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Highly Enantioselective Alkynylzinc Addition to Aromatic Aldehydes Catalyzed by Self-Assembled Titanium Catalysts

Xingshu Li, Gui Lu, Wai Him Kwok, and Albert S. C. Chan*

Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong

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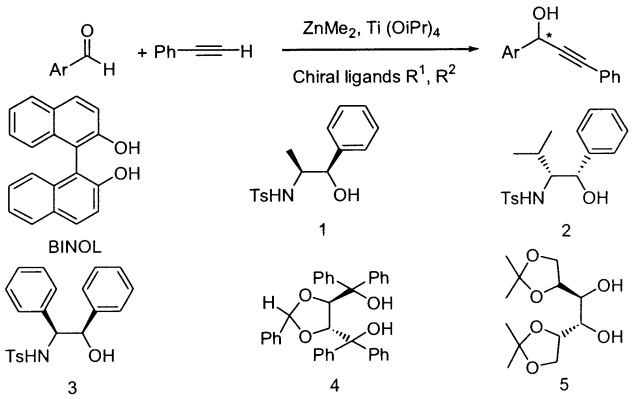
The asymmetric alkynylzinc addition to aldehydes is a useful method for the production of chiral secondary propargylic alcohols which are versatile building blocks for asymmetric synthesis.[1] As compared with the asymmetric reduction of ynones,[2] the addition of alkynylzinc to aldehydes has a substantial advantage because the formations of the stereogenic center and the C−C bond of the propargylic alcohol targets are concomitant. However, in contrast to the enantioselective addition of dialkyl compounds to aldehydes in which considerable progress has been made,[3] the enantioselective alkynylzinc addition to aldehydes is still less developed. Several previous studies of the alkynylation of aldehydes using amino alcohol ligands gave moderate to good yields and ee's.[4,5] Recently, Carreira et al. reported that a system using $Zn(OTf)_2$ and Et_3N with stoichiometric[6] or catalytic[7] amounts of ligands gave high product yields and enantioselectivities in the addition of terminal acetylenes to aliphatic aldehydes; however, the catalytic system is substantially less effective for aromatic substrates.

We previously studied the Ti(BINOL)- and Ti(H_8-BINOL)-catalyzed addition of diethylzinc and triethylaluminum to aldehydes and obtained good to excellent ee's.[8] More recently, we found that these catalysts were also effective for the alkynylzinc addition to aldehydes.[9] In the examination of other chiral ligands for this reaction, we found that some titanium catalysts, which were effective for the addition of diethylzinc to aldehydes, were ineffective for alkynylzinc addition. In a different development, Mikami et al. reported the self-assembly of several chiral ligand components into a highly enantioselective titanium catalyst for carbonyl-ene reactions.[10] The interesting results obtained by these investigators clearly showed that both the rate and the enantioselectivity were enhanced when a combination of chiral ligand components was used instead of its single chiral ligand component in the enantioselective catalysis of the carbonyl-ene reaction. Herein, we report the self-assembly of BINOL and other chiral ligands into a highly effective titanium catalyst for the addition of alkynylzinc to aldehydes in up to >99% ee.

The preliminary results showed that in combination with BINOL, other chiral ligands such as a diol or a sulfonamide increased the catalytic activity and enantioselectivity of the alkynylation of aldehydes using Ti(O*i*Pr)$_4$ as catalyst precursor (see Table 1).

The use of titanium taddol (entry 4) and titanium mannitol derivative (entry 5) gave no ee and suffered from the production of alkylated byproducts, while titanium sulfonamides (entry 1−3) gave essentially no enantioselectivity. In the presence of 10 mol % (*R*)-BINOL, the alkynylation of benzaldehyde produced 77% ee (entry 6). However, when (*R*)-BINOL or (*S*)-BINOL and one of these chiral ligands (R^2 = **1**−**5**, 10 mol % each) were added together, the ee values of the products were found to increase to



85−90% (entries 7−8, 10−13). As ephedrine is a low cost and readily available material, we chose sulfonamide **1** for the further study of this reaction.

It is noteworthy that the use of (*R*)-BINOL in this self-assembled catalyst system produced the *S* configuration of the product, while the use of (*S*)-BINOL gave the product in *R* configuration (entries 7−8, 16−17). These results suggested that the chiral ligand R^1

Table 1. Asymmetric Catalysis of the Alkynylzinc Addition of Benzaldehyde[a]

entry	R^1	R^2	Ti/(R^1 + R^2)	yield, %[b]	ee, %[c]	config[d]
1	none	1	7/1	100	0	
2	none	2	7/1	100	0	
3	none	3	7/1	100	0	
4	none	4	7/1	10[e]	0	
5	none	5	7/1	12[e]	0	
6	*R*-BINOL	none	7/1	90	77	*S*
7	*R*-BINOL	1	7/1	90	87	*S*
8	*S*-BINOL	1	7/1	88	90	*R*
9	*rac*-BINOL	1[f]	7/1	91	18	*R*
10	*S*-BINOL	2	7/1	89	89	*R*
11	*S*-BINOL	3	7/1	90	90	*R*
12	*S*-BINOL	4	7/1	87	86	*R*
13	*S*-BINOL	5	7/1	86	85	*R*
14	*S*-BINOL	1	3.5/1	85	93	*R*
15	none	1	1.5/1	43	0	
16	*S*-BINOL	1	1.5/1	83	96	*R*
17	*R*-BINOL	1	1.5/1	80	94	*S*
18	*S*-BINOL	1	1.25/1	81	**97**	*R*
19	*S*-BINOL	none	1.25/1	74	91	*R*
20	*S*-BINOL	1	1/1	84	94	*R*
21	*S*-BINOL	none	1/1	66	87	*R*

[a] Aldehyde:$ZnMe_2$:R^1:R^2 = 1:2:0.1:0.1 (molar ratio); the reaction was carried out at 0 °C under nitrogen gas for 24−48 h. [b] Isolated yield of the corresponding products. [c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column. [d] The configurations were based on the measurements of the optical rotations and in comparison with the relevant literature values.[11] [e] The major product is α-methylbenzyl alcohol. [f] 5% ligand, R^2.

