Asymmetric Synthesis of γ-Hydroxy-α,β-acetylenic Esters Catalyzed by Oxazolidine–Titanium Complex

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Abstract: An efficient catalytic system has been developed for the enantioselective reaction of alkynoates with aromatic aldehydes for the synthesis of optically active γ-hydroxy-α,β-acetylenic esters (with up to 81% isolated yield and up to 84% enantioselectivity).

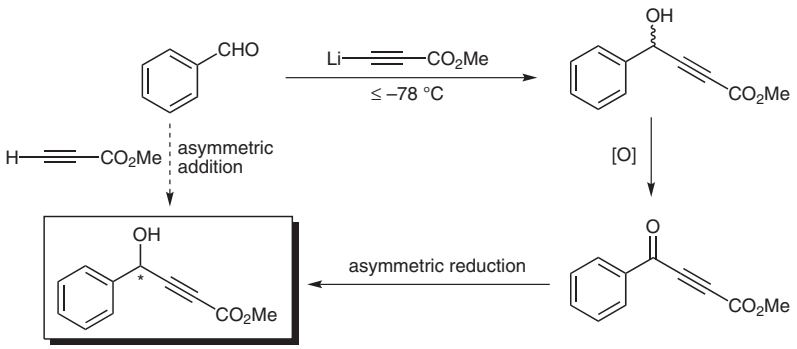
Key words: asymmetric synthesis, oxazolidine, aldehyde, addition, asymmetric alkynylation

In the past decades, it was of great interest to aim at the catalytic enantioselective addition of terminal alkynes to aldehydes because of the versatility of the resulting propargylic alcohols.[1] Thus, various catalytic methods have been developed.[2] Among them, two typical protocols proved to be the most practical. One was discovered by Carreira, who used stoichiometric or catalytic quantities of $Zn(OTf)_2$, *N*-methylephedrine, and Et_3N to afford the corresponding products in high yields and enantioselectivities through the alkynylzinc addition to aliphatic aldehydes.[3] The other was developed independently by Pu[4] and Chan.[5] They used BINOL/Ti(O*i*-Pr)$_4$ to catalyze the asymmetric addition of terminal alkynes to various aldehydes with high ee values. In this way, great progress has been made in this asymmetric addition reaction.[6,7]

γ-Hydroxy-α,β-acetylenic esters containing three different functional groups are very important precursors in the synthesis of highly functionalized organic molecules. The traditional way to prepare the optically active product is shown in Scheme 1.[8] Obviously, this route is troublesome and tedious. Thus, a straightforward way was developed by the direct asymmetric addition of an alkyl propiolate to aldehydes. Although great efforts have been made in asymmetric alkynylations, few attentions on the enantioselective reactions of alkynoates to aldehydes have been paid.[9–12] Recently, Pu discovered that 2.0 equivalents of hexamethylphosphoramide (HMPA) could accelerate the addition of methyl propiolate to various aldehydes in good yields and enantioselectivities in the presence of 40 mol% of BINOL as the chiral ligand.[10] In contrast, Wang and coworkers found that 1.0 equivalent of 1,2-dimethoxyethane (DME) as an additive could facilitate the asymmetric addition of methyl propiolate to aldehydes with moderate to good ee values and yields using 30 mol% of β-sulfonamide alcohol.[12] Therefore, development of novel efficient chiral catalysts with low loading for this important asymmetric transition is still desirable.

Recently, we have reported that the readily available and inexpensive new chiral oxazolidine **1** in combination with Ti(O*i*-Pr)$_4$ could catalyze the asymmetric alkynylation of various aldehydes to generate chiral propargylic alcohols with high enantioselectivities (up to 95% ee) and excellent yields (up to 98%).[13] In this paper, we wish to report the use of chiral oxazolidines (**1**–**4**) in the synthesis of γ-hydroxy-α,β-acetylenic esters (Figure 1).

Chiral oxazolidines (**1**–**4**) were easily prepared from (1*R*,2*S*)-*cis*-1-amino-2-indanol with different aromatic aldehydes with high yields. These stable chiral compounds were then employed in the asymmetric addition of methyl propiolate to benzaldehyde, and the results are listed in



Scheme 1 The traditional way to prepare the optically active γ-hydroxy-α,β-acetylenic esters

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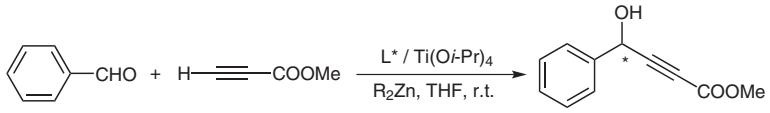
Table 1. Using **1** as the model ligand, there is no desired product when THF was employed as solvent (Table 1, entry 1), even using DME and HMPA as the additives (entries 2 and 3). Using toluene as the solvent, we got the promising result of 53% yield and 15% ee (entry 4). Addition of DIMPEG (dimethoxy polyethylene glycol,

