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Effective activation of chiral BINOL/Ti(O*i*Pr)$_4$ catalyst with phenolic additives for the enantioselective alkynylation of aldehydes

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Abstract—The activation of chiral titanium(IV) complexes with achiral activators, e.g. phenol, is found to provide higher levels of enantioselectivity than those attained with an enantiopure catalyst in the alkynylations of both aromatic and aliphatic aldehydes.

1. Introduction

Chiral propargylic alcohols constitute important building blocks for asymmetric synthesis. They are used in diverse areas including the synthesis of natural products, pharmaceuticals, and macromolecules.[1–3] The preparation of propargylic alcohols via the addition of alkynes to aldehydes is of great interest because both the C–C bond and the stereogenic center can be formed in one step. Until now, nucleophilic alkynylation has enjoyed only very limited success and a few examples of enantioselective alkynylation of aldehydes by organometallic compounds in combination with chiral catalysts have been reported.[4–11]

Carreira and co-workers[5–7] discovered a highly enantioselective catalyst based on *N*-methylephedrine for the alkynylation of aliphatic aldehydes. We have investigated the asymmetric alkynylzinc addition in the presence of a catalyst prepared in situ from titanium tetraisopropoxide and (*R*)-H$_8$-binaphthol and found the simple catalyst to be highly enantioselective, giving products with up to 96.2% e.e.[8,9] Subsequently, Pu et al.[10,11] reported a somewhat different procedure for the effective preparation of propargylic alcohols using a BINOL/Ti(O*i*Pr)$_4$ catalyst. More recently we employed the first example of the self-assembly of BINOL with other chiral ligands into a highly effective titanium catalyst for the addition of alkynylzinc to aldehydes to give products in up to >99% e.e.[12] Herein, we wish to report a highly enantioselective catalyst system for the alkynylation of aldehydes based on a chiral BINOL–Ti(O*i*Pr)$_4$ catalyst in combination with an achiral activator.

2. Results and discussion

The self-assembly of several components into a highly enantioselective catalyst for asymmetric reaction is a new field in organic synthesis.[13,14] Recently, Mikami et al.[15] found that addition of phenol derivatives to chiral BINOL/Ti(O*i*Pr)$_4$ catalyst for Mukaiyama aldol reaction provided e.e.s equal to or better than the best literature data. Vallee et al.[16] reported similar results for ene-reactions. In our study on the alkynylation of aldehydes using BINOL/Ti(O*i*Pr)$_4$ catalyst and a phenolic additive as activator, we have observed similarly interesting effects. In the presence of phenol, the alkynyl addition to benzaldehyde gave the propargylic alcohol product in 96% e.e. In contrast, only 91% e.e. was obtained under similar conditions without any phenolic additives. More detailed results are summarized in Table 1.

Titanium tetraisopropoxide played an important role in the catalytic reaction, and a preferred ratio of ligands (BINOL + additive) to titanium tetraisopropoxide was found to be about 1:1.5.[9] At first the methods for the preparation of the catalyst were investigated and partic-

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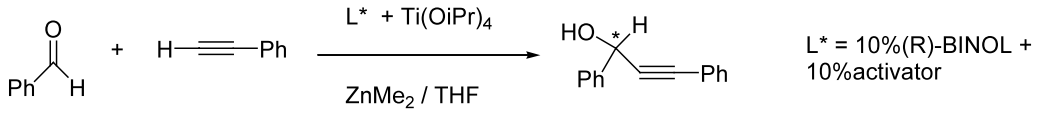
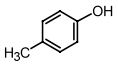
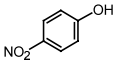
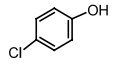
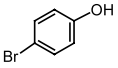
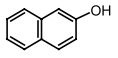
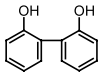
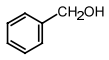
Table 1. The effect of additives on the enantioselectivity of the alkynylation of benzaldehyde[a]



Entry	Catalyst	Ti(O*i*Pr)$_4$/substrate	Additive	Yield (%)	E.e. (%)[b]
1	(*R*)-BINOL	15%	None	78	90
2	(*R*)-BINOL	30%	None	84	91
3	(*R*)-BINOL	30%	(*R*)-BINOL	84	95
4	(*R*)-BINOL	30%	Phenol	85	96
5	(*R*)-BINOL	30%		91	94
6	(*R*)-BINOL	30%		91	91
7	(*R*)-BINOL	30%		82	91
8	(*R*)-BINOL	30%		85	93
9	(*R*)-BINOL	30%		82	94
10	(*R*)-BINOL	30%		83	71
11	(*R*)-BINOL	30%	H_2O	71	41
12	(*R*)-BINOL	30%		92	94

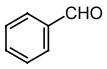
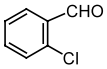
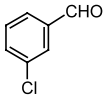
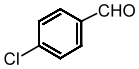
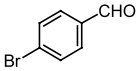
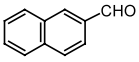
[a] Aldehyde : (*R*)-BINOL : additive : Me_2Zn = 1 : 0.1 : 0.1 : 1.2 (molar ratio), THF as solvent, 0°C, 18–24 h.

