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Highly Enantioselective Zinc/Amino Alcohol-Catalyzed Alkynylation of Aldehydes

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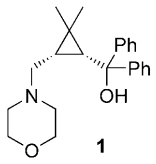
Enantioselective addition of terminal alkynes to carbonyl compounds is an area of intense research aimed at, for example, producing optically active propargylic alcohols, which are important and versatile building blocks for many natural products, pharmaceuticals, etc.[1] Recently, a number of catalytic protocols[2] have achieved significant progress in the asymmetric addition of terminal alkynes to aldehydes, but only *N*-methylephedrine-Zn(OTf)$_2$,[3] BINOL–Ti,[4] and amide alcohol–Ti[5] are practicable as catalytic systems. However, these catalytic systems also hold obvious drawbacks like high catalyst loading and the need for additional reagents such as Ti(O*i*Pr)$_4$. Herein, we report a highly enantioselective and practical alkynylation of aldehydes catalyzed by a cyclopropane-based amino alcohol zinc catalytic system which does not require any additional titanium alkoxide.

Chiral amino alcohols are one of the most widely employed types of ligands for asymmetric catalysis, and zinc amino alcohol complexes have been shown to exhibit excellent enantioselectivity in the alkylzinc addition to aldehydes,[6] but not, as yet, in the similar alkynylzinc addition to aldehydes.[7] Chiral cyclopropane-based amino alcohols possess an advantageous combination of structural rigidity, low molecular weight on a well-defined and highly variable platform, and unusual bond angle. Earlier we found that the amino alcohol ligand **1** exhibited a high asymmetric induction capability in the asymmetric addition of alkylzinc or phenylzinc to aldehydes.[8] These studies prompted us to investigate the enantioselective performance of cyclopropane-based amino alcohol in the alkynylzinc addition to aldehydes.



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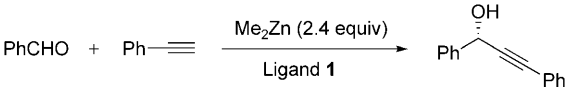
Initially, in the presence of 10 mol% of **1**, the asymmetric addition of alkynylzinc to benzaldehyde afforded the corresponding propargylic alcohol in heptane at 0°C in 43% yield with 85% *ee* (Table 1, entry 1); however, half of the benzaldehyde was not converted. As a possible reason for the poor yield was the low solubility of the catalytic complex in the reaction solution, subsequently toluene was used instead of heptane and the reaction yield increased to 91%, whilst retaining the good *ee* of 84% (Table 1, entry 2). Dahmen and Wang and coworkers reported that the use of DiMPEG [dimethoxypoly(ethylene glycol), MW 2000] markedly improved the enantioselectivity in the addition of alkynes to aldehydes.[7d,i] In our

Table 1. Enantioselective addition of phenylacetylene to benzaldehyde.[a]



Entry	Ligand **1** [mol%]	Solvent	*T* [°C]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	10%	heptane	0	36	43	85
2	10%	toluene	0	36	91	84
3	10% + 10% DiMPEG	toluene	0	48	99	94
4	10% + 10% DiMPEGt	toluene	20	48	97	92
5	10% + 10% DiMPEG	toluene	−10	48	90	95
6	10% + 10% DiMPEG	toluene	−20	65	45	96
7	10% + 10% DiMPEG	toluene	−20	94	43	96

[a] Reaction conditions: 2.6 mmol phenylacetylene, 2.4 mmol Me_2Zn. [b] Yield of isolated product. [c] Determined by HPLC on Chiralcel OD.

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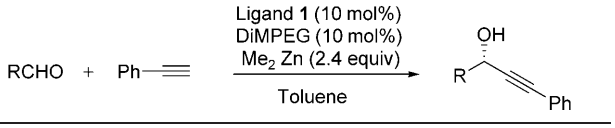
case, the addition of 10 mol% of DiMPEG led to a dramatic increase in the *ee* from 84% to 94% (Table 1, entries 2 and 3). This was the first time that such a high *ee* value was obtained in the alkynylation of benzaldehyde using an amino alcohol–zinc complex as catalyst system. Encouraged by this exciting result, we further optimized the reaction conditions as follows. Increasing the reaction temperature from 0°C to 20°C led to a decrease in the optical purity of the propargylic alcohols to 92% *ee* (Table 1, entry 4), whereas decreasing the reaction temperature from 0°C to −20°C led to a slight increase to 96% *ee* but this was accompanied by a decrease in the yield of the reaction product to 45% (Table 1, entry 6). Prolonging the reaction time to 94 h did not lead to a distinct change in yield (Table 1, entry 7).