Table 1 Asymmetric Addition of Methyl Propiolate to Benzaldehyde in the Presence of Chiral Oxazolidine Ligands **1**–**4**[a]



Entry	**L*** (mol%)	Base (equiv)	DIMPEG (mol%)	R	Yield (%)[b]	ee (%)[c]
1	**1** (20)	–	–	Et	–	–
2	**1** (20)	DME (1.0)	–	Et	–	–
3	**1** (20)	HMPA (1.0)	–	Et	–	–
4[d]	**1** (20)	–	–	Et	53	15
5[d]	**1** (20)	–	1	Et	53	25
6[d]	**1** (20)	–	10	Et	59	30
7[d]	**1** (20)	HMPA (1.0)	1	Et	57	27
8[d]	**1** (20)	HMPA (1.0)	10	Et	63	67
9[d]	**1** (20)	HMPA (1.0)	10	Me	75	79
10[d]	**1** (20)	DME (1.0)	1	Me	51	10
11[d]	**1** (20)	DME (1.0)	10	Me	63	56
12[d]	**1** (20)	HMPA (2.0)	10	Me	56	82
13[d,e]	**1** (20)	HMPA (2.0)	10	Me	52	75
14[d,f]	**1** (20)	HMPA (2.0)	10	Me	64	75
15[d]	**2** (20)	HMPA (2.0)	10	Me	76	84
16[d]	**3** (20)	HMPA (2.0)	10	Me	65	80
17[d]	**4** (20)	HMPA (2.0)	10	Me	61	79
18[d]	**2** (10)	HMPA (2.0)	10	Me	66	65
19[d]	**2** (30)	HMPA (2.0)	10	Me	56	79
20[d]	**2** (40)	HMPA (2.0)	10	Me	31	79
21[d]	**2** (20)	Et_3N (3.0)	10	Me	11	80
22[d,g]	**2** (20)	HMPA (2.0)	10	Me	26	73
23[d,h]	**2** (20)	HMPA (2.0)	10	Me	UD	–
24[d,i]	**2** (20)	HMPA (2.0)	10	Me	UD	–
25[d,j]	**2** (20)	NMI (0.05)	10	Me	UD	–

[a] All the reactions were processed under argon at r.t. for 20 h. Ti(O*i*-Pr)$_4$ was freshly distilled. Alkynoate/R_2Zn/benzaldehyde/ligand/Ti(O*i*-Pr)$_4$ = 3:3:0.5:0.1:0.2.
[b] Isolated yield.
[c] The ee was determined by chiral HPLC analysis of the corresponding products on a Chiralcel OD-H column.
[d] Toluene was used as the solvent.
[e] Ti(O*i*-Pr)$_4$ = 0.1 mmol.
[f] Ti(O*i*-Pr)$_4$ = 0.4 mmol.
[g] DMAP (10 mol%) as the additive.
[h] (*S*)-BINOL (10 mol%) as the additive.
[i] *i*-PrOH (1.0 equiv) as the additive.
[j] NMI (5 mol%) was employed in the absence of HMPA.

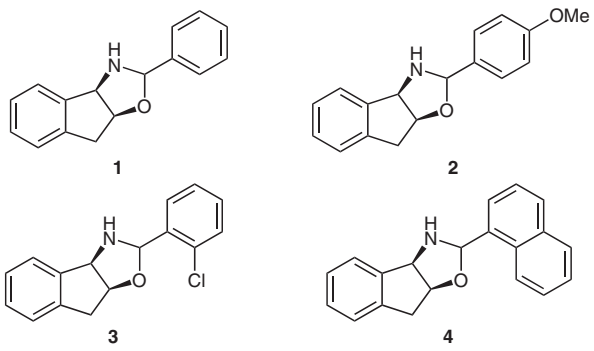
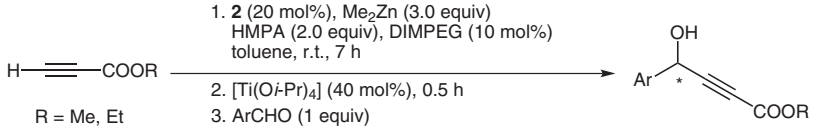


