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Highly Enantioselective Phenylacetylene Additions to Ketones Catalyzed by (*S*)-BINOL−Ti Complex

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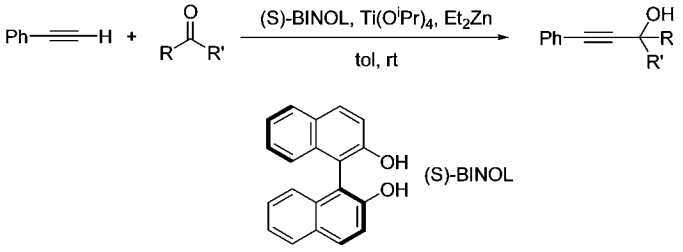
ABSTRACT



The readily available and inexpensive (*S*)-BINOL ligand in combination with Ti(O^{i}Pr)$_4$ is an effective chiral catalyst for the catalytic asymmetric addition of alkynylzinc to unactivated simple ketones. Good to excellent enantioselectivities were achieved. No previous case has been reported successfully using BINOL to catalyze the addition of phenylacetylene to unactivated ketones, and thus the utility of BINOL in asymmetric catalysis is expanded.

The asymmetric addition of alkynylzinc to aldehydes and ketones is an important method of synthesizing chiral propargyl alcohols, which are important pharmaceutical intermediates. In the past few years, asymmetric alkynylzinc addition to aldehydes has reached an impressive level of complexity.[1] However, alkynylation of ketones to formate chiral tertiary propargylic alcohols has met with only very limited success. The difficulty was mainly due to the inertness of ketones and controlled facial stereoselectivity. Grabowski[2−5] and Jiang[6] obtained the *p*-methoxybenzyl-protected ketoaniline in 98−99% ee, a key intermediate in the manufacturing of Efavirenz (DMP266), a drug used in the treatment of AIDS.[7] Carreira[8] and co-workers developed a method that was applied to the enantioselective alkynylation of ketoesters[9] and exhibited only reactivity with ketones. So,

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there are great efforts to develop efficient ligands that can be applied to widespread substrates.

Cozzi[10] used Zn(salen) complexes to catalyze enantioselective alkynylation of ketones and achieved moderate ee. Chan[11] used chiral camphorsulfonamide $Cu(OTf)_2$ complexs as catalysts and got the desired products with good results. They did the pioneering studies in the enantioselective alkynylation of unactivated simple ketones. In their work, they attempted to use chiral binaphthol, titanium tetraisopropoxide, and alkynylzinc reagents, which are known to be effective catalyst systems for the addition of alkynyl groups to aldehydes[12] for the asymmetric alkynylation of ketones. However, they were unsuccessful. Among asymmetric addition reactions catalyzed by BINOL−Ti complex, when BINOL and $Ti(O^iPr)_4$ are mixed in different proportions, the Lewis acidity of the complex differs with the different coordinate titanium centers. When BINOL/$Ti(O^iPr)_4$ is 1:1, the complex (BINOLate)$Ti(O^iPr)_2$ is the strongest Lewis acid.[13] In asymmetric addition of alkynylzinc to aldehydes catalyzed by BINOL−Ti complex, the best proportion of BINOL to Ti is 1:5 because of the activity of aldehydes. However, when the substrates are ketones, the above proportion is not suitable because ketones are more inert than aldehydes. So a more acidic Lewis acid may be needed to activate the ketones. On the basis of our previous work[14] and an understanding of the mechanism of the action of titanium in the asymmetric addition reaction using BINOL as the catalyst, we considered that the complex (BINOLate)-$Ti(O^iPr)_2$ (BINOL/$Ti(O^iPr)_4$ =1:1) was acidic enough to catalyze this reaction. The results showed that this change resulted in a surprising jump in the enantioselectivity and reactivity. The relationship between the amount of $Ti(O^iPr)_4$ and the enantiomeric excess is demonstrated in Figure 1.

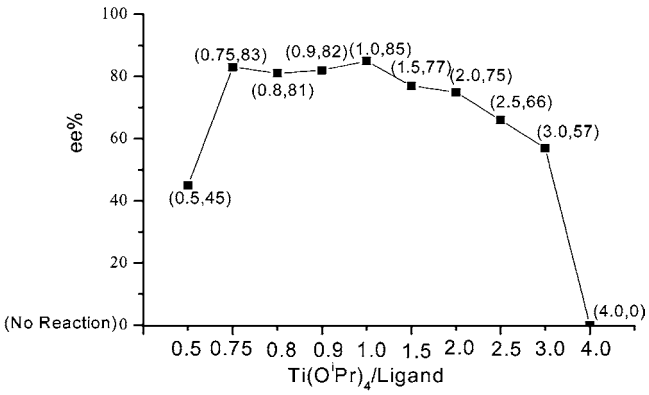
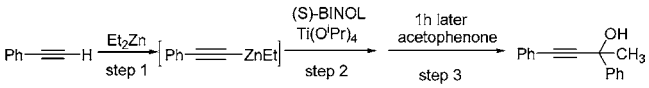


Figure 1. Relationship between the amount of $Ti(O^iPr)_4$ and the enantiomeric excess. When the ratio exceeded 1.5, the yield of products decreased quickly.

We conducted the asymmetric alkynylzinc addition to ketones in several steps (Scheme 1). First, we prepared the active zinc reagent by stirring phenylacetylene with diethylzinc in toluene at room temperature for 3 h. Second was the addition of (*S*)-BINOL and $Ti(O^iPr)_4$. One hour later, the orange solution was treated with acetophenone. Interestingly, when the former two steps were reversed, the product had a lower ee (44% ee). This indicated that good formation of higher reactive alkynylzinc was very important to the high enantioselectivity of the reaction.

