DOI: 10.1002/ejoc.200800561

# Catalytic Asymmetric Alkylation of Aldehydes by Using Trialkylboranes

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**Keywords:** Asymmetric catalysis / Alkylation / asymmetric synthesis / Boron / Titanium

Triethylborane can be used in the asymmetric alkylation of aldehydes by using a 3-(3,5-diphenylphenyl)-$H_8$-BINOL-derived titanium(IV) catalyst in the presence of an excess amount of titanium tetraisopropoxide. The reaction proceeds with a low catalyst loading (2 mol-%), exhibiting high enantioselectivity for aromatic and unsaturated aldehydes.


## Introduction

The catalytic asymmetric addition of organometallic reagents to aldehydes and ketones is a reaction of fundamental importance in modern synthetic organic chemistry. The resulting enantiomerically enriched chiral alcohols are valuable intermediates, for example, in the production of pharmacologically active compounds. Generally, diorganozinc reagents have been utilized for this transformation in combination with a variety of catalyst systems.[1–3] Unfortunately, however, few organozinc reagents are commercially available and their preparation is not always straightforward.

To circumvent such limitations, most recently, attention has been focused on the use of other organometallic reagents.[4–7] For asymmetric arylation reactions, the scope of aryl groups that could be introduced has been extended significantly by the use of arylboronic acids and their derivatives either through in situ transformation to arylzinc reagents with diethylzinc[4] or through direct catalysis by chiral rhodium complexes.[5] A recent report from this laboratory[8] showed that readily available alkyl Grignard reagents can be employed in the asymmetric alkylation of aldehydes by using a titanium(IV) catalyst derived from 3-(3,5-diphenylphenyl)-BINOL (DPP-BINOL **3**) in the presence of an excess amount of titanium tetraisopropoxide.[9]

Because a variety of alkylboranes are commercially available and can be readily prepared by hydroboration of alkenes, they are also promising candidates for practical alkylating reagents. Indirect use of trialkylboranes in asymmetric alkylation reactions has been reported by a boron–zinc exchange reaction.[10,3d] Although there has been no literature precedent, the direct use of trialkylboranes without converting into alkylzinc species would significantly expand the scope of the catalytic asymmetric alkylation of aldehydes.

Herein, we wish to report the asymmetric alkylation of aldehydes with a mixture of triethylborane and titanium tetraisopropoxide catalyzed by a titanium complex derived from 3-(3,5-diphenylphenyl)-$H_8$-BINOL (DPP-$H_8$-BINOL **4**). High enantioselectivity (up to 97%*ee*) could be obtained at a low catalyst loading (2 mol-%) by a simple reaction procedure.

## Results and Discussion

When a mixture of 1-naphthaldehyde, triethylborane (1.5 equiv.), (*R*)-BINOL (**1**;[11] 5 mol-%), and titanium tetraisopropoxide (5.6 equiv.) in THF was heated under reflux for 2 h, the corresponding ethylation product (*R*)-**5a** was obtained in 78% yield and in 84%*ee* [Equation (1); Table 1, Entry 1). The minor formation of a reduction product, 1-naphthylmethanol, (8%) was observed. Encouraged by this result, we surveyed other BINOL derivatives. Improved enantioselectivity of 89%*ee* was obtained with (*R*)-$H_8$-BINOL (**2**;[12] Table 1, Entry 2). (*R*)-DPP-BINOL (**3**)[13] exhibited better enantioselectivity of 91%*ee* either under refluxing conditions or at room temperature (Table 1, Entries 3 and 4). We recently reported that (*R*)-DPP-$H_8$-BINOL (**4**) showed enantioselectivity higher than DPP-BINOL (**3**) in the asymmetric alkylation of aldehydes with $Et_2Zn$.[14] The best result of 97%*ee* was obtained with this ligand (Table 1, Entry 5).

