Asymmetric Synthesis

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Highly Enantioselective Synthesis of γ-Hydroxy-α,β-acetylenic Esters by Asymmetric Alkyne Addition to Aldehydes**

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γ-Hydroxy-α,β-acetylenic esters containing three adjacent and structurally very different functional groups are very useful in the synthesis of highly functionalized organic molecules.[1,2] This class of compound is normally prepared by treatment of an alkyl propiolate with *n*BuLi at $\leq -78\,^{\circ}C$

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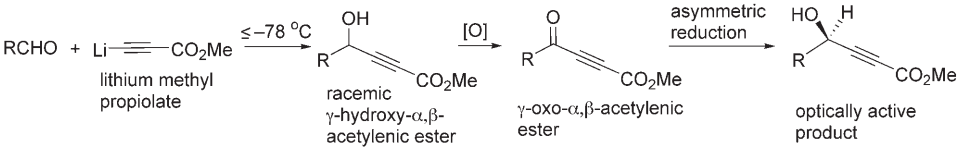
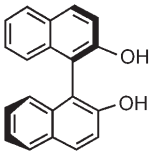
followed by the addition of aldehydes,[1] as originally reported by Midland et al.[1a] Recently, Shahi and Koide reported a milder method in which AgC≡CCO$_2$Me was reacted with aldehydes in the presence of [Cp$_2$ZrCl$_2$] (Cp = cyclopentadienyl) and AgOTf (Tf = trifluoromethanesulfonyl) at room temperature.[3] Asymmetric reductions of γ-oxo-α,β-acetylenic esters have been used to synthesize optically active γ-hydroxy-α,β-acetylenic esters (Scheme 1).[2] This process first



Scheme 1. Synthesis of optically active γ-hydroxy-α,β-acetylenic esters by asymmetric reduction of γ-oxo-α,β-acetylenic esters.

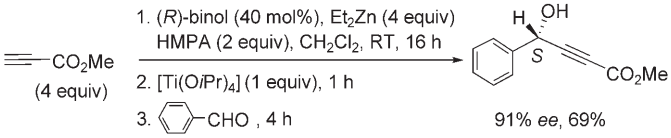
requires the synthesis of racemic γ-hydroxy-α,β-acetylenic esters, which are then oxidized to γ-oxo-α,β-acetylenic esters before asymmetric reduction. However, the most efficient way to prepare optically active γ-hydroxy-α,β-acetylenic esters should be the direct asymmetric addition of an alkyl propiolate to aldehydes, as this one-step reaction simultaneously produces both a carbon–carbon bond and a stereogenic propargylic alcohol center. Although major progress has been made in recent years in the area of asymmetric addition of alkynes to aldehydes,[4–7] no enantioselective reaction of alkynoates with aldehydes has been reported.[8,9] Herein, we report a highly enantioselective, as well as practical, method for the addition of methyl propiolate to aromatic aldehydes to generate optically active γ-hydroxy-α,β-acetylenic esters.



(*R*)-binol

Earlier, we discovered that 1,1′-bi-2-naphthol (binol) in combination with [Ti(O*i*Pr)$_4$] can catalyze the highly enantioselective addition of alkynes to both aliphatic and aromatic aldehydes with high enantioselectivity.[6a,b] However, this method cannot be used for the reaction of methyl propiolate with aldehydes because the solution of the alkyne in toluene needs to be heated with Et$_2$Zn at reflux, which leads to the decomposition of methyl propiolate. Later, we found that addition of hexamethylphosphoramide (HMPA) greatly accelerates the reaction of Et$_2$Zn with terminal alkynes at room temperature while maintaining the high enantioselectivity for the addition to aldehydes.[6c] When we initially tested the use of this method for the addition of methyl propiolate to benzaldehyde, the product was obtained only in low yield.

Further investigation revealed that prolonging the treatment of methyl propiolate with Et$_2$Zn in the presence of (*R*)-binol and HMPA at room temperature before the addition of [Ti(O*i*Pr)$_4$] and benzaldehyde led to the desired γ-hydroxy-α,β-acetylenic product both in good yield and with high enantioselectivity (Scheme 2): methyl 4-hydroxy-4-phenylbut-2-ynoate was obtained in 69% yield and with 91% *ee* (see the Experimental Section for further details). The specific



Scheme 2. Asymmetric addition of methyl propiolate to benzaldehyde.

optical rotation was found to be $[\alpha]_D^{28} = -3.56$ ($c = 0.73$, $CHCl_3$), and the absolute configuration was determined to be *S* by studying the ^{19}F NMR spectra of its Mosher ester.[10] This configuration assignment is consistent with other studies on the binol-catalyzed alkyne addition to aldehydes.[6a]

