Titanium-catalyzed enantioselective alkynylation of aldehydes

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A simple and practical method to make chiral propargylic alcohols has been developed: in the presence of a titanium alkoxide catalyst prepared *in situ* from titanium tetra-isopropoxide and (*R*)-H$_8$-binaphthol, a variety of aromatic aldehydes were converted to the corresponding chiral propargylic alcohols with very good enantioselectivities (up to 96.2% e.e.) and yields.

Chiral propargylic alcohols are useful building blocks for the enantioselective synthesis of complex molecules.[1] Two general approaches to the preparation of optically active propargylic alcohols have been reported starting from either ynones[2] or aldehydes.[3,4] The method of alkynyl addition has a strategic synthetic advantage over the ynone reduction method because the former forms a new C–C bond with concomitant creation of a stereogenic center in a single transformation, while in the latter the C–C bond and the stereogenic center are formed separately. The catalytic alkynylation with high enantioselectivity is relatively rare.[3,4]

The successful resolution of racemic BINOL provides an economic production of (*S*)- or (*R*)-BINOL[5] and consequently provides an excellent opportunity for the exploitation of (*S*)- and (*R*)-BINOL and their derivatives as readily available and potentially low-cost chiral auxiliaries for asymmetric synthesis. Recent studies[6,7] have shown that chiral catalysts derived from 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthyl ligands (H$_8$-BINOL) exhibited higher efficiency and enantioselectivity for many asymmetric reactions than those obtained from BINOL, due to the steric and electronic modulations in the binaphthyl backbone. In this respect, it is of great interest to examine the effect of BINOL and H$_8$-BINOL and their derivatives in asymmetric catalysis.‡

Titanium chiral alkoxide complexes, which are easily obtainable and inexpensive, have been found to be highly enantioselective in many asymmetric additions.[8–12] To our knowledge, there is no report of the use of titanium-based catalysts for alkynylation reactions. In order to find a simple and practical method to prepare chiral propargylic alcohols, we tried the asymmetric alkynylation using a complex conveniently generated *in situ* from titanium tetraisopropoxide and (*R*)-BINOL or (*R*)-H$_8$-BINOL as accelerator. The preliminary results were found to be highly encouraging and a variety of arylaldehydes were smoothly alkynylated to the corresponding propargylic alcohols (Table 1).

Since benzaldehyde has been most extensively studied previously, we focused our effort on the alkynylation of benzaldehyde in our initial study. Some common factors such as the choice of solvents, reaction temperature, ligand–substrate ratio *etc.*, which are known to affect the enantioselectivity of the reaction, have been examined. The temperature effect was rather insignificant in the range of −20 ∼ 25 °C, while the rate of reaction decreased with the decrease of reaction temperature. The enantioselectivities attained in the present study were found to be rather sensitive to the choice of solvents. At 0 °C, the use

of toluene, ether, hexane, dichloromethane and THF gave a product with e.e.'s ranging from 65 to 92%.
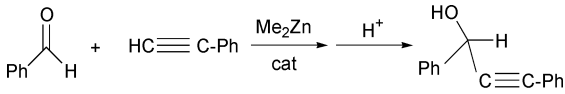
Titanium tetraisopropoxide played an important role in the catalytic reaction. When the alkynylation was catalyzed by (*R*)-H$_8$-BINOL alone, there was no enantioselectivity at all. The enantioselectivity of the reaction was found to be sensitive to the molar ratio of chiral ligand to substrate. As the molar ratio increased, the e.e. increased. When the ligand–substrate ratio reached about 20%, the product e.e. reached a plateau.

The results of the addition of alkynes to a variety of aldehydes catalyzed by (*R*)-H$_8$-BINOL were summarized in Table 2. Similar to the catalytic addition of diethylzinc to aldehydes, it was clearly observed that the enantioselectivities of the reactions catalyzed by (*R*)-H$_8$-BINOL were higher than those obtained using (*R*)-BINOL.

The electronic effect of the substrate was substantially less important than the steric hindrance effect for the enantioselectivity of the reaction. For example, while *p*-chloro- or *m*-chlorobenzaldehydes gave products with only slightly higher e.e.'s than those from *p*-methylbenzaldehyde and benzaldehyde, the *o*-chlorobenzaldehyde gave a product of significantly lower e.e. This was probably due to the strong steric hindrance effect of the *ortho*-substituent which weakened the coordination of the substrate to the chiral catalyst and thus lowered the influence of the chiral environment of the catalyst on the orientation of the substrate. Consequently lower enantioselectivities were obtained for the alkynylation of such aldehydes. Moderate to good e.e.'s were also obtained in the alkynylation of aliphatic aldehydes. The best enantioselectivity of 96% was obtained in the alkynylation of 3-nitrobenzaldehyde catalyzed by (*R*)-H$_8$-BINOL complex.

