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Highly Enantioselective Addition of Phenylacetylene to Aldehydes Catalyzed by a Camphorsulfonamide Ligand

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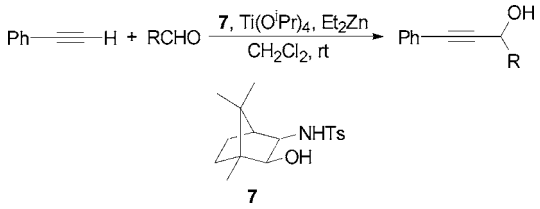
ABSTRACT



The asymmetric addition of phenylacetylene to aldehydes was carried out by using a camphorsulfonamide titanium complex as a catalyst. The reactions proceeded under mild conditions and gave the products with good yields and high ees. This system is very useful for the synthesis of chiral propargylic alcohol.

The asymmetric addition of alkynyl regents to aldehydes is very useful for the synthesis of chiral secondary propargylic alcohols,[1,2] which are very important building blocks for many chiral organic compounds.[3] The acetylene and hydroxyl functions of the propargylic alcohol products can be used to construct very diverse molecular structures. Recently, Carreira reported that amino alcohol **1** can effectively catalyze this reaction, but the substrates were limited in aliphatic aldehydes due to the significant Cannizzaro reaction.[4] Pu reported that BINOL−Ti complex can catalyze alkynylzinc addition to both aromatic and aliphatic aldehydes with high ees and good yields. In his system, he used a separate step to synthesize alkynylzinc at high temperature.[5] Chan reported that a 1:1 combination of BINOL **2** with sulfonamide as the ligand can also catalyze this reaction. The reactions were run at temperatures below 0 °C for 1−2 days and give the products with high ees.[6]

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(1) For review, see: (a)Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757. (b) Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873.

(2) Selected recent examples of our group: (a) Liu, D. X.; Zhang, L. C.; Wang, Q.; Da, C. S.; Xin, Z. Q.; Wang, R.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2001**, *3*, 2733. (b) Yang, X. W.; Su, W.; Liu, D. X.; Wang, H. S.; Shen, J. H.; Da, C. S.; Wang, R.; Chan, A. S. C. *Tetrahedron* **2000**, *56*, 3511. (c) Yang, X. W.; Shen, J. H.; Da, C. S.; Wang, H. S.; Su, W.; Liu, D. X.; Wang, R.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **2001**, *42*, 6573. (d) Yang, X. W.; Shen, J. H.; Da, C. S.; Wang, H. S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295. (e) Xu, Z.; Wang, R.; Xu, J.; Da, C.; Yan, W.; Chen, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5747.

(3) (a) Marsh, J. A.; Wang, X. J. *J. Org. Chem.* **1992**, *57*, 1242. (b) Meyers, A. G.; Zhang, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. (c) Fox, M. E.; Li, C.; Marino, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467.

(4) (a) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (c) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605. (d) Boyall, D.; Lopez, F.; Sasaki, H.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233. (e) El-Sayed, E.; Anand, N. K. Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017.

(5) (a) Gao, G.; Moore, D.; Xie, R. G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143. (b) Xu M. H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555.

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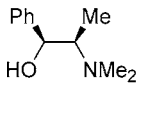
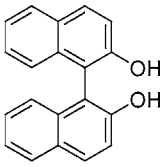


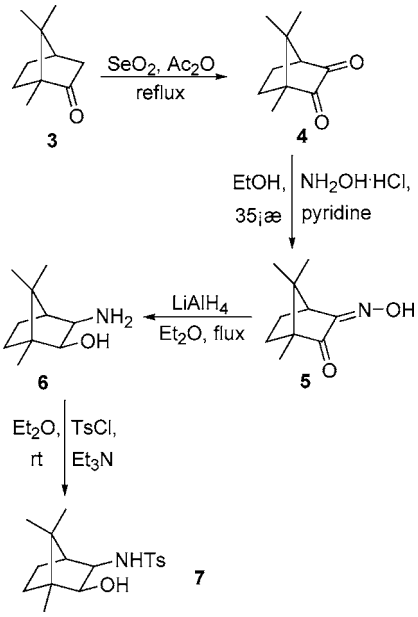
1



2

Sulfonamide has the property that the N−H of sulfonamide is acidic due to the highly electron-withdrawing nature of the sulfonyl group. Therefore, unlike traditional metal amides (M-NR_2), the sulfonamide nitrogen is a poor electron donor, and the resulting complexes are Lewis acidic.[7] Camphor derivatives are among the most efficient chiral ligands reported in catalytic asymmetric reaction.[8] We used (+)-camphor as a starting material. After four simple steps, we got a camphorsulfonamide in an overall yield of 42% (Scheme 1) and used it as a catalyst in the asymmetric addition of

Scheme 1. Synthesis of the Camphorsulfonamide Ligand **7**[9]



phenylacetylene to aldehydes. To our astonishment, this ligand can catalyze the reaction with high speed, under mild conditions, and in good yields, and the ee values are also high. Herein, we report our results.

