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Highly Enantioselective Catalytic Alkyl Propiolate Addition to Aliphatic Aldehydes

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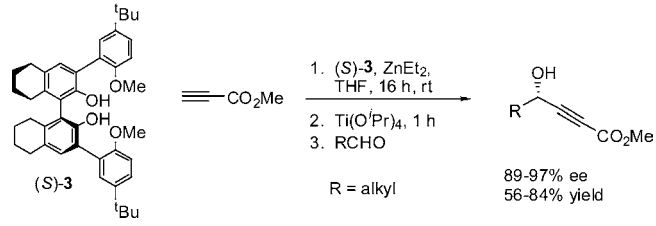
ABSTRACT



A novel H_8BINOL-based chiral ligand (*S*)-3 is found to catalyze the alkyl propiolate addition to aliphatic aldehydes in the presence of $ZnEt_2$ and $Ti(O^iPr)_4$ at room temperature with excellent enantioselectivity (89−97% ee).

γ-Hydroxy-α,β-acetylenic esters contain three adjacent but chemically distinct functional groups and are versatile synthetic precursors to many organic compounds.[1] Racemic γ-hydroxy-α,β-acetylenic esters are usually prepared according to Midland's original report by treating an alkynoate with ^{n}BuLi at low temperatures, followed by addition of an aldehyde.[2] Direct access to optically active γ-hydroxy-α,β-acetylenic esters proved to be more challenging. Although significant strides had been made in the catalytic asymmetric addition of monoaryl or monoalkyl alkynes to aldehydes,[3] no catalytic asymmetric alkyl propiolate addition was reported before our recent work.[4,5] This could be attributed to the higher sensitivity and dissimilar reactivity of alkynoates in comparison with simple alkyl and aryl alkynes. In particular, our original 1,1′-bi-2-naphthol (BINOL)-$Ti(O^iPr)_4$ system for the asymmetric alkyne addition to aldehydes[6] proved unsuitable for propiolate addition. This is because the conditions for the alkynylzinc formation, stirring the alkyne with $ZnEt_2$ in refluxing toluene, led to decomposition of methyl propiolate. A solution to the problem was realized when our laboratory discovered that the addition of HMPA facilitated the formation of alkynylzinc reagents at room temperature for asymmetric alkyne additions.[4] It is thought that HMPA, acting as a Lewis base, coordinates with $ZnEt_2$ and activates it toward deprotonation of the alkyne. This methodology was successfully applied in the addition of methyl propiolate to aromatic aldehydes to generate γ-hydroxy-α,β-acetylenic esters with high enantioselectivity.[5]

The development of other catalytic systems quickly followed. In 2006, Trost demonstrated a highly enantioselective addition of methyl propiolate to α,β-unsaturated aldehydes using a proline-derived catalyst and $ZnMe_2$.[7] In 2007, Wang reported the use of a β-sulfonamide ligand in

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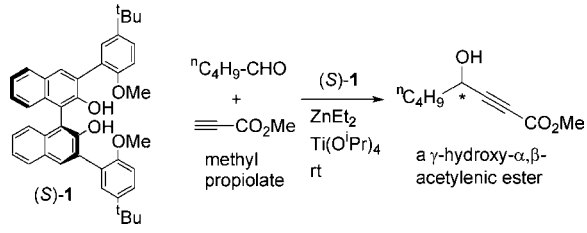
combination with $ZnEt_2$ and $Ti(O^iPr)_4$ for the addition of methyl propiolate to aromatic aldehydes.[8] Later that year, You further modified the BINOL-$Ti(O^iPr)_4$ system by substituting HMPA with NMI, which reduced the amount of the Lewis base and BINOL required for the catalysis.[9] Wang recently reported the use of $ZnMe_2$ and a chiral cyclopropane based amino alcohol for the addition of methyl propiolate to aromatic aldehydes without $Ti(O^iPr)_4$.[10]

Whereas several systems have been developed for the highly enantioselective addition of methyl propiolate to aromatic aldehydes, aliphatic aldehydes remain challenging substrates. Only one aliphatic aldehyde was reported to react with methyl propiolate in the presence of a chiral catalyst to give >90% ee.[11] Our BINOL-HMPA system afforded 81−89% ee for a small range of aliphatic aldehyde substrates.[5b] Wang's sulfonamide system could catalyze the addition of methyl propiolate to cyclohexanecarboxaldehyde with only 79% ee.[8] Our attempts to catalyze the addition of methyl propiolate to valeraldehyde with a bifunctional H_8BINOL ligand without the use of $Ti(O^iPr)_4$ resulted in 70% ee.[12] Given these unsatisfactory results, we set out to explore the addition of methyl propiolate to aliphatic aldehydes. Herein, we report a catalytic system capable of promoting the addition of alkyl propiolates to a variety of aliphatic aldehydes with excellent enantioselectivity.