[b] *S* configuration was observed in all cases. The absolute configuration of the product was determined by comparison of the HPLC trace and the direction of optical rotation with known compounds.

ular attention was given to the order of the introduction of the ligand. Interestingly, mixing (*R*)-BINOL, phenol and Ti(O*i*Pr)$_4$ together at the same time or adding phenol to the (*R*)-BINOL–Ti(O*i*Pr)$_4$ precatalyst system gave essentially the same results. In most cases, the effects of activation by the phenolic additives were observed. A similar degree of enantioselectivity enhancement was achieved using benzyl alcohol, *p*-cresol or 2-naphthol as the additive. The use of phenol as the activator provided the highest enantioselectivity (96% e.e.).

The results from the addition of alkynes to a variety of aldehydes catalyzed by (*R*)-BINOL and phenol are summarized in Table 2. The direction of chiral induction in these reactions was predominantly determined by (*R*)-BINOL, and the presence of phenol increased the efficiency of the asymmetric induction. The activation effect was quite significant for *ortho*-substituted benzaldehydes and aliphatic aldehydes. In the presence of phenol, the e.e. values were improved to >85% (10 mol% chiral catalyst) from 70–80% (even with 20 mol% catalyst).

Table 2. The alkynylation of aldehydes using chiral BINOL–Ti(O*i*Pr)$_4$ catalysts (phenol as additive)[a]

Entry	Aldehyde	Yield (%)	E.e. (%)	Config.[b]	Literature value[c] (without activator)
1		85	96	(–)-(*S*)	92, (*R*)-H$_8$-BINOL 90, (*R*)-BINOL
2		82	88	(+)	76, (*R*)-H$_8$-BINOL 64, (*R*)-BINOL
3		84	95	(–)	95, (*R*)-H$_8$-BINOL 92, (*R*)-BINOL
4		83	95	(–)	94, (*R*)-H$_8$-BINOL 92, (*R*)-BINOL
5		81	94	(–)	94, (*R*)-BINOL
6		63	94	(+)	80, (*R*)-H$_8$-BINOL
7		82	86	(+)-(*S*)	74, (*R*)-H$_8$-BINOL
8	$CH_3CH_2CH_2CHO$	91	88	(–)	77, (*R*)-H$_8$-BINOL
9	$(CH_3)_2CHCHO$	92	90	(–)-(*S*)	82, (*R*)-H$_8$-BINOL

[a] Aldehyde : (*R*)-BINOL : phenol : Ti(O*i*Pr)$_4$: Me_2Zn = 1 : 0.1 : 0.1 : 0.3 : 1.2 (molar ratio), THF as solvent, 0°C, 18–24 h.

[b] 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.

[c] Literature values are e.e.s from experiments using 20 mol % (*R*)-H$_8$-BINOL or (*R*)-BINOL as the chiral ligand under other identical conditions.[9]

As shown in Table 2, the effect of phenol and similar additives on the product yield and/or enantioselectivity of the reaction is quite obvious. This activation effect is interesting not only from the viewpoint of lower catalyst loading and higher e.e.s for the alkynylation of both aromatic and aliphatic aldehydes, but also from the perspective that new frontiers can be opened in the use of metal–BINOL complexes in asymmetric catalytic applications.

3. Conclusions

In summary, the catalytic enantioselective alkynylation using chiral BINOL–Ti(O*i*Pr)$_4$ catalyst with phenolic additives has been developed. Wide substrate generality and high enantioselectivities have been achieved.

4. Experiments

4.1. General methods

All reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. THF was distilled and dried before use. Reagents were purchased from either Acros or Aldrich and were used without further purification except for the aldehydes which were redistilled before use. NMR spectra were recorded on a

Varian-500 spectrometer. Optical rotations were measured with a Perkin–Elmer model 341 polarimeter at 20°C. HPLC analyses (Chiralcel OD or OD-H column from Daicel, IPA-hexane as eluent) were performed using a Hewlett–Packard model HP 1050 LC interfaced to an HP 1050 Series computer workstation.

4.2. A general procedure for the nucleophilic addition of alkynes to aldehydes

Titanium tetraisopropoxide (90 μL, 0.3 mmol) was added to a solution of (*R*)-BINOL (28.5 mg, 0.1 mmol) and phenol (10 mg, 0.1 mmol) in THF (1.0 mL) and stirred for 0.5 hour. At the same time, 2.0 M dimethylzinc in toluene (0.6 mL, 1.2 mmol) was added to another flask containing phenylacetylene (143 μL, 1.3 mmol) and stirred at 0°C for 30 min. The titanium catalyst was transferred to alkynylzinc solution via syringe. After 30 min, the aldehyde (1.0 mmol) was added and the mixture was kept at 0°C for 18–24 h. The reaction was quenched with 5% HCl solution (2 mL), extracted with diethyl ether (3×5 mL) and purified using flash chromatography to afford the chiral propargylic alcohol. The e.e. value of the product was determined by HPLC analysis.

Acknowledgements

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