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Highly Enantioselective Synthesis of γ-Hydroxy-α,β-acetylenic Esters Catalyzed by a β-Sulfonamide Alcohol

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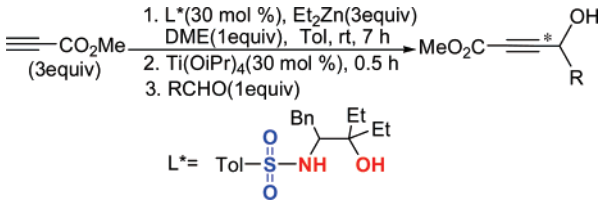
ABSTRACT



This work concerns the asymmetric addition of methyl propiolate to aldehydes with 1,2-dimethoxyethane (DME) as additive and β-sulfonamide alcohol titanium complex as a catalyst. The reactions proceeded under mild conditions and gave the highly functionalized chiral propargylic alcohols with high ee values and good yields. Differences between three types of ligands have also been discussed.

The asymmetric alkynylation of aldehydes is one of the most powerful procedures for organic synthetic chemistry, where the formation of one carbon−carbon bond and one chiral center of propargylic alcohol can be achieved in one step.[1] Recently, several studies have been reported in this area.[2] However, most studies were focused on the addition of phenylacetylene to carbonyl compounds. Highly functionalized γ-hydroxy-α,β-acetylenic esters are very important precursors for many bioactive and natural organic compounds in organic synthesis.[3] Few studies on the enantioselective reactions of alkynoates to aldehydes have been reported.[4] Trost reported the proline-derived dinuclear zinc catalyst system catalyzed the addition of alkynes to unsaturated aldehydes with high ee values and yields.[4a] While using HMPA as an additive, Pu reported that the BINOL-Ti

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(1) Recent reviews: (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886. (b) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757−824.

(2) (a) Fassler, D. E.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688. (c) Gao, G.; Xie, R. G.; Pu, L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5417−5420. (d) Lu, G.; Li, X.-S.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057−5058. (e) Jiang, B.; Chen, Z.-L.; Xiong, W.-N. *Chem. Commun.* **2002**, 1524−1525. (f) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895−2898. (g) Cozzi, P. G.; Rudolph, J.; Bolm, C.; Norrby, P.-O.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 5733−5736.

(3) (a) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28−29. (b) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867−869. (c) Trost, B. M.; Crawley, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 9328−9329. (d) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2004**, *126*, 13942−13944. (e) Molander, G. A.; St. Jean, D. J., Jr. *J. Org. Chem.* **2002**, *67*, 3861−3865. (f) Shahi, S. P.; Koide, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 2525−2527. (g) Meta, C. T.; Koide, K. *Org. Lett.* **2004**, *6*, 1785−1787. (h) Albert, B. J.; Sivaramakrishnan, A.; Naka, T.; Koide, K. *J. Am. Chem. Soc.* **2006**, *128*, 2792−2793. (i) Guillarme, S.; Ple, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* **2006**, *106*, 2355−2403 and references cited therein.

(4) (a) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8−9. (b) Trost, B. M.; Weiss, A. H. *Org. Lett.* **2006**, *8*, 4461−4464. (c) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem., Int. Ed.* **2005**, *45*, 122−125. (d) Rajaram, A. R.; Pu, L. *Org. Lett.* **2006**, *8*, 2019−2021.

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complex can catalyze the addition of methyl propiolate to both aromatic and aliphatic aldehydes with high ee values and moderate to good yields.[4c,d] They found that HMPA can greatly accelerate the reaction rate of $ZnEt_2$ with terminal alkynes. However, HMPA is a strong Lewis base and a very dangerous carcinogen.

Recently, we[5] have developed a new system for the catalytic alkynylation of carbonyl compounds without a separate step to prepare alkynylzinc. With use of β-sulfonamide alcohols as ligands, synthesized from inexpensive natural amino acids[5a,c,d] and camphor,[5b] the asymmetric addition of phenylacetylene to aldehydes proceeds under mild conditions with high ee values and yields. In our previous studies,[5c] while combining $ZnEt_2$, alkyne, and aldehyde in one pot (Scheme 1, method A, see the Supporting Information), we obtained very different ratios of the products of ethylation and alkynylation (Table 1) using different Ti complexes of BINOL, TADDOL, and β-sulfonamide alcohol (**L***) (Figure 1) as catalysts. The studies suggested that different ligands affect the Lewis acidity of Ti complexes markedly. A great ratio of alkynylation products was obtained under our catalytic condition (entry 3, Table 1), since the β-sulfonamide alcohol−Ti complex acted as a much weaker Lewis acid.