To improve the enantioselectivity of BINOL for the asymmetric reaction of alkyl propiolates with aliphatic aldehydes,[5b] we have examined the 3,3′-bisanisyl substituted BINOL ligand (*S*)-**1**. Previously, (*S*)-**1** was found to catalyze the reaction of phenylacetylene with benzaldehyde in the presence of $ZnEt_2$ and $Ti(O^iPr)_4$ to generate 1,3-diphenyl-2-propyn-1-ol with 88% ee.[13] When (*S*)-**1** 20 mol% is used to catalyze the reaction of methyl propiolate with pentyl aldehyde, it gives the desired product with 62% yield and 85% ee (Scheme 1). This reaction is carried out at room

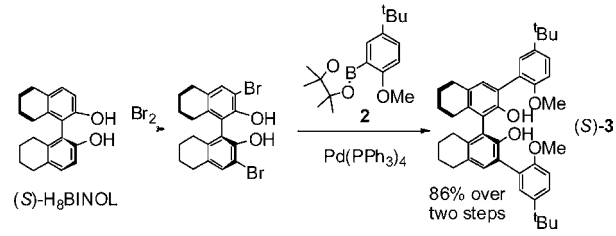
Scheme 1. Asymmetric Addition of Methyl Propiolate to Pentyl Aldehyde Catalyzed by (*S*)-**1** in Combination with $ZnEt_2$ and $Ti(O^iPr)_4$



temperature without the use of a Lewis base additive. Encouraged by this result, we have conducted a further modification of the catalyst structure.

Ligand (*S*)-**3** is designed as a structurally modified analog of (*S*)-**1** (Scheme 2). In (*S*)-**3**, a partially hydrogenated

Scheme 2. Synthesis of H_8BINOL-Based Ligand (*S*)-**3**



BINOL unit, H_8BINOL, is incorporated. The nonplanar tetrahedral CH_2 units in (*S*)-**3** are expected to increase the steric bulkiness of the ligand as well as the central biaryl dihedral angle. This could potentially lead to improved chiral induction in asymmetric catalysis.[14] As shown in Scheme 2, (*S*)-**3** can be readily synthesized from (*S*)-H_8BINOL by bromination followed by the Suzuki coupling with the boronic ester **2** via modification of a literature procedure.[15] The two-step reaction can be completed with an overall yield of 86%. The ee of the resulting (*S*)-**3** is determined to be 98% by HPLC analysis (Chiralcel OD column).

We have tested the use of (*S*)-**3** to catalyze the reaction of methyl propiolate with octyl aldehyde under various conditions. The screening experiments are summarized in Table 1. A large solvent effect on the enantioselectivity of this reaction is observed (entries 1−5). It is found that in THF, (*S*)-**3** can catalyze the highly enantioselective reaction of methyl propiolate with octyl aldehyde (91% ee and 70% yield, entry 5). The other less coordinative solvents such as CH_2Cl_2, Et_2O, and toluene give poorer results. The enantioselectivity in dioxane (87% ee) is found to be close to that in THF but in a lower yield (entry 4). The effect of various amounts of $Ti(O^iPr)_4$ on the reaction is examined (entries 5−9). When no or only 10 mol % of $Ti(O^iPr)_4$ is used, no enantioselectivity is observed also with low yields (entries 7 and 8). Increasing the amount of $Ti(O^iPr)_4$ from 50 to 100 mol % (entry 9) leads to reduced yield while maintaining the enantioselectivity. Thus, 50 mol % of $Ti(O^iPr)_4$ is optimal (entry 5). Dilution and concentration (entries 10 and 11) have no effect on enantioselectivity, though both diminish the yield. Addition of $Ti(O^iPr)_4$ in the first step decreases the yield (entry 12). Finally, when the amount of the chiral ligand (*S*)-**3** is increased from 10 to 20 mol %, both the yield and ee are increased (84% yield and 95% ee, entry 13).