With this ligand, the catalyst loading and the amount of titanium tetraisopropoxide could be reduced to 2 mol-% and 3 equiv., respectively, without degrading the enantioselectivity and yield of the product (Table 1, Entry 7). Further reduction of the catalyst loading resulted in degraded enantioselectivity and an increase in the formation of the reduction product (Table 1, Entry 11). The amount of the

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Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

  

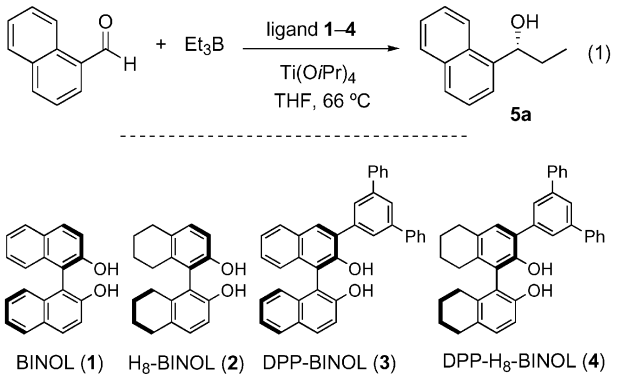


Table 1. Asymmetric ethylation of 1-naphthaldehyde with $Et_3B$ catalyzed by titanium complexes derived from BINOL derivatives **1**–**4**.[a]

| Entry | Ligand (mol-%) | $Ti(OiPr)_4$ [equiv.] | Yield [%] | *ee* [%] | Red.[b] [%] |
|---|---|---|---|---|---|
| 1 | **1** (5) | 5.6 | 78 | 84 | 8 |
| 2 | **2** (5) | 5.6 | 70 | 89 | 12 |
| 3 | **3** (5) | 5.6 | 73 | 91 | 4 |
| 4[c] | **3** (5) | 5.6 | 76 | 91 | 11 |
| 5 | **4** (5) | 5.6 | 86 | 97 | 3 |
| 6 | **4** (5) | 3.0 | 73 | 97 | 7 |
| 7 | **4** (2) | 3.0 | 83 | 96 | 6 |
| 8 | **4** (2) | 1.2 | 70 | 96 | 12 |
| 9 | **4** (2) | 0.1 | 0 | – | 9 |
| 10 | **4** (2) | 0.0 | 0 | – | 8 |
| 11 | **4** (1) | 3.0 | 74 | 93 | 11 |
| 12 | – (0) | 3.0 | 21 | – | 6 |

[a] Reactions were carried out with $Et_3B$ (1.5 equiv.) in THF at 66 °C for 2–3 h. [b] The yield of a reduction product, 1-naphthylmethanol. [c] The reaction was carried out at room temperature for 24 h.

byproduct was also increased when the amount of titanium tetraisopropoxide was reduced to 1.2 equiv. (Table 1, Entry 8).

Under the optimized conditions with 2 mol-% of DPP-$H_8$-BINOL (**4**; Table 1, Entry 7), a variety of aromatic aldehydes underwent a smooth reaction with triethylborane to give the corresponding ethylation products **5a**–**k** in high enantioselectivity (93–97%*ee*) except for the reaction of *o*-chlorobenzaldehyde and 2-furaldehyde [Equation (2); Table 2, Entries 1–11). Lower, still acceptable, enantioselectivity was obtained in the reaction of an α,β-unsaturated aldehyde (Table 2, Entry 12). The reaction of an aliphatic aldehyde was sluggish, affording the ethylation product in low yield but with high enantioselectivity (Table 2, Entry 13). When tributylboron was used instead of triethylborane, the reaction was also sluggish (Table 2, Entry 14). The reaction of 1-naphthaldehyde after 5 h afforded (*R*)-1-(naphthalen-1-yl)pentan-1-ol (**6**) in 92%*ee* and 28% yield. 1-Naphthylmethanol (49%) was obtained as a major product.

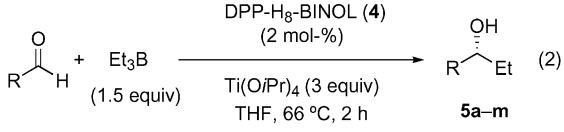


Table 2. Asymmetric alkylation of aldehydes with $Et_3B$ catalyzed by the DPP-$H_8$-BINOL derived titanium complex.[a]

| Entry | Aldehyde | Product | Yield [%] | *ee* [%] |
|---|---|---|---|---|
| 1 | 1-Naphthyl-CHO | **5a** | 83 | 96 |
| 2 | PhCHO | **5b** | 93 | 96 |
| 3 | *p*-$MeC_6H_4$-CHO | **5c** | 85 | 96 |
| 4 | *p*-$PhC_6H_4$-CHO | **5d** | 87 | 93 |
| 5 | *p*-$ClC_6H_4$-CHO | **5e** | 74 | 96 |
| 6 | *p*-$FC_6H_4$-CHO | **5f** | 87 | 97 |
| 7 | *p*-$CF_3C_6H_4$-CHO | **5g** | 73 | 94 |
| 8 | *m*-$MeOC_6H_4$-CHO | **5h** | 94 | 97 |
| 9 | *o*-$ClC_6H_4$-CHO | **5i** | 49 | 84 |
| 10 | 2-Naphthyl-CHO | **5j** | 90 | 96 |
| 11 | 2-Furyl-CHO | **5k** | 83 | 57 |
| 12 | PhCH=CHCHO | **5l** | 73 | 85 |
| 13 | $PhCH_2CH_2$-CHO | **5m** | 37 | 92 |
| 14[b] | 1-Naphthyl-CHO | **6**[c] | 28 | 92 |

