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Highly enantioselective catalytic methyl propiolate addition to both aromatic and aliphatic aldehydes

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ABSTRACT

The excellent catalytic effect on methyl propiolate addition to a wide range of aromatic and aliphatic aldehydes promoted by inexpensive and commercially available BINOL-based ligand is reported. The catalyst systems showed high yields and excellent enantioselectivities for aromatic aldehydes, and excellent yields and high enantioselectivities for aliphatic aldehydes.

1. Introduction

Chiral propargylic alcohols have found extensive applications in yjr synthesis of fine chemicals, pharmaceuticals, and natural products.[1] Over the past few years, we have focused on the development of the use of 1,1′-binaphthol (BINOL) in combination with a Ti(IV) complex to catalyze the asymmetric alkyne addition to aldehydes as well as the application of chiral propargylic alcohols in the synthesis of cyclic organic compounds.[2] Chiral γ-hydroxy-α,β-acetylenic esters represent a class of functional propargylic alcohols that are very useful and versatile structural subunits in many biologically active compounds.[1–3]

Only a small number of catalysts are applicable for the asymmetric propiolate addition to aldehydes, due to the high sensitivity and very different reactivity of the propiolate in comparison with normal terminal alkyl and aryl alkynes.[4–9] Previously, we reported the first highly enantioselective catalyst for the asymmetric reaction of methyl propiolate with aromatic aldehydes to generate γ-hydroxy-α,β-acetylenic esters by using a BINOL-Ti(IV)-HMPA catalyst system.[4] Later, You et al. modified the BINOL-Ti system by substituting HMPA with NMI, which reduced the amount of the base and BINOL required for the catalysis.[5] We further developed the BINOL-based catalyst system by using a catalytic amount of Cy_2NH in place of HMPA for the asymmetric alkyne addition to aldehydes and achieved excellent enantioselectivity.[6] Trost et al. reported on a highly enantioselective addition of methyl propiolate to α,β-chiral amino alcohol ligand in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ for the addition of unsaturated aldehydes using a proline-derived catalyst and $ZnMe_2$ in 2006.[7] Later, Wang and Hui reported the use of methyl propiolate to aromatic and aliphatic aldehydes, independently.[8] Recently, Wang and Kojima independently reported the use of $ZnMe_2$ and a chiral amino alcohol for the asymmetric addition of methyl propiolate to aromatic and aliphatic aldehydes without $Ti(O^iPr)_4$.[9]

In spite of the significant progress in this area, there are still a number of limitations in the scope of the substrates for the reported catalyst systems. Our BINOL or H_8BINOL-based chiral catalytic systems were independently shown to achieve excellent enantioselectivities and yields for the addition of methyl propiolate to aromatic or aliphatic aldehydes; however, the different catalytic systems require multiple syntheses for the special efficient ligands.[4,6,10] The amino alcohol–Zn catalytic system, reported by Wang and Hui, also requires the design and synthesis of the individual ligands, respectively.[8,9a] Kojima's amino alcohol–Zn system afforded good yield and excellent enantioselectivity for only a small range of aromatic and aliphatic aldehydes.[9b] Herein, we report our work on the development of an easily available BINOL-based catalyst to catalyze the reaction of methyl propiolate with a wide range of aromatic and aliphatic aldehydes to generate various γ-hydroxy-α,β-acetylenic esters.

2. Results and discussions

Previously, we reported that BINOL in combination with Cy_2NH, $ZnEt_2$ and $Ti(O^iPr)_4$ can catalyze the addition of various alkynes to aldehydes with high enantioselectivity. However, when we tested the application of this catalyst for the reaction of methyl propiolate

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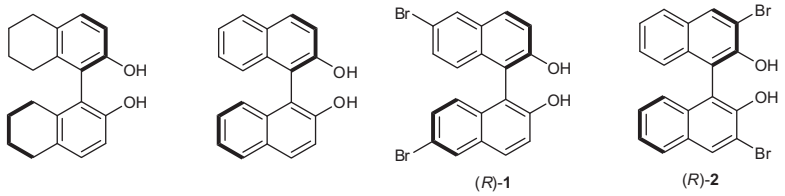
with aldehydes, only a low yield (<20%) of the product was obtained. Similar results were obtained when H_8BINOL and (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol ((*R*)-**2**) were used. When using (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol (*R*)-**1** as the catalyst for the asymmetric addition of methyl propiolate to benzaldehyde, a good yield and excellent enantioselectivity were achieved (for detailed results of the catalyst screening see Supplementary material, Table S1).