Under the optimized reaction conditions of entry 5 in Table 1, **1** was used to catalyze the enantioselective addition of phenylacetylene to a variety of aldehydes. As the results summarized in Table 2 show, excellent enantioselectivity

Table 2. Enantioselective addition of alkynylzinc to aldehydes catalyzed by **1**.[a]



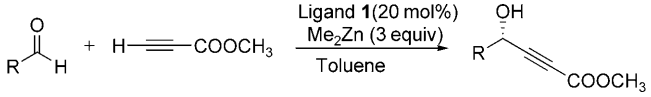
Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph	90	95
2	*o*-FC_6H_4	91	94
3	*p*-FC_6H_4	96	94
4	*p*-BrC_6H_4	85	92
5	*o*-$CH_3C_6H_4$	90	95
6	*m*-$CH_3C_6H_4$	84	93
7	*p*-$CH_3C_6H_4$	88	95
8	*o*-$CH_3OC_6H_4$	86	95
9	*m*-$CH_3OC_6H_4$	85	93
10	*p*-$CH_3OC_6H_4$	95	93
11	*o*-ClC_6H_4	95	93
12	*m*-ClC_6H_4	90	94
13	*p*-ClC_6H_4	90	91
14	1-naphthyl	80	94
15	2-naphthyl	92	92
16	cyclohexyl	95	79
17	isopropyl	92	88

[a] Reaction conditions: 2.6 mmol phenylacetylene, 2.4 mmol Me_2Zn. [b] Yield of isolated product. [c] Determined by HPLC on Chiralcel OD.

(91–95% *ee*) was achieved for the reaction of phenylacetylene with aromatic aldehydes containing electron-donating or electron-withdrawing substituents at the *ortho*-, *meta*-, or *para*-positions, and good enantioselectivity (79%, 88%) was also afforded in the reaction of phenylacetylene with aliphatic aldehydes (Table 2, entries 16 and 17). These results showed that **1** is one of most efficient ligands for the asymmetric addition of phenylacetylene to aldehydes.

To expand the scope of this reaction, we also examined methyl propiolate as a nucleophile, with the aim to produce optically active γ-hydroxy-α,β-acetylenic esters, which are a class of more versatile building blocks containing multifunctional groups. With respect to its preparation, only a few of studies[9] have been reported to date that utilize the direct asymmetric addition of an alkylpropiolate to aldehydes rather than the traditional approach that involves the addition of propargyllithium and aldehyde, followed by oxidation, and asymmetric reduction.[10] We attempted to use **1** with zinc to achieve the challenging asymmetric addition reaction of methyl propiolate to benzaldehyde. Unfortunately, when the optimized procedure used for the asymmetric addition of phenylacetylene to aldehydes was applied to the reaction of methyl propiolate to benzaldehyde, the desired reaction did not occur. However, in the absence of DiMPEG, 10 mol% of **1** catalyzed the above reaction at 20°C to give the highly optically active γ-hydroxy-α,β-acetylenic esters in 87% yield and 88% *ee*. Decreasing the reaction temperature to −10°C led to an increase in the *ee* value to 93%, but the yield decreased to 33%. Subsequently, by increasing the catalyst loading to 20 mol%, the reaction yield at 0°C was improved to 66%, while the *ee* value remained high at 92%. A series of aromatic aldehydes were tested under these conditions; in all cases, **1** exhibited excellent enantioselectivity (90–92% *ee*), and the results are summarized in Table 3.