* To whom correspondence should be addressed. E-mail: bcachan@polyu.edu.hk.

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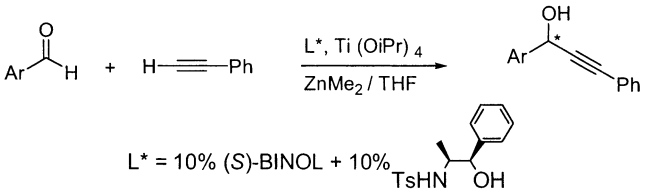
Table 2. The Alkynylzinc Addition to Aromatic Aldehydes Catalyzed by Titanium (*S*)-BINOL in the Presence of Chiral Sulfonamide Ligand **1**[a]



entry	aldehydes, Ar =	yield, %	ee, %[b]
1	phenyl	83	96
2	2-nitrophenyl	83	88
3	3-nitrophenyl	82	>99
4	4-nitrophenyl	82	99[12]
5	4-bromophenyl	85	99
6	3-chlorophenyl	84	97
7	4-chlorophenyl	86	95
8	2-naphthyl	81	95
9	4-methoxyphenyl	78	95
10	4-methylphenyl	79	92

[a] The ratio of ligands (BINOL + sulfonamide **1**) to titanium tetraisopropoxide was 1.5:1.0 in each case, and the reaction was carried out under nitrogen gas at 0 °C for 24−48 h; the titanium tetraisopropoxide and the substrates were distilled before use. [b] The ee's were determined by HPLC analysis of the products on a Chiralcel OD column.

(BINOL) dominated the stereochemistry of this reaction, and the chiral ligand R^2 acted as an activator in this self-assembled catalyst system. Moreover, the use of (*S*)-BINOL gave products with higher ee's than those obtained by using (*R*)-BINOL in the reactions (entries 7−8, 16−17). If *rac*-BINOL was used, 18% ee of the product was obtained with *R* configuration instead of racemic product (entry 9). The enantiomer (*S*)-BINOL in *rac*-BINOL seemed to produce a more active self-assembled catalyst with the other chiral ligand R^2 than the (*R*)-BINOL in the same mixture.

The effects of the reaction conditions such as the choice of solvent and the ratio of chiral ligands (R^1 + R^2)-to-titanium tetraisopropoxide were investigated, and it was found that the latter was important in influencing the enantioselectivity of the catalyst. While keeping other conditions unchanged, the chiral ligands-to-titanium tetraisoproppoxide ratio of 1:1.25−1.5 was found to be optimum. Under this condition, the ee values of the product were found to be 96−97% (entries 16, 18). When the level of the chiral ligand was close to that of the titanium ion, the rate of the reaction decreased somewhat.

A variety of aromatic aldehydes were tested under the optimal reaction conditions, and the results were summarized in Table 2. Good to excellent ee's were obtained in each case (88−>99% ee). These results compared favorably with the highest enantioselectivities reported for the reactions of terminal alkynes with aromatic aldehydes using stoichiometric amounts of *N*-methylephedrine and $Zn(OTf)_2$ (94% ee for benzaldehyde with phenylacetylene and 96% ee for benzaldehyde with 1-phenyl-4-butyne).[6a] From Table 2, it can be seen that the influence of the position of substituent on the phenyl ring of the substrates on the enantioselectivity of the product was quite significant. For example, the alkynylation of *o*-nitrobenzaldehyde gave only 88% ee, while the same reactions for *m*-nitrobenzaldehyde and *p*-nitrobenzaldehyde gave >99% and 99% ee, respectively (entries 2−4). This could be explained by the strong steric hindrance effect of the *ortho*-substituent which significantly weakened the coordination of the aldehyde to the catalyst. On the other hand, the substituent on the *meta*- or *para*-position of the phenyl ring of the substrates exerted significantly less steric hindrance effect on the aldehyde coordination. The electronic effect of the substituents on the substrates also had some influences on the enantioselectivity of the products. Electron-withdrawing groups on the phenyl ring were favored for higher enantioselectivity (entries 3−7), while electron-donating substituents were found to lower the ee's of the products (entries 9−10).

In conclusion, we have developed a highly enantioselective catalyst for the synthesis of propargylic alcohols via the alkynylzinc addition to aromatic aldehydes. The study showed that a combination of chiral ligands, such as BINOL and a sulfonamide, with $Ti(OiPr)_4$ generated a highly enantioselective catalyst which gave products with up to >99% ee. The study of the mechanism of the reaction and the application of this catalyst system in other asymmetric catalytic reactions are in progress.

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(12) In the absence of chiral sulfonamide ligand **1**, when 10 mol % or 20 mol % of (*S*)-BINOL was added, the yield and the ee values are 70%, 95% ee and 79%, 97% ee, respectively.

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