Scheme 1. Two Possible Products in the One-Pot Procedure

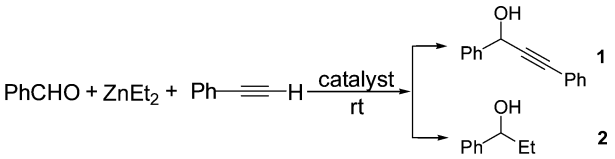


Table 1. Addition of Phenylacetylene to Benzaldehyde by the One-Pot Method[a]

entry	ligand	ligand/Ti(O^{i}Pr)$_4$ (mol %)	**1/2** (mol %)
1	BINOL	1:3	3:97
2	TADDOL	1:3	62:38
3	**L***	1:3	93:7

[a] Data have been published in ref 5c.

Looking into the structures of the ligands shown in Figure 1, we find that there are similar frames (red) which can be directly chelated with metal via two organometallic bonds. However, we also find the obvious differences among these three ligands. There are two ether oxygen atoms (blue) in TADDOL which may chelate metal via coordination bonds and act as Lewis bases. Previous reports indicated the sulfonyl oxygen atoms of the sulfonamide group of the β-sulfonamide alcohol can also chelate metal.[6] These are much stronger Lewis bases compared with the ether oxygen atoms in TADDOL. However, there is no such similar frame in BINOL. Then these three ligands can be arranged in the following sequence by the Lewis base of the groups: β-sulfonamide alcohol > TADDOL > BINOL.

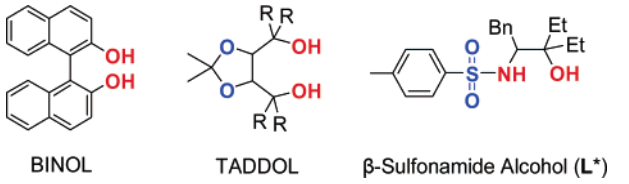
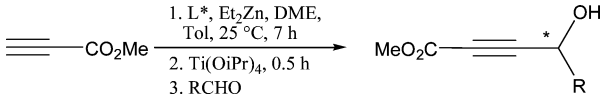


Figure 1. Structural comparison of different ligands.

In fact, this catalytic reaction was a two-step but one-pot procedure: (1) the formation of alkynylzinc and (2) the transfer of alkynyl to aldyhyde. Reports showed that BINOL[7a] and β-sulfonamide alcohol[7c,d] can be used as ligands for the addition of diethylzinc to aldehyde. Then we proposed that the first step of the one-pot procedure plays an important role in the ratio of the products of ethylation and alkynylation. Reports also suggested that the Lewis base can enhance the reactivity of $ZnEt_2$.[2c,4c,8] So, the structure of the Lewis base present in the ligands may play an important role. This presumption encouraged us to prove it and investigate the possibility of using methyl propiolate as a nucleophile.

According to our hypothesis, we supposed that the addition of methyl propiolate to benzaldehyde might proceed favorably when using **L*** (Figure 1) as the ligand under our initial method (Method B, see the Supporting Information).[5a] On the primary investigation, only a low yield (38%) was obtained. Then we chose 1,2-dimethoxyethane (DME) as an additive to optimize the reaction condition. The best conditions for our system are shown in Scheme 2.

Scheme 2. Asymmetric Addition of Methyl Propiolate to Aldehydes Catalyzed by **L***



We found that the enantioselectivity of the reaction is greatly affected by the amount of Ti(O^{i}Pr)$_4$ as shown in Table 2. When the ratio of **L***/Ti(O^{i}Pr)$_4$ was 1:1, the highest ee

(5) Selected reports: (a) Xu, Z. Q.; Wang, R.; Xu, J. K.; Da, C.-S.; Yan, W. J.; Chen, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5747−5749. (b) Xu, Z. Q.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193−1195. (c) Xu, Z. Q.; Lin, L.; Xu, J. K.; Yan, W. J.; Wang, R. *Adv. Synth. Catal.* **2006**, *348*, 506−514. (d) Ni, M.; Wang, R.; Han, Z. J.; Mao, B.; Da, C.-S.; Liu, L.; Chen, C. *Adv. Synth. Catal.* **2005**, *347*, 1659−1665. (e) Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z. *Org. Lett.* **2004**, *6*, 4147−4149. (f) Chen, C.; Hong, L.; Xu, Z.-Q.; Liu, L.; Wang, R. *Org. Lett.* **2006**, *8*, 2277−2280.