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Table 1. Optimization of Conditions for the Reaction of Methyl Propiolate with Octyl Aldehyde Catalyzed by (*S*)-**3**[a]

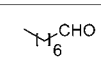
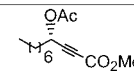
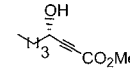
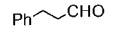
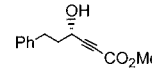
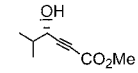
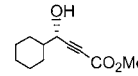
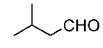
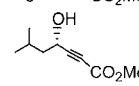
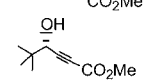
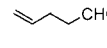
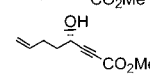
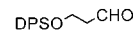
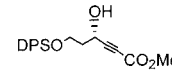
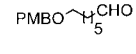
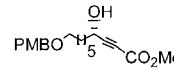
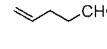
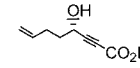
entry	(*S*)-**3** (mol %)	solvent (aldehyde concn M)	$Ti(O^iPr)_4$ (mol %)	yield (%)	ee (%)[f]
1	10	CH_2Cl_2 (0.1)	50	51	78
2	10	Et_2O (0.1)	50	73	37
3	10	toluene (0.1)	50	44	69
4	10	1,4-dioxane (0.1)	50	49	87
5	10	THF (0.1)	50	70	91
6	10	THF (0.1)	0	28	0
7	10	THF (0.1)	10	27	0
8	10	THF (0.1)	25	51	76
9	10	THF (0.1)	100	47	91
10[b]	10	THF (0.2)	50	65	90
11[c]	10	THF (0.05)	50	40	90
12[d]	10	THF (0.1)	50	48	90
13[e]	**20**	THF (0.1)	50	84	95

[a] Unless otherwise indicated, the following conditions were employed: 0.025 mmol (*S*)-**3** (10 mol %), 2.5 mL solvent, 0.5 mmol $ZnEt_2$ (2 equiv), and 0.5 mmol methyl propiolate (2 equiv) were combined and stirred for 16 h at rt. Then 0.125 mmol $Ti(O^iPr)_4$ (0.5 equiv, 50 mol %) was added, and the mixture was stirred for 1 h, followed by the addition of 0.25 mmol octyl aldehyde (1 equiv). After consumption of the aldehyde the reaction was quenched with 1.0 mmol acetic anhydride (4 equiv) for ease of purification and HPLC analysis. [b] 1.25 mL THF. [c] 5 mL THF. [d] $Ti(O^iPr)_4$ was added in the first step. [e] 0.5 mmol octyl aldehyde was used; 0.1 mmol (*S*)-**3** (0.2 equiv, 20 mol %) was used. The equivalents of the other reagents remained the same, i.e., their quantities were doubled. [f] Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column).

We have applied the optimized conditions in entry 13 in Table 1 to the asymmetric reaction of methyl propiolate with various aliphatic aldehydes. The results are summarized in Table 2. In general, good yields and excellent enantioselectivities are obtained for linear, α-branched, and β-branched aliphatic aldehydes (entries 1−6). The more bulky trimethylacetaldehyde shows reduced reactivity, requiring higher loadings of the ligand (40 mol %) and other reagents to give 55% yield and 97% ee (entry 7). In comparison, 40% yield is obtained using the general conditions. Functionalized aliphatic aldehydes are also examined and high enantioselectivity is achieved (entries 8−10). In entry 11, the reaction of ethyl propiolate with 4-pentenal gives the corresponding product with the same high enantioselectivity as that of methyl propiolate in entry 8.

The following gives the general procedure for the reaction catalyzed by (*S*)-**3**. Under nitrogen, (*S*)-**3** (61.9 mg, 0.1 mmol, 20 mol %) was dissolved in THF (5 mL) in a 10 mL flame-dried flask. $ZnEt_2$ (103 μL, 1 mmol, 2 equiv) and methyl propiolate (89 μL, 1 mmol, 2 equiv) were added sequentially, and the mixture was stirred at room temperature for 16 h, yielding a light yellow solution. $Ti(O^iPr)_4$ (74 μL, 0.25 mmol, 50 mol %) was then added, and the mixture was stirred for 1 h. To the resulting dark orange solution was added an aldehyde, and the reaction was monitored by TLC or ^1H NMR. Upon consumption of the aldehyde, the reaction was quenched with ammonium chloride (saturated aqueous). The reaction mixture was extracted three times with CH_2Cl_2, and the organic layer was dried with sodium sulfate and concentrated. The resultant oil was purified by flash chromatography on silica gel. First eluting with 2:1 CH_2Cl_2/hexanes cleanly separates the ligand from the product, providing an efficient means of recovering the ligand. After removal of the ligand, the column was eluted with hexanes/ethyl acetate (10−30% ethyl acetate) to give the desired product. The ee was determined by HPLC analysis (Chiralcel OD or Chiralpak AD-H column).

