\beta$ -Hydroxy carbonyls, 1,3-diols, and related polyols are common structural motifs in natural products. As such, much attention has been devoted to development of methods for the synthesis of these  $\beta$ -oxygenated systems. Significant effort has been focused on the asymmetric aldol reaction, which is particularly powerful for the generation of polypropionate backbone.<sup>1–7</sup> In contrast, the asymmetric acetate aldol reaction that leads directly to an aldehyde functionality has proven to be a more challenging problem.<sup>8,9</sup>

The difficulties associated with acetate aldol reactions have prompted investigations into alternative methods to generate  $\beta$ -hydroxy aldehydes. One of the most popular non-aldol entries into  $\beta$ -hydroxy aldehydes involves the catalytic asymmetric allylation of aldehydes followed by oxidative cleavage of the allyl group (Scheme 1, A). It is limited, however, to substrates that do not contain additional functional groups that are sensitive toward the oxidative cleavage

### Scheme 1. Non-Aldol Approach to $\beta$ -Hydroxy Aldehydes



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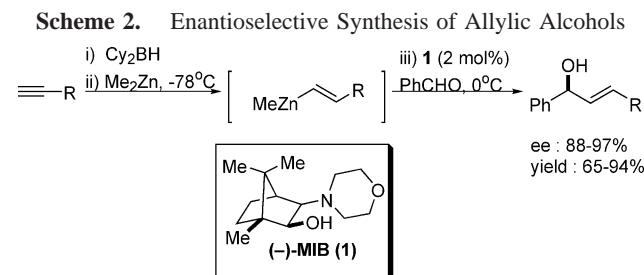
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conditions.<sup>10,11</sup> A less common approach entails a one-carbon homologation of an  $\alpha$ -hydroxy aldehyde with a Wittig reagent and subsequent hydrolysis of the resultant hydroxy enol ether<sup>12–16</sup> (Scheme 1, reaction B).

In this letter, we report a new non-aldol approach to the enantioenriched  $\beta$ -hydroxy aldehydes involving catalytic asymmetric addition of a vinyl ether to an aldehyde and hydrolysis of the newly formed enol ether (Scheme 1, reaction C).

We recently reported<sup>17–20</sup> a catalytic asymmetric alkenylzinc addition to aldehydes using Nugent's  $\beta$ -amino alcohol (MIB) as a chiral ligand (Scheme 2).<sup>21</sup> Alkenylzinc reagents



were generated in situ following Oppolzer's procedure.<sup>22,23</sup> Thus, hydroboration of a terminal alkyne was followed by transmetalation to zinc. Upon introduction of 2 mol % (-)-MIB and aldehyde substrate, vinylation proceeds smoothly to afford a variety of allylic alcohols with high levels of enantioselectivity and yields. We have successfully employed this procedure in the synthesis of enantioenriched  $\alpha$ -amino acids,<sup>18</sup>  $\gamma$ -unsaturated  $\beta$ -amino acids,<sup>19</sup> and epoxy alcohols containing up to three contiguous stereocenters.<sup>17,20</sup> Other groups have also studied the asymmetric vinylation of aldehydes.<sup>24–26</sup>

We envisioned that asymmetric vinylation of aldehydes employing ethoxy acetylene might allow access to highly

enantioenriched hydroxy enol ethers, which in turn could be transformed into  $\beta$ -hydroxy aldehydes. Notably, the subsequent hydrolysis of the protected hydroxy enol ether can be performed selectively in the presence of other sensitive functionality. This sequence amounts to an asymmetric two-carbon homologation of aldehydes to  $\beta$ -hydroxy aldehydes.

In our initial investigations, we applied the conditions employed in Scheme 2 using ethoxy acetylene as the terminal alkyne and diethylzinc as a transmetalating reagent. It is known that ethoxy acetylene undergoes hydroboration with high regioselectivity to provide the *trans*-alkenylborane.<sup>27</sup> We initially employed catalyst loading of 4 mol % to achieve modest to good levels of enantioselectivity with benzaldehyde (Table 1, entries 1–3). Increasing ligand loading to