First, we tested it in the asymmetric addition of phenylacetylene to benzaldehyde in the presence of diethylzinc (Scheme 2). We found that the reaction was influenced by the amount of $Ti(O^iPr)_4$, and the ee was greatest when **7**/$Ti(O^iPr)_4$ was 1/4 (Table 1, entries 1−4). The solvents also can influence the ees (entry 5). When the amount of the ligand was increased from 2 to 5% and 10%, the ee increased slightly (entries 6, 7). Decreasing the temperature of the

(6) (a) Li, X. S.; Lu, G.; W. Kwok, H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636. (b) Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002**, 172.

(7) Pritchett, S.; Gantzel, P.; Walsh, P. J. *Organometallics* **1997**, *16*, 5130.

Scheme 2. Reaction of Phenylacetylene with Benzaldehyde in the Presence of Et_2Zn, **7**, and $Ti(O^iPr)_4$[10]

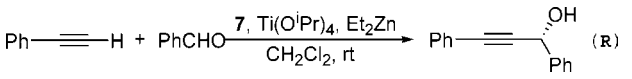


Table 1. Asymmetric Addition of Phenylacetylene to Benzaldehyde Using **7** as a Ligand[a]

entry	ligand (mol %)	ligand/ $Ti(O^iPr)_4$[b]	Et_2Zn (mol %)	solvent	temp	ee[c] (%)
1	10%	1/2	300	CH_2Cl_2	rt	93
2	10%	1/3	300	CH_2Cl_2	rt	94
3	10%	1/4	300	CH_2Cl_2	rt	97
4	10%	1/5	300	CH_2Cl_2	rt	93
5	10%	1/4	300	toluene	rt	85
6	2%	1/4	300	CH_2Cl_2	rt	78
7	5%	1/4	300	CH_2Cl_2	rt	84
8	10%	1/4	300	CH_2Cl_2	0 °C	90
9	10%	1/4	200	CH_2Cl_2	rt	81
10	10%	1/4	150	CH_2Cl_2	rt	79

[a] Phenylacetylene/Et_2Zn = 1:1. [b] $Ti(O^iPr)_4$was freshly distilled. [c] Enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column.

reaction from room temperature to 0 °C increased the reaction time and decreased the ee (entry 8). When we decreased the amount of Et_2Zn from 300 to 200 and 150 mol %, the enantioselectivity also decreased (entries 9, 10).

Under the above optimized reaction conditions, ligand **7** was employed to induce the enantioselective addition of phenylacetylene to a family of aldehydes. As the results summarized in Table 2 show, all the aromatic aldehydes afforded high enantioselectivities, and the aliphatic aldehydes also gave good ees.

Table 2. Asymmetric Addition of Phenylacetylene to Aldehydes Promoted by Ligand **7**[a−c]

entry	aldehydes	time (h)	isolated yield (%)	ee (%)[d]
1	benzaldehyde	12	93	97
2	2-anisaldehyde	12	89	97
3	3-anisaldehyde	12	85	95
4	4-ansialdehyde	12	90	92
5	3-bromobenzaldehyde	12	91	94
6	4-bromobenzaldehyde	12	85	92
7	4-chlorobenzaldehyde	12	81	92
8	4-fluorohenzaldehyde	12	87	93
9	α-naphthaldehyde	14	67	91
10	β-naphthaldehyde	14	75	98
11	cinnamicaldehyde	12	71	93
12	butylaldehyde	12	82	85
13	isobutylaldehyde	12	88	75

[a] In all of the entries, Et_2Zn/phenylacetylene/aldehyde/$Ti(O^iPr)_4$/**7** = 3:3:1:0.4:0.1. [b] All reactions were processed under argon and at room temperature. [c] $Ti(O^iPr)_4$was freshly distilled before use. [d] Ee values were determined by chiral HPLC with a Chiracel OD column.

In conclusion, we have conveniently synthesized a sulfonamide ligand from natural camphor in four steps with good yield. The ligand is an excellent catalyst for the reaction of enantioselective addition of phenylacetylene to aldehydes under very mild conditions. In this system, severe conditions are not needed to prepare alkynylzinc in a separate step. This low-cost catalyst will substantially improve the availability of the reaction.

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Supporting Information Available: Characterization of ligand **7** and the propargylic alcohols and procedures for addition of phenylacethylene to aldehydes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For some selected examples of camphor derivatives, see: (a) Kitamura, M.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (b) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 3250. (c) Garcia, C.; LaRochelle, L. K.;Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970.

(9) Camphorsulfonylamino **7** was synthesized according to literature procedures: (a) Chittenden, R. A.; Cooper, G. H. *J. Chem. Soc. C*, **1970**, 49. (b) You, J. S.; Shao, M. Y.; Gau, H. M. *Tetrahedron: Asymmetry* **2001**, *12*, 2971. (c) Itsuno, S.; Watanabe, K.; Matsunomo, T.; Kuroda, S.; Yokoi, A.; El-Shehawy, A. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 2011−2016.

(10) Absolute configuration is based on measurement of the optical rotation and comparison with the literature values: Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.