In conclusion, we have developed a new, highly efficient method for the production of chiral propargylic alcohols from

Table 1 The effect of reaction conditions on the enantioselectivity of the alkynylation of benzaldehyde[a]

cat = Ti(OiPr)$_4$ + ligand

Entry	Temperature	Solvent	Ligand ratio	Yield (%)[b]	E.e. (%)*	Config.[c]
1	25 °C	THF	20%	86	85	(−)-(*S*)
2	0 °C	THF	20%	85	92	(−)-(*S*)
3	−20 °C	THF	20%	83	92	(−)-(*S*)
4	0 °C	Toluene	20%	86	82	(−)-(*S*)
5	0 °C	Et$_2$O	20%	54	75	(−)-(*S*)
6	0 °C	Hexane	20%	85	65	(−)-(*S*)
7	0 °C	CH$_2$Cl$_2$	20%	84	76	(−)-(*S*)
8	0 °C	THF	10%	82	79	(−)-(*S*)
9	0 °C	THF	5%	64	48	(−)-(*S*)

[a] (*R*)-H$_8$-BINOL as ligand; aldehyde–Ti(OiPr)$_4$–Me$_2$Zn = 1 : 1.5 : 1.2 (molar ratio). [b] Isolated yield of the corresponding products. [c] The absolute configuration is based on measurement of the optical rotation and comparison with the literature values.[13]

Table 2 A comparison of the alkynylation of aldehydes using titanium catalysts with (R)-BINOL and (R)-H$_8$-BINOL ligands[a]

Entry	Aldehyde	Ligand	Yield (%)[b]	E.e. (%)	Config.[c]
1	Benzaldehyde	(R)-H$_8$-BINOL	85	92	(−)-(S)
2	Benzaldehyde	(R)-BINOL	84	90	(−)-(S)
3	2-Chlorobenzaldehyde	(R)-H$_8$-BINOL	90	76	(+)
4	2-Chlorobenzaldehyde	(R)-BINOL	88	64	(+)
5	3-Chlorobenzaldehyde	(R)-H$_8$-BINOL	87	95	(−)
6	3-Chlorobenzaldehyde	(R)-BINOL	88	92	(−)
7	4-Chlorobenzaldehyde	(R)-H$_8$-BINOL	91	94	(−)
8	4-Chlorobenzaldehyde	(R)-BINOL	87	92	(−)
9	4-Methylbenzaldehyde	(R)-H$_8$-BINOL	84	86	(−)
10	4-Methylbenzaldehyde	(R)-BINOL	83	86	(−)
11	4-Fluorobenzaldehyde	(R)-H$_8$-BINOL	82	87	(−)
12	4-Bromobenzaldehyde	(R)-H$_8$-BINOL	89	94	(−)
13	4-Nitrobenzaldehyde	(R)-H$_8$-BINOL	89	95	(−)
14	3-Nitrobenzaldehyde	(R)-H$_8$-BINOL	88	96	(−)
15	2-Naphthaldehyde	(R)-H$_8$-BINOL	75	80	(+)
16	4-Trifluoromethylbenzaldehyde	(R)-H$_8$-BINOL	89	93	(−)
17	(CH$_3$)$_2$CHCHO	(R)-H$_8$-BINOL	84	82	(−)
18	C$_6$H$_{11}$CHO	(R)-H$_8$-BINOL	86	74	(+)
19	CH$_3$CH$_2$CH$_2$CHO	(R)-H$_8$-BINOL	87	77	(−)

[a] Aldehyde–ligand–Ti(OiPr)$_4$–Me$_2$Zn = 1 : 0.2 : 1.5 : 1.2 (molar ratio); solvent = THF; reaction temperature = 0 °C; reaction time = 18 h. [b] Isolated yield of the product. [c] The absolute configuration is based on measurement of the optical rotation and comparison with the literature values.[13]

aldehydes and alkynes using catalysts which can be conveniently prepared from commercially available or easily prepared reagents. A more detailed study of this new class of reaction with different kinds of catalysts is underway.

Notes and references

‡ All experiments were carried out under a nitrogen atmosphere. Unless otherwise stated, commercial reagents were used as received without further purification. The reactions were carried out in solvents distilled from standard drying agents. Aldehydes were distilled under reduced pressure before use. NMR spectra were recorded on a Varian-500 spectrometer. The absolute configurations of the products were estimated based on the comparison of HPLC traces and/or the direction of optical rotation with known compounds. A typical procedure for the catalytic addition of alkyne to benzaldehyde is as follows. Titanium tetraisopropoxide (0.45 mL, 1.5 mmol) was added to a 1.0 mL THF solution of (R)-H$_8$-BINOL (59 mg, 0.2 mmol) at rt and stirred for 15 min. to prepare the titanium complex. Phenylacetylene (143 μL, 1.3 mmol) and a solution of 2.0 M dimethylzinc in toluene (0.6 mL, 1.2 mmol) were added to a dry flask at 0 °C under N$_2$ with continued stirring for 15 min. The titanium complex was added *via* a syringe and the homogenous solution was stirred at 0 °C for 15 min. Benzaldehyde (102 μL, 1 mmol) was added and the mixture was allowed to stir at 0 °C overnight. The reaction was quenched with 5.0 mL 5% hydrochloric acid solution and the product was extracted with 5.0 mL × 2 ethyl acetate and dried with Na$_2$SO$_4$. The compound was purified *via* flash chromatography (silica gel) by elution with 20% EtOAc–hexane. The enantiomeric excess was determined by HPLC analysis on a Chiralcel OD column.

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