**Table 1.** Optimization of Reaction Conditions

entry	substrates	$\text{R}_2\text{BH}^a$	$\text{R}'_2\text{Zn}$	mol% $\text{L}^*$	temp. ( $^\circ\text{C}$ )	yield (%)	ee (%)
1		$\text{R} = \text{Cy}$	$\text{R}' = \text{Et}$	1.5	0	83	65
2		$\text{R} = \text{Cy}$	$\text{R}' = \text{Et}$	4	0	80	85
3		$\text{R} = \text{Cy}$	$\text{R}' = \text{Et}$	10	0	81	85
4		$\text{R} = \text{Cy}$	$\text{R}' = \text{Et}$	4	-20	82	85
5		$\text{R} = \text{Cy}$	$\text{R}' = \text{Et}$	4	-50	80	76
6		$\text{R} = \text{Cy}$	$\text{R}' = \text{Et}$	4	0	85	78
7		$\text{R} = \text{Et}$	$\text{R}' = \text{Et}$	4	0	88	83
8		$\text{R} = \text{Et}$	$\text{R}' = \text{Me}$	4	0	89	82
9		$\text{R} = \text{Et}$	$\text{R}' = \text{Me}$	4	0 <sup>b</sup>	87	87
10		$\text{R} = \text{Et}$	$\text{R}' = \text{Me}$	8	0 <sup>b</sup>	85	90
11		$\text{R} = \text{Et}$	$\text{R}' = \text{Et}$	4	0 <sup>b</sup>	87	87
12		$\text{R} = \text{Et}$	$\text{R}' = \text{Et}$	8	0 <sup>b</sup>	89	90

<sup>a</sup>  $\text{R}_2\text{BH}$ :ethoxy acetylene: $\text{R}'_2\text{Zn}$ :aldehyde = 1.2:1.2:1.4:1. <sup>b</sup> Syringe pump addition of substrate solution (1 M in toluene) for 30 min.

10 mol % did not improve enantioselectivity and reducing the catalyst loading to 1.5 mol % resulted in product of only 65% ee. Decreasing the reaction temperature to  $-20^\circ\text{C}$  had no beneficial effect. A further decrease to  $-50^\circ\text{C}$  resulted in a reduction in the enantioselectivity (entries 4 and 5). Similar results were obtained with 4-chlorobenzaldehyde under the same conditions (entry 6).

We next examined alternative methods to generate the vinyl zinc reagent. No effect was observed on use of dimethylzinc in place of diethylzinc (entries 7 and 8). To minimize the background reaction between the reactive vinyl reagent and the aldehyde, we added the substrate to the preformed vinylzinc reagent dropwise. In principle, the slow

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addition allows more of the reaction to proceed through the ligand-accelerated pathway.<sup>28</sup>

As illustrated in entries 6 and 7, changing the hydroboration reagent from  $\text{Cy}_2\text{BH}$  to  $\text{Et}_2\text{BH}$  resulted in a small increase in enantioselectivity. This led us to examine the use of an alternative vinyl ether borane, namely tris(vinyl ether) borane prepared by hydroboration of ethoxyacetylene with  $\text{BH}_3\cdot\text{SMe}_2$ .<sup>27</sup> Fortunately, employing 0.4 equiv of this reagent in the asymmetric vinylation reaction with 4 mol % (-)-MIB and slow addition of the aldehyde at  $-10^\circ\text{C}$ , followed by warming to  $0^\circ\text{C}$  furnished the hydroxy enol ether with excellent enantioselectivities.

As illustrated in Table 2, enantioselectivities and yields in the vinylation of benzaldehyde and related derivatives

**Table 2.** Modified Synthesis of Hydroxy Enol Ethers

entry	substrates	yield (%)	ee (%)
1		98	95
2		98	89
3		93	92
4		93	91
5		90	94
6		97	91
7		82	92
8		98	73
9		97	78
10		90	60
11		98	73

<sup>a</sup> All reactions employed 4 mol % of (-)-MIB and slow substrate addition.

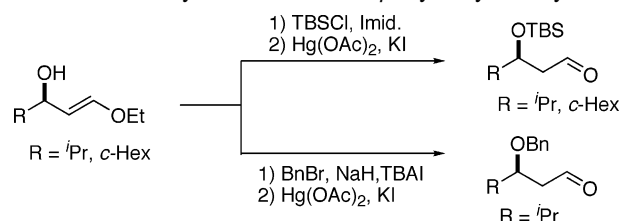
provided the hydroxy enol ethers with enantioselectivities ranging from 89% to 95% and yields >93% (entries 1–4). Aliphatic aldehydes containing  $\alpha$ -branching, such as cyclohexane carboxaldehyde, isobutyraldehyde, and pivalaldehyde, un-

derwent smooth vinylation to afford the desired hydroxy enol ethers with high enantioselectivities (92–94%) and yields between 82% and 97% (entries 5–7).

In contrast to aldehydes with  $\alpha$ -branching, substrates bearing  $\beta$ -branching or devoid of branching afforded products with moderate enantioselectivities. As shown in Table 2 (entries 8 and 9), isovaleraldehyde and 3-(naphthalene-2-ylmethoxy)propanal were converted to the enol ether products in 73% and 78% enantioselectivities with yields >95%. Aldehydes containing protected  $\alpha$ -hydroxy groups likewise exhibited low enantioselectivities (entries 10 and 11).