Figure 1 Structures of chiral oxazolidine ligands

M_n = 2000) resulted in clear enhancement of enantioselectivities (entries 5 and 6).[14] Furthermore, use of 1.0 equivalent of HMPA afforded better ee value (67% ee, entry 8). Replacement of Et_2Zn with Me_2Zn led to good enantioselectivity (79% ee, entry 9). Under the same conditions, DME instead of HMPA gave decreased enantioselectivities (entries 10 and 11). Subsequently, 2 equivalents of HMPA were investigated in the reaction. To our delight, 82% ee of the desired product was obtained (entry 12). Varying the amount of Ti(O*i*-Pr)$_4$ did not get better results (entries 13 and 14). Thus, other chiral oxazolidines (**2**–**4**) have also been investigated in the same asymmetric reaction (entries 15–17). It can be seen that ligand **2** gave the best result (84% ee, entry 15). Varying the amount of ligand **2** was not favorable for the enantioselectivities (entries 18–20). Et_3N instead of HMPA afforded very low yield, though the enantioselectivity was good (entry 21). In addition, several additives, such as DMAP, (*S*)-BINOL, and *i*-PrOH, did not afford better results (entries 22–24). Using You's protocol, NMI did not favor the catalytic reaction (entry 25).[12]

The influence of various aromatic aldehyde substrates on the reactivity and enantioselectivity was examined using the reaction with **2** under the standard conditions. The first step is about the formation of an active alkynylzinc reagent, the second step is the addition of Ti(O*i*-Pr)$_4$, while the final step is the reaction with an aldehyde.[15] From Table 2, it can be seen that *para* substitution on the aromatic ring of aldehydes gave similar yields (57–74%) and enantioselectivities (80–83% ee, Table 1, entries 2–5), except for the electron-donating MeO substituent (entry 6). *Ortho* or *meta* substituents on the aromatic ring did not affect the enantiomeric excess (entries 7 and 8). As expected, α-naphthaldehyde gave higher ee values than β-naphthaldehyde (entries 9 and 10). Comparing to methyl propiolate, the asymmetric addition of ethyl propiolate to aldehydes gained less attention. Thus, in this paper, several aromatic aldehydes have also been investigated in the asymmetric addition of ethyl propiolate. The results showed that slightly reduced ee values and higher yields were obtained in comparison with the reaction of methyl propiolate (entries 11–13).

Table 2 Asymmetric Alkyne Addtions to Various Aromatic Aldehydes Catalyzed by **2**[a]



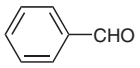
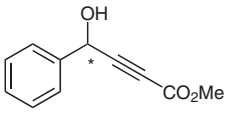
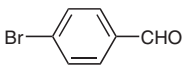
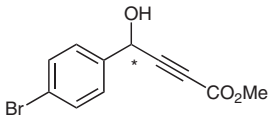
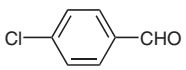
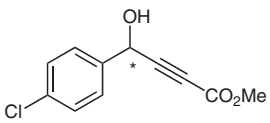
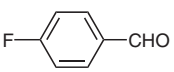
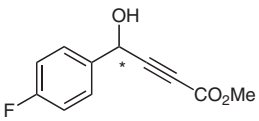
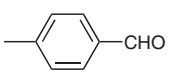
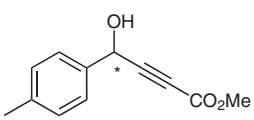
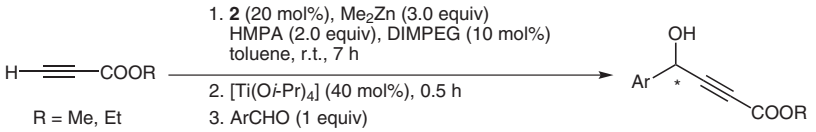
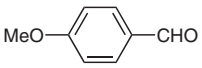
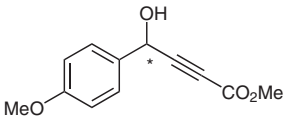
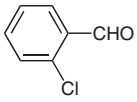
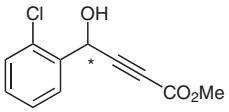
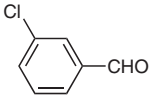
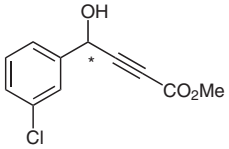
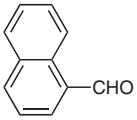
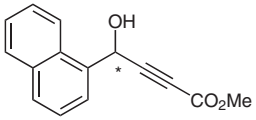
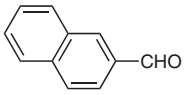
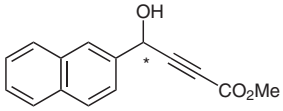
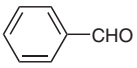
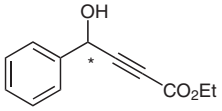
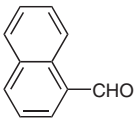
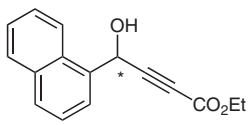
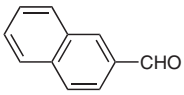
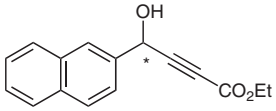
Entry	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1			78	84
2			56	83
3			73	82
4			65	80
5			61	82