Table 2. Addition of Methyl Propiolate to Aliphatic Aldehydes Catalyzed by (*S*)-**3**[a]

entry	aldehyde	product	yield (%)	ee (%)[b]
1[c]			84	95
2			84	94
3			83	93
4			67	89[d]
5			84	95
6			71	90
7[e]			55	97
8			63	95
9[f]			60	90
10			56	92
11[g]			60	95

[a] $ZnEt_2$/methyl propiolate/(*S*)-**3**/$Ti(O^iPr)_4$/aldehyde = 2:2:0.2:0.5:1. [b] Determined by HPLC analysis on Chiralcel OD or Chiralpak AD-H colum. [c] The reaction was quenched with 2.0 mmol acetic anhydride (4 equiv) to yield the acetate product for ease of purification and HPLC analysis. [d] Determined by ^1H NMR analysis of mandelate acetate. [e] $ZnEt_2$/methyl propiolate/(*S*)-**3**/$Ti(O^iPr)_4$/aldehyde = 4:4:0.4:1:1. [f] 100 mol % $Ti(O^iPr)_4$. [g] Ethyl propiolate was used in place of methyl propiolate.

The absolute configuration of the product in entry 11 of Table 2 is determined to be *S* by comparing its optical rotation with that in the literature.[16] By analogy, all other products in Table 2 are assigned to be *S*. The absolute configuration of the γ-hydroxy-α,β-acetylenic esters obtained by using (*S*)-**3** as the catalyst is opposite to that by using (*S*)-BINOL.[5b] Thus, using this structurally modified BINOL ligand provides stereocontrol very different from using BINOL.

Ligands (*S*)-**4** and (*S*)-**5** are prepared in order to study the effects on the reaction by replacing the ^{t}Bu groups of (*S*)-**3**

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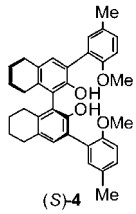
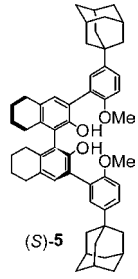
with a smaller group like Me in (*S*)-**4** or a bigger group like adamantanyl in (*S*)-**5**. When these ligands (10 mol %) are used to catalyze the reaction of methyl propiolate with octyl aldehyde under the conditions of entry 5 in Table 1, the corresponding products are obtained with 90% ee in both cases. That is, the enantioselectivity of (*S*)-**4** and (*S*)-**5** is very close to that of (*S*)-**3** with little influence by the size of the alkyl substituents. Ligands (*S*)-**4** and (*S*)-**5** lead to product yields of 59% and 63%, respectively.

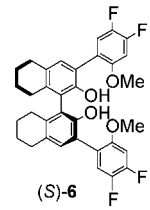


(*S*)-**4**

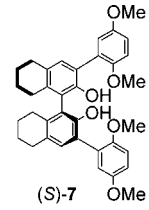


(*S*)-**5**

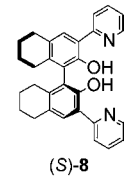
The electronic effects are also investigated with the preparation of ligands (*S*)-**6** and (*S*)-**7**. Under the conditions of entry 5 in Table 1, the electron-withdrawing fluorine substituents in (*S*)-**6** lead to a reduced enantioselectivity (70% ee) for the reaction of methyl propiolate with octyl aldehyde, whereas the more electron-donating ligand (*S*)-**7** gives 86% ee, closer to that of (*S*)-**3**. The yield using (*S*)-**7** (52%) is also better than that using (*S*)-**6** (34%). The poorer enantioselectivity of (*S*)-**6** versus those of (*S*)-**3** and (*S*)-**7** indicates that the coordination of the Lewis basic MeO groups of these ligands to a metal center should be important for the stereocontrol of the reaction. When pyridine is used to replace the 3,3′-bisanisyl groups of (*S*)-**3**, the resulting ligand (*S*)-**8** gives both poor enantioselectivity (34% ee) and poor yield (48%).



(*S*)-**6**



(*S*)-**7**



(*S*)-**8**

In summary, we have developed a catalytic system capable of catalyzing the addition of alkyl propiolates to aliphatic aldehydes with high enantioselectivity. This system's effectiveness for aliphatic substrates under simple and mild reaction conditions makes it especially useful, as no system has currently been shown to afford high enantioselectivities for a wide range of aliphatic aldehydes. We are currently working on further expanding the substrate scope for the reaction in both the alkynes and aldehydes.

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Supporting Information Available: Synthesis and characterization of new compounds and ee determination of the chiral alcohol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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