With the hydroxy enol ethers in hand, we next turned our attention to their hydrolysis. As illustrated in Scheme 3, the

**Scheme 3.** Synthesis of Masked  $\beta$ -Hydroxy Aldehydes



two-step procedure for hydrolysis of the hydroxy enol ethers began with protection of the hydroxyl group as the TBS or benzyl ether. Subsequent treatment with  $\text{Hg}(\text{OAc})_2$  in wet THF followed by KI induced elimination led to the clean formation of the protected  $\beta$ -hydroxy aldehydes in high yields. As depicted in Scheme 3, asymmetric vinylation of isobutyraldehyde, followed by TBS protection led to the corresponding enol ether in 88% yield. Hydrolysis and workup with saturated KI afforded the desired  $\beta$ -oxygenated aldehyde in 71% yield. Likewise, the benzyl protected  $\beta$ -hydroxy aldehyde was obtained by an analogous sequence in 80% for the addition and protection and 71% yield in the hydrolysis step. The enol ether derived from cyclohexyl aldehyde was transformed to the corresponding  $\beta$ -hydroxy aldehyde by applying the same protocol (85% and 71%, respectively). Other metal salts are known to catalyze the hydrolysis of enol ethers.<sup>29</sup> Unfortunately, due to the increased sensitivity of the hydroxy enol ethers toward Lewis acid-catalyzed eliminations, other metals led to formation of elimination products.

We proceeded next to the construction of 1,3-diol moieties, which are ubiquitous structural motifs in biologically active compounds. We envisioned that 1,3-diols could be assembled by diastereoselective vinyl ether addition to enantioenriched  $\beta$ -hydroxy aldehydes. To our knowledge, there are few investigations of catalyst controlled diastereoselective additions of organozinc reagents to chiral aldehydes.<sup>30–32</sup> In the

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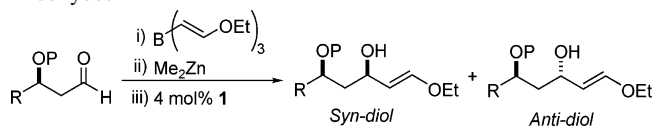
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absence of catalyst, the sense of asymmetric induction of  $\beta$ -hydroxy aldehydes is enforced by either  $\beta$ -chelation or Felkin control depending on protection groups. Both controlling elements result in the same preferential *anti*-diol product.<sup>33</sup>

We studied the effect of the chiral ligand (MIB) on the diastereoselective addition of vinyl ethers to chiral  $\beta$ -hydroxy aldehydes as shown in Table 3. Examination of the mis-

**Table 3.** Diastereoselective Additions to Masked  $\beta$ -Hydroxy Aldehydes



entry	R	P	ligand	yield (%)	syn:anti
1	<i>c</i> -hexyl	TBS	(-)-MIB	93	2.3:1
2			(+)-MIB	95	1:7.8
3	isopropyl	TBS	(-)-MIB	96	2.4:1
4			(+)-MIB	95	1:8
5	isopropyl	Bn	(-)-MIB	97	3.8:1
6			(+)-MIB	96	1:9.3

matched and matched catalyst–substrate combinations indicated that moderate to good control over diastereoselectivity can be achieved. When the (*S*)-enantiomer of the TBS protected  $\beta$ -hydroxy aldehydes were used, (-)-MIB was the mismatched catalyst, giving diastereomeric ratios of 2.3:1 favoring the *syn*-diol products. The dr increased with the

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benzyl protected substrate to 3.8:1. Combination of the protected (*S*)- $\beta$ -hydroxy aldehydes with (+)-MIB resulted in dr values of 1:7.8–8.0 for the TBS derivatives and 1:9.3 for the benzyl analogue, favoring the *anti*-diol. Both the matched and mismatched combinations proceeded with excellent yields. The resulting  $\beta$ -hydroxy enol ethers could, in principle, be protected and hydrolyzed to prepare 1,3-polyols. Configurational assignment of diastereomers was done by inspection of the <sup>13</sup>C chemical shifts of the corresponding acetonides.<sup>34</sup>

In conclusion, we have developed a non-aldol method to prepare acetate aldol products. Our procedure involves an efficient and enantioselective addition of vinyl enol ether to an aldehyde to furnish hydroxy enol ethers with high levels of enantioselectivity. Protection of the hydroxyl group followed by hydrolysis provides the desired protected  $\beta$ -hydroxy aldehydes in good yields. We have also demonstrated that this cycle can be repeated to afford 1,3-oxygenated products with moderate to good control over diastereoselectivity. The advantage of this method over the asymmetric aldehyde allylation/ozonolysis protocol is that our method can be applied to substrates containing additional C–C double bonds.

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**Supporting Information Available:** Experimental details and full characterizations of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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