Table 2 Asymmetric Alkyne Addtions to Various Aromatic Aldehydes Catalyzed by **2**[a] (continued)



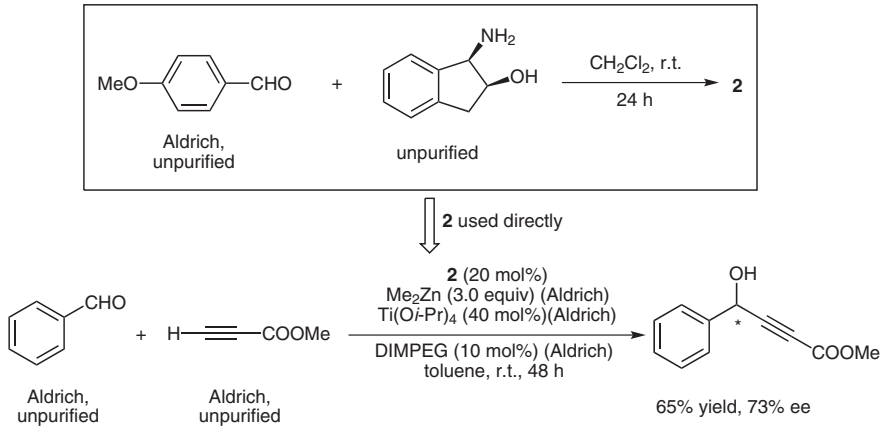
Entry	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
6			47	63
7			75	81
8			57	80
9			73	83
10			43	73
11			81	81
12			76	77
13			70	74

[a] All the reactions were processed under argon at r.t. for 48 h. Ti(O*i*-Pr)$_4$ was freshly distilled. Alkynoate/Me_2Zn/aromatic aldehyde/ligand **2**/Ti(O*i*-Pr)$_4$ = 3:3:0.5:0.1:0.2.
[b] Isolated yield.
[c] The ee was determined by chiral HPLC analysis of the corresponding products on a Chiralcel OD-H column.

A mixture of 20 mol% of 4-methoxybenzaldehyde and (1*R*,2*S*)-*cis*-1-amino-2-indanol was stirred in 1 mL of dichloromethane at room temperature for 24 hours. The solvent was evaporated and then directly used to catalyze the asymmetric addition reaction. These two substrates were also directly used without being purified. Thus, the desired product was obtained in 73% ee and 65% yield (Scheme 2).

Noteworthy is that in our protocol additional Lewis bases, such as HMPA or DME, played a crucial role for the catalytic reactions. It is presumed that these bases may participate in the coordination, which could avoid other possible side reactions.[12]

In summary, we have developed an efficient catalytic system for the enantioselective reaction of alkynoates with aromatic aldehydes for the synthesis of optically active γ-hydroxy-α,β-acetylenic esters. Using 20 mol% of easily prepared oxazolidine **2** as the chiral ligand, the desired products were obtained in moderate to good yields and enantioselectivities. It is noteworthy that our protocol could be further simplified and still retain its efficiency. Thus, the easily available catalyst made this catalytic process potentially practical and useful. Further studies on



Scheme 2 Asymmetric addition of methyl propiolate to benzaldehyde with commercially available materials

highly effective asymmetric addition reactions using novel catalysts are in progress in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) **General Procedure for the Addition of Methyl Propiolate to Benzaldehyde**
All manipulations were carried out under an argon atmosphere. The ligand **2** (0.1 mmol), base (0.5 mmol), and DIMPEG (0.05 mmol) were mixed in dry toluene (2.0 mL) at r.t. Then, a solution of Me_2Zn (1.2 M in toluene, 1.5 mmol) and methyl propiolate (1.5 mmol) were added in turn.

After the mixture was stirred at r.t. for 7 h, Ti(O*i*-Pr)$_4$ (0.2 mmol, 60 μL) was added and the stirring continued for another 0.5 h. The yellow solution was cooled to 0 °C and treated with benzaldehyde (0.5 mmol, 50 μL), then the resultant mixture was allowed to warm up to r.t. naturally and stirred for 20 h. After the reaction was completed, it was cooled to 0 °C again and quenched by 5% aq HCl (2 mL). The mixture was extracted with EtOAc (2 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel H, 10% EtOAc in PE) to give the pure product.

Methyl 4-Hydroxy-4-phenylbut-2-ynoate

Yield 78%; 84% ee determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane = 20:80). t_R(minor) = 6.60 min, t_R(major) = 7.33 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67 (d, *J* = 6.4 Hz, 1 H), 3.80 (s, 3 H), 5.58 (d, *J* = 6.4 Hz, 1 H), 7.35–7.43 (m, 3 H), 7.52 (d, *J* = 6.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.4, 64.4, 77.8, 87.4, 127.1, 29.22, 129.3, 138.9, 154.4.