(*R*)-**1** (*R*)-**2**

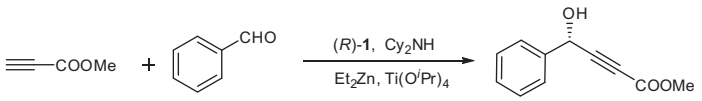
The results from the (*R*)-**1** survey in combination with Ti(O^{i}Pr)$_4$ are summarized in Table 1. As shown in entries 1–4, when the solvent changed from THF to CH_2Cl_2, the yield of the desired product increased with high enantioselectivity. The catalytic effects of various amounts of Cy_2NH were also investigated. As shown in entries 4–8, when the amount of Cy_2NH was increased from 2.5 mol % to 30 mol %, the yields were simultaneously increased but the enantioselectivities remained the same. Increasing the amount of Cy_2NH to 60 mol % reduced the yield (entry 9). Therefore, this catalysis system was found to be inferior to 30 mol % Cy_2NH in CH_2Cl_2. Further optimization of reaction conditions revealed that an increase in the amount of (*R*)-**1** (40 mol %) and Ti(O^{i}Pr)$_4$ (100 mol %) led to an excellent enantioselectivity of 94% ee and 65% yield while the amount of Cy_2NH was 30 mol %. The absolute configuration of the product was determined to be (*S*) by studying the ^{19}F NMR spectra of its Mosher ester, which is consistent with other studies.[4,10]

With the optimized conditions in hand, the asymmetric reaction of methyl propiolate with various aromatic and aliphatic aldehydes was screened. The results shown in Table 2 demonstrate that our catalytic system was capable of tolerating both aromatic aldehydes (entries 1–12) and aliphatic aldehydes (entries 13–24) with good yields and excellent enantioselectivities. As can be seen from entries 2–9, the yields of benzaldehydes containing an electron-withdrawing substituent were better than those of benzaldehydes containing an electron-donating substituent except for *ortho*-methylbenzaldehyde, due to the electron-withdrawing effect. The heteroaromatic aldehydes, furan-2-carbaldehyde and thiophene-2-carbaldehyde, and 1-naphthaldehyde showed good yields and high enantioselectivities (up to 97%, entry 10–12). As is evident in entries 13–24, the linear (*n*-butyraldehyde, *n*-pentanal, *n*-octanal and *n*-decanal), α-branched aliphatic aldehydes (isobutyraldehyde and 2-ethylbutanal), and α-cyclopropanecarbaldehyde underwent the addition reaction in excellent yields (up to 99%) and with high enantioselectivities. The β-branched aliphatic aldehyde 3-methylbutanal, and bulky trimethyl acetaldehyde showed low reactivity with good yields and moderate enantioselectivities. Functionalized aldehydes, such as phenylacetaldehyde, cinnamaldehyde, and *trans*-2-pentenal, are also examined with good yields and enantioselectivities. These results demonstrate that this catalytic system has a broad generality for both aromatic and aliphatic aldehydes.

3. Conclusion

In conclusion, we have described a highly effective method for the asymmetric catalysis of methyl propiolates to various aromatic and aliphatic aldehydes with high enantioselectivities and yields using a commercially available BINOL-based catalyst. By using the inexpensive and easily available ligand (*R*)-**1**, it is possible to conveniently prepare structurally diverse optically active γ-hydroxy-α,β-acetylenic esters under very mild reaction conditions. Further research on the application of these chiral propargylic alcohols in the synthesis of pharmaceutical compound currently in process.

Table 1
Optimization of the reaction conditions[a]



Entry	(*R*)-**1**/Ti(O^{i}Pr)$_4$ (mol %)	Solvent	Cy_2NH (mol %)	Yield (%)	ee[b] (%)
1	20/50	THF	5	Trace	
2	20/50	Et_2O	5	38	85
3	20/50	Toluene	5	48	83
4	20/50	CH_2Cl_2	5	45	87
5	20/50	CH_2Cl_2	2.5	36	87
6	20/50	CH_2Cl_2	10	52	87
7[c]	20/50	CH_2Cl_2	10	51	87
8	20/50	CH_2Cl_2	30	65	87
9	20/50	CH_2Cl_2	60	50	87
10[d]	40/100	CH_2Cl_2	30	65	94

[a] The following conditions were used unless otherwise indicated: methyl propiolate:Et_2Zn:Ti(O^{i}Pr)$_4$:(*R*)-**1**:aldehyde = 3:3:0.5:0.2:1. A mixture of (*R*)-**1**, methyl propiolate, solvent, Cy_2NH and Et_2Zn was stirred at room temperature for 24 h. Ti(O^{i}Pr)$_4$ was then added with stirring for 2 h at room temperature. Benzaldehyde was added and the mixture was stirred for 24 h at room temperature.
[b] Enantiomeric excess determined by chiral HPLC.
[c] After the aldehyde was added, the reaction solution was stirred for 48 h.
[d] Methyl propiolate:Et_2Zn:Ti(O^{i}Pr)$_4$:(*R*)-**1**:aldehyde = 4:4:1:0.4:1.