(6) (a) Kanai, M.; Kuramochi, A.; Shibasaki, M. *Synthesis* **2002**, 1956−1958. (b) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423−6424. (c) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739−749.

Table 2. Results for Optimizing the Reaction Conditions[a]

entry	L* (mol %)	$Ti(O^iPr)_4$ (mol %)[b]	DME (equiv)[b]	$ZnEt_2$ (equiv)[c]	ee (%)
1	40	120	2	4	78
2	40	80	2	4	84
3	40	50	2	4	91
4	40	40	2	4	92
5	40	30	2	4	90
6	40	20	2	4	34
7	30	30	1	3	91
8	20	20	1	3	81

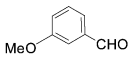
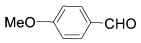
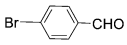
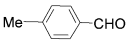
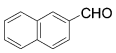
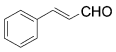
[a] All reaction proceed in toluene as the main solvent. [b] Freshly distilled before use. [c] Alkyne:$ZnEt_2$ = 1:1.

value was obtained. Different loadings of ligand, DME, $ZnEt_2$, and alkyne were also investigated. Under the optimal condition (entry 7, Table 2), the asymmetric addition of methyl propiolate to benzaldehyde led to γ-hydroxy-α,β-acetylenic product with high enantioselecticity (ee 91%).

Under the optimized condition, high enantioselectivity and moderate to good yields were obtained in the reaction of methyl propiolate to a number of aldehydes. The results are summarized in Table 3.

The high ee values were obtained when the aromatic aldehydes have either electron-donating or electron withdrawing-substituents under the optimized condition (entries 2−7, Table 3). Exploring 1-naphthaldehyde, 2-naphthaldehyde, and 2-furaldehyde as substrates, high enantioselectivity was also obtained (entries 8−10, Table 3). The ee values were 85% and 82% for two α,β-unsaturated aldehydes (entries 11 and 12, Table 3). A good result was also observed when aliphatic aldehyde was employed as a substrate (entry 13, Table 3). Notably, high enantioselecticity and morderate yields were also obtained when substrates had technical purity (entries 2, 5, and 8, Table 3).

Table 3. Asymmetric Addition of Methyl Propiolate to Aldehydes Catalyzed by **L*** [a,b]

entry	aldehydes	isolated yield (%)	ee (%)[c]
1		79	91 (R)[e]
2[d]		77	90
3		78	92
4		76	94
5[d]		77	93
6		67	92
7		76	94
8[d]		72	92
9		73	93
10		65	92
11		64	85
12		65	82
13		80	79 (R)[e]

[a] In all of the entries: Et_2Zn:alkyne:DME:aldehyde:$Ti(OiPr)_4$:**L*** = 3:3:1:1:0.3:0.3. [b] 9−15 h were required after the addition of aldehydes determined by TLC. [c] The ee values were determined by chiral HPLC. [d] Technical purity. [e] Absolute configuration is based on the comparison of of the optical rotation with the literature values (refs 4c and 4d).

Comparing with the catalytic system which uses BINOL as a ligand, a much weaker Lewis base (DME) was introduced into our system. However, the formation of alkynylzinc was much faster. The significant difference between these two catalytic systems indicates well that the Lewis base of the ligand was favorable in the catalytic procedure. The proposed mechanism is shown in Figure 2.