Table 3. Enantioselective addition of methyl propiolate to aldehydes.[a]



Entry	R	Ligand **1** [mol%]	*T* [°C]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	Ph	10	20	24	87	88
2	Ph	10	0	48	49	87
3	Ph	10	−10	48	33	93
4	Ph	20	0	24	66	92
5	*o*-$CH_3C_6H_4$	20	0	24	85	92
6	*m*-$CH_3C_6H_4$	20	0	24	63	90
7	*p*-$CH_3C_6H_4$	20	0	24	56	91
8	*m*-$CH_3OC_6H_4$	20	0	24	68	91
9	*p*-$CH_3OC_6H_4$	20	0	24	65	91
10	*o*-ClC_6H_4	20	0	24	73	92
11	*m*-ClC_6H_4	20	0	24	76	93
12	*p*-ClC_6H_4	20	0	24	85	93
13	1-naphthyl	20	0	24	75	90

[a] Reaction conditions: 3.2 mmol Methyl propiolate, 3.0 mmol Me_2Zn, 1 mmol aldehyde, toluene. [b] Yield of isolated product. [c] Determined by HPLC on Chiralcel OD and AD.

In conclusion, we have demonstrated that the cyclopropane-based amino alcohol–zinc complex is a highly enantioselective catalyst for the alkynylation of aldehydes under mild reaction conditions, which alleviates the need for a titanium alkoxide additive. Furthermore, this catalytic system exhibited excellent enantioselectivity in the challenging asymmetric reaction of methyl propiolate with aldehydes. To the best of our knowledge, ligand **1** with zinc is the most effective system reported to date for the asymmetric addition of alkynylzinc to aromatic aldehydes. Based on the results we have obtained, the optically active cyclopropane derivative with its special structural configuration is a good po-

tential chiral ligand unit for asymmetric catalytic reactions. Currently, we are further expanding the applicability of **1** to other kinds of asymmetric catalysis as well as developing other novel cyclopropane-based ligand systems.

Experimental Section

General procedure for the asymmetric addition of phenylacetylene to aldehydes: Phenylacetylene (0.26 mL, 2.4 mmol, 2.4 equiv) was added to a solution of Me_2Zn (2 mL, 1.2 M in toluene, 2.4 mmol, 2.4 equiv) in dry toluene (2.5 mL) at room temperature under an atmosphere of argon, and stirred for 30 min. Subsequently the solution was transferred by syringe to another test tube containing the amino alcohol ligand **1** (35 mg, 0.1 mmol, 0.1equiv) and DiMPEG (0.2 g, 0.1 mmol, 0.1 equiv) in dry toluene (1 mL). After the reaction solution was stirred for 30 min at −10 °C, the aldehyde (1 mmol) was added. Upon completion of the reaction (48 h), the mixture was treated with saturated NH_4Cl solution and extracted with Et_2O (3×10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography (SiO_2, particle size 32–63 μm; eluent: 5–15% ethyl acetate in hexanes) afforded the pure propargylic alcohols. The enantiomeric excess was determined by HPLC (Chiralcel OD, 25% *i*PrOH in hexanes if not stated otherwise).

General procedure for the asymmetric addition of methyl propiolate to aldehydes: Methyl propiolate (0.29 mL, 3.2 mmol, 3.2 equiv) was added to a solution of Me_2Zn (2.5 mL, 1.2 M in toluene, 3 mmol, 3.0 equiv) in dry toluene (3.5 mL) at room temperature under an atmosphere of argon, and stirred for 90 min. Then the solution was transferred by syringe to another test tube containing neat amino alchohol ligand **1** (70 mg, 0.2 mmol, 0.2 equiv) at 0 °C. After 30 min, the aldehyde (1 mmol) was added. Subsequently the solution was kept at 0 °C for 24 h. The mixture was treated with saturated NH_4Cl solution and extracted with Et_2O (3×10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography (SiO_2, particle size 32–63 μm, 5–15% ethyl acetate in hexanes) afforded the pure propargylic alcohols. The enantiomeric excess was determined by HPLC (Chiralcel OD, 10% *i*PrOH in hexanes if not stated otherwise).

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Keywords: alkynylation · amino alcohols · asymmetric catalysis · zinc

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