Scheme 1. Reaction of Phenylacetylene with Acetophenone in the Presence of Et_2Zn, (*S*)-BINOL, and $Ti(OiPr)_4$.



The reaction was also strongly influenced by the amount of diethylzinc. When the dialkynylzinc was prepared selectively by the reaction of diethylzinc and excess phenylacetylene (2.0 equiv) at room temperature, no reaction was observed (Table 1, entry 9). When we prepared the alkynylzinc at 80 °C for 5 h, the product had a low ee (14% ee, entry 14). We supposed that the alkynylzinc disproportionated to give the dialkynylzinc and diethylzinc at higher temperature (>80 °C). Because no reactivity of the dialkynylzinc was observed in the reaction, the result was similar to using excess diethylzinc compared with phenylacetylene (entry 11).

The solvents strongly influenced the results of the reaction. Low enantioselectiveties and reactivity were afforded in CH_2Cl_2 (entry 7), ether (entry 6), and THF (entry 8). From experimental results, the sequence of enantioselectivities and reactivity in solvents was toluene > ether > CH_2Cl_2 > THF. The amount of the ligand was increased from 10% to 30% and the ee's increased from 61% to 85%. The temperature of the reaction was decreased from room temperature to 0 °C, and no reaction was observed. All the conditions influencing the reaction are summarized in Table 1.

Most of the chiral tertiary propargyl alcohols that were generated from other aromatic ketones were obtained with 85−92% ee at room temperature when using the above procedure, and the results are summarized in Table 2. Astonishingly, the fluoro-substituted acetophenone showed lower ee's. The reactions of the phenylacetylene addition to aliphatic ketones and α,β-unsaturated ketones were also observed. The product that was generated from 4-methyl-

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Table 1. Asymmetric Addition of Phenylacetylene to Acetophenone Using (*S*)-BINOL−Ti[a,b] Complex as Ligand[c]

entry	conditions for step 1	conditions for step 2	phenylacetylene/Et_2Zn[d] (%)	(*S*)-BINOL (%)	ee[e] (%)
1	0.5 mL of toluene, stir 3 h, rt	2 mL of toluene	300/300	10	61
2	0.5 mL of toluene, stir 3 h, rt	2 mL of toluene	300/300	15	80
3	0.5 mL of toluene, stir 3 h, rt	2 mL of toluene	300/300	20	85
4	0.5 mL of toluene, stir 3 h, rt	2 mL of toluene	300/300	25	80
5	0.5 mL of toluene, stir 3 h, rt	2 mL of toluene	300/300	30	80
6	0.5 mL of ether, stir 3 h, rt	2 mL of ether	300/300	20	59
7	0.5 mL of DCM, stir 3 h, rt	2 mL of DCM	300/300	20	48
8	0.5 mL of THF, stir 3 h, rt	2 mL of THF	300/300	20	
9	0.5 mL of toluene, stir 3 h, rt	2 mL of toluene	300/150	20	
10	0.5 mL of toluene, stir 3 h, rt	2 mL of toluene	300/200	20	77
11	0.5 mL of toluene, stir 3 h, rt	2 mL of toluene	300/400	20	3
12	0.5 mL of toluene, stir 3 h, 50°C	2 mL of toluene	300/300	20	85
13	0.5 mL of toluene, stir 3 h, 80°C	2 mL of toluene	300/300	20	48
14	0.5 mL of toluene, stir 5 h, 80°C	2 mL of toluene	300/300	20	14

[a] (*S*)-BINOL/Ti(O^iPr)$_4$ = 1:1 [b] Ti(O^iPr)$_4$ was freshly distilled. [c] All reactions were processed at room temperature. At 0 °C no reaction was observed. [d] 1 M Et_2Zn in toluene. [e] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column.

2-pentanone was obtained with 63% ee, and the one that was generated from benzalacetone was obtained with 73% ee.

Table 2. Asymmetric Addition of Phenylacetylene to Other Ketones Promoted by the Ligand (*S*)-BINOL−Ti Complex[a−e]

entry	substrate	isolated yield (%)	ee (%)
1	acetophenone	67	85
2	3′-methoxyacetophenone	81	92
3	3′-methylacetophenone	66	90
4	4′-methylacetophenone	64	87
5	4′-chloroacetophenone	73	89
6	3′-bromoacetophenone	68	86
7	2′-naphthacetophenone	72	85
8	1′-naphthacetophenone	71	91
9	2′-fluoroacetophenone	80	66
10	4-methyl-2-pentanone	91	63
11	benzalacetone	88	73

[a] In all of the entries, Et_2Zn/phenylacetylene/ketone/Ti(O^iPr)$_4$/(*S*)-BINOL = 3:3:1:0.2:0.2. [b] All reactions were processed under argon and at room temperature. [c] Ti(O^iPr)$_4$was freshly distilled before use. [d] The ee values were determined by HPLC with Chiracel OD column. [e] All reactions were carried out for 48 h for aromatic ketones and 18 h for aliphatic and α,β-unsaturated ketones.

In summary, we have demonstrated that a readily available and inexpensive (*S*)-BINOL ligand in combination with Ti(O^iPr)$_4$ is an effective chiral catalyst for the catalytic asymmetric addition of alkynylzinc to unactivated simple ketones. Good to excellent enantioselectivities were achieved. The monomer (BINOLate) Ti(O^iPr)$_2$ is sufficiently Lewis acidic that it can activate ketones. Further studies are underway to use this system for the asymmetric addition of alkylzinc reagents to ketones and for catalytic reactions using other ligands that are similar to BINOL.

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Supporting Information Available: Characterizations of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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