[a] Unless otherwise noted, reactions were carried out with $Et_3B$ (1.5 equiv.), DPP-$H_8$-BINOL (2 mol-%), and $Ti(OiPr)_4$ (3 equiv.) in THF at 66 °C for 2–3 h. [b] The reaction was carried out with $nBu_3B$ (1.5 equiv.) for 5 h. [c] **6**: 1-(Naphthalen-1-yl)pentan-1-ol.

To gain insight into the mechanism of the present asymmetric alkylation reaction, several control experiments were carried out.[15] In the absence of ligand **4**, a slow alkylation reaction of 1-naphthaldehyde was observed with a mixture of triethylborane and titanium tetraisopropoxide (3 equiv.; Table 1, Entry 12).[16] In the presence of **4** (2 mol-%), the ethylation reaction with triethylborane did not proceed at all either with a catalytic amount of titanium tetraisopropoxide or without it (Table 1, Entries 9 and 10). Although transmetalation of a trialkylborane to give alkyltitanium compounds has not been reported,[17] the requirement of titanium tetraisopropoxide in more than a stoichiometric amount suggests that the active alkylating reagent of the present reaction is $EtTi(OiPr)_3$, or its aggregate with $Et_2B(OiPr)$, generated in equilibrium. $EtTi(OiPr)_3$ has been demonstrated to be an active alkylating reagent in BINOL-ate-Ti-catalyzed asymmetric alkylation reactions with $Et_2Zn$.[15a] The above supposition is also in accord with the observed trends in enantioselectivity for various aldehydes that are similar to those observed with $Et_2Zn$ by using DPP-$H_8$-BINOL (**4**).[14]

## Conclusions

We demonstrated that triethylborane can be used in asymmetric alkylation of aldehydes by using a DPP-BINOL-derived titanium(IV) catalyst in the presence of an excess amount of titanium tetraisopropoxide. The reaction proceeds with a low catalyst loading (2 mol-%), exhibiting high enantioselectivity for aromatic and unsaturated aldehydes. Work is in progress to investigate the full scope of the reaction.

## Experimental Section

**Preparation of (*R*)-1-Naphthalen-1-ylpropan-1-ol (5a) as a Representative Procedure for the Asymmetric Alkylation Reaction:** A solution

  

of triethylborane (1 M in THF, 0.75 mL, 0.75 mmol) was added to (*R*)-DPP-$H_8$-BINOL (**4**; 5.2 mg, 0.010 mmol) under an argon atmosphere. To the resulting solution at room temperature was added titanium tetraisopropoxide (0.45 mL, 1.5 mmol) and 1-naphthaldehyde (78.1 mg, 0.500 mmol). The resulting mixture was heated under reflux for 2 h. The reaction mixture was quenched by the addition of aqueous 1 N HCl and extracted with $Et_2O$ (3×). The organic layers were washed successively with aqueous 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel, 1–20% ethyl acetate in toluene) of the residue gave, in order of elution, 76.8 mg (83%) of **5a**, 4.6 mg (6%) of 1-naphthylmethanol, and 4.5 mg (87% recovery) of **4**. The *ee* value of **5** was determined to be 96% by HPLC analysis by using a Chiralcel OD column (0.8 mL $min^{-1}$, 10% *i*PrOH in hexane); retention times: 16.8 min (major *R* enantiomer) and 9.9 min (minor *S* enantiomer). The absolute structure of the product was determined by comparing the retention time with that of an authentic sample prepared by asymmetric ethylation with $Et_2Zn$ by using (*R*)-BINOL as a ligand[11b] (Table 1, Entry 7).

**Supporting Information** (see also the footnote on the first page of this article): Determination of the *ee* values of alkylation products **5a**–**m** and **6**.

## Acknowledgments

This work was supported partially by a grant from Kyoto Institute of Technology Research Fund.

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Received: June 11, 2008
Published Online: July 29, 2008

  