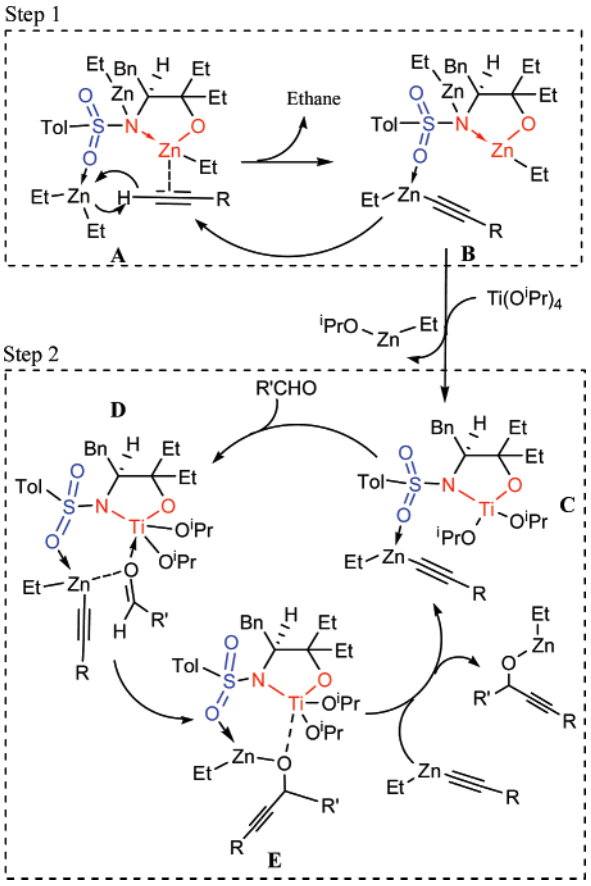


Figure 2. Proposed catalytic cycle.

In Step 1, ligand, $ZnEt_2$, and alkyne were mixed together. The catalytic center was formed when the sulfonamide and

(7) Selected examples: (a)Yang, X.-W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295−296 and references cited therein. (c) Yus, M.; Ram'on, D. J.; Preito, O. *Tetrahedron*: *Asymmetry* **2002**, *13*, 1573−1579. (d) Bauer, T.; Tarasiuk, J.; Pasniczek, K. *Tetrahedron*: *Asymmetry* **2002**, *13*, 77−82.

(8) Kitamura, M.; Okada, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036.

hydroxy group reacted with diethylzinc. This species might coordinate with diethylzinc and alkyne to form **A**.[6c,9] Then ethyl-transfer occurred under the intramolecular cooperation of Lewis base (blue frame, Figure 2) and Lewis acid (red frame, Figure 2).[2f,4a,10] However, in the BINOL-Ti catalytic system, this process might take place via the intermolecular cooperation of HMPA and BINOL-$(ZnEt)_2$ complexes. This difference indicated that a shorter time was needed by our catalytic system in Step 1.[11] When the R group was ester (methyl propiolate), it could also be chelated to metal (Lewis acid). But this may not be favorable for the formation of alkynylzinc. So a strong Lewis acid should be avoided in Step 1, and extra Lewis base was introduced to promote the formation of alkynylzinc. Step 1 took a longer reaction time if a larger dosage of DME was added. We suspected that DME might chelate $ZnEt_2$ to avoid other side reactions.[12] So different efforts were required for the extra Lewis bases used in the BINOL-Ti catalytic system (HMPA) and the β-sulfonamide alcohol-Ti catalytic system (DME).

In Step 2, zinc, which chelated N and O atoms of the ligand, was replaced by the newly added $Ti(O^iPr)_4$, and formed a new Lewis acid center (**C**) for the alkynyl addition to aldehyde. Under the same intramolecular cooperation of Lewis base (blue frame, **C**, **B**, and **D**, Figure 2) and the new Lewis acid center (red frame, **C**,**B**,**D**, Figure 2), alkynyl transfer proceeds successfully via a proposed catalytic cycle in Step 2, Figure 2.

In summary, we have extended the applicability of our catalytic system for the alkynylation of aldehydes. Exploring DME as an additive, the addition of methyl propiolate to both aromatic and aliphatic aldehydes proceeds under very mild conditions. Our results indicated that β-sulfonamide alcohol (**L***) can accelerate the formation of alkynylzinc much more effectively than BINOL. In addition, a highly toxic reagent was avoided under our conditions.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373−381.

(10) Similar reports about the intramolecular cooperation of the ligand: (a) Hatano, M.; Miyamoto, T.; Ishihara, K. *J. Org. Chem.* **2006**, *71*, 6474−6484. (b) Qin, Y.-C.; Pu, L. *Angew. Chem., Int. Ed.* **2005**, *45*, 273−277. (c) Qin, Y.-C.; Liu, L.; Sabat, M.; Pu, L. *Tetrahedron* **2006**, *62*, 9335−9348.

(11) In Step 1, which needed 16 h for the BINOL-Ti catalytic system, and 7 h for our catalytic system.

(12) We are grateful for the reviewers who gave us some good advice. The side reaction is under investigation.