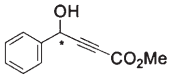
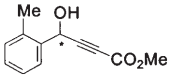
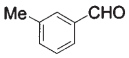
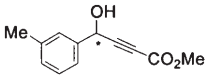
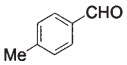
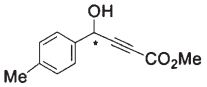
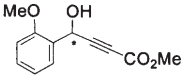
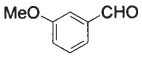
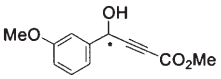
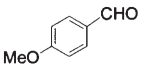
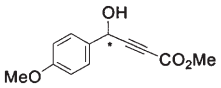
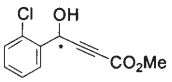
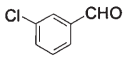
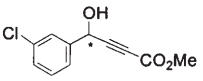
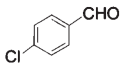
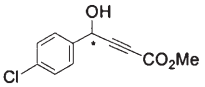
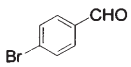
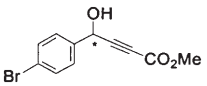
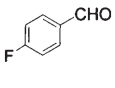
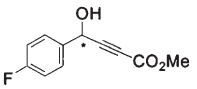
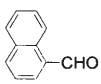
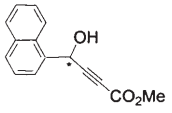
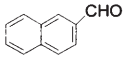
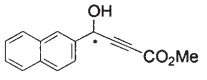
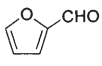
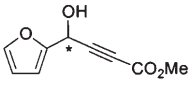
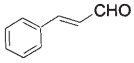
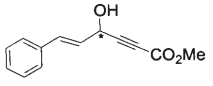
We applied this procedure to the reaction of methyl propiolate with a variety of aromatic and α,β-unsaturated aldehydes. The results summarized in Table 1 show that high enantioselectivities (85–95% *ee*) were achieved for the reaction of benzaldehyde derivatives with either electron-donating or -withdrawing substituents at the *ortho*, *meta*, or *para* positions in the presence of a substoichiometric amount of the chiral ligand (*R*)-binol (Table 1, entries 1–12). Other types of aromatic aldehydes, such as 1-naphthaldehyde, 2-naphthaldehyde, and 2-furaldehyde, also showed high enantioselectivity (87–95% *ee*; Table 1, entries 13–15). An excellent result was obtained as well when the α,β-unsaturated aldehyde cinnamaldehyde was used (91% *ee*; Table 1, entry 16).

In summary, we have discovered the first highly enantioselective reaction of an alkynoate with aromatic and α,β-unsaturated aldehydes for the synthesis of optically active γ-hydroxy-α,β-acetylenic esters. This reaction can be carried out at room temperature by using a substoichiometric amount of the chiral binol ligand. The easy availability of the chiral ligand as well as the metal reagents and the mild reaction conditions make this process practically very useful. Currently, we are further expanding the scope of this reaction to include substrates such as aliphatic and other functionalized aldehydes.

Experimental Section

HMPA (88 μL, 0.50 mmol), methyl propiolate (85 μL, 1.0 mmol), and Et$_2$Zn (0.91 mL (1.1M in toluene), 1.0 mmol) were added sequentially to (*R*)-binol (28.6 mg, 0.10 mmol, 40 mol%) in dry CH_2Cl_2 (3 mL) in a 10-mL round-bottomed flask under argon. The reaction mixture was allowed to stir at room temperature for 16 h. After the addition of [Ti(O*i*Pr)$_4$] (74 μL, 0.25 mmol), the solution was stirred for another hour. Benzaldehyde (25.5 μL, 0.25 mmol) was then added and the reaction was allowed to proceed for 4 h. Saturated ammonium chloride was added to quench the reaction, and CH_2Cl_2 was used for extraction. After removal of the organic solvent under reduced pressure, the residue was purified by using a short column of silica gel with petroleum ether/ethyl acetate (9:1) as the eluant to afford methyl 4-hydroxy-4-phenylbut-2-ynoate in 69% yield with 91% *ee*, as

Table 1: Enantioselective addition of methyl propiolate to aldehydes.

Entry	Aldehyde	Product	Yield of isolated product [%]	*ee* [%]
1			69	91
2			96	91
3			91	93
4			81	93
5			91	90
6			52	90
7			82	91
8			94	91
9			90	93
10			84	95
11			82	93
12			76	85
13			87	95
14			84	93
15			55[a]	87
16			65[a]	91

[a] Determined by NMR spectroscopic analysis.

determined with a HPLC-Diacel Chiralcel OD column; $[\alpha]_D^{28} = -3.56$ ($c = 0.73$, $CHCl_3$).

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[8] The Carreira asymmetric alkyne addition to aldehydes[5] was found not to be suitable for this reaction.[3]

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[11] Experimental details of the synthesis and characterization of the chiral γ-hydroxy-α,β-acetylenic esters and the assignment of the absolute configuration, determined by preparation of the Mosher esters, are given in the Supporting Information.

