Asymmetric Alkenylzinc Additions to Aldehydes Catalyzed by a Binaphthyl-Based N,O-Ligand

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Numerous chiral ligands for enantioselective addition of organozincs to aldehydes have been studied for the last two decades.1 Despite the very successful catalytic asymmetric inductions, the scope of this reaction is relatively narrow due to the limited availability of the organozinc reagents. Asymmetric addition of vinylzinc to aldehydes can afford the synthetically very useful chiral allylic alcohols. Several methods have been used to generate vinylzinc reagents, including the reactions of alkenyllithium or magnesium reagents with zinc halides,2 and hydrozirconation of alkynes followed by Zr-Zn transmetalation.3 Oppolzer and Radinov prepared alkenylzincs by boron-zinc exchange of the alkenylboranes with sequential treatments of terminal alkynes with dicyclohexylborane and diethylzinc, and good enantoiselectivity was achieved with both aromatic and aliphatic aldehydes by the use of chiral DAIB ligand 1.4,5

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\begin{align*}
\text{Et}_2\text{Zn} & \quad \text{hexane, } 0^\circ\text{C} \\
& \quad \text{ZnEt} \\
& \quad \text{R}^\prime \text{CHO} \\
& \quad \text{OH} \\
& \quad \text{R}^\prime \text{R} \\
& \quad \text{B}(\text{C}_6\text{H}_{11})_2 \\
\end{align*}
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Amino alcohols, including the structures of 1 and 2, are reported to show moderate to high enantioselectivity in the alkenylation of aldehydes with alkenylzinc prepared by boron-zinc exchange.6 But, the degree of stereoselection depends heavily on the types of aldehydes used and the methods to generate the alkenylzinc compounds. With the alkenylzinc prepared by zirconocne-zinc exchange, these amino alcohol ligands showed very poor asymmetric inductions. Higher enantoiselectivity was obtained with the use of 10 mol % of amino thiol ligand 3 and alkenylzinc prepared by the Zr-Zn exchange method, but with decreased reaction yield.3b Recently, a paracyclophane-based chiral imino alcohol ligand 4 was reported to give reasonably high enantoiselectioselections and reaction yields in the alkenylation of aldehydes.7

In our previous report, we showed the amino alcohol 5, a morpholine derivative of the homologs of binaphthyl-based N,O-ligand, can be used for highly enantioselective addition of diphenylzinc to different types of aldehydes.8 Enantioselectivity in the phenylation of aldehyde is usually low because of the rapid competitive uncatalyzed background reaction. One solution to this problem is to use a mixture of Ph2Zn and Et2Zn for an in situ generation of the less reactive PhZnEt.8 But the reaction yield using this method and 5, in our hands, is usually much lower than the use of Ph2Zn only due to the decreased phenylation rate under the reaction temperature for optimum enantoiselectivity.8a Despite the extensive use of the binaphthyl-based chiral ligands in the catalytic asymmetric synthesis, limited number of the ligands are employed in the catalytic asymmetric organozinc additions to aldehydes.1e Only one example of binaphthyl-based ligand, 3,3’-diaryl-1,1’-bi-2-naphthol, is known for the phenylation of aldehydes with moderate enantoiselectivity by using PhZn and EtZn mixture and 20 mol % of the ligand.10 There is no report about the asymmetric alkenylation of aldehyde with the use of binaphthyl-based ligand. Ligand 5 in our study showed high yields and asymmetric induction in the phenylation of aldehydes with Ph2Zn only and 5 mol % of the ligand. Encouraged with this result, we studied catalytic asymmetric alkenylation of aldehyde with the use of ligand 5.

Optimum condition for the asymmetric addition of alkenylzinc to aldehyde had been searched for the reaction between 1-octenylzinc and benzaldehyde (Table 1). Dicyclohexylborane, prepared in situ with BH3·SM2 and cyclohexene at 0 °C for 2 h in hexane, was treated with 1-octyne at ambient temperature for 1 h. The resulting 1-octenylborane solution was reacted with Et2Zn at -78 °C for the boron-zinc exchange to generate 1-octenylzinc. It is known that alkenylzinc is in equilibrium with diethylzinc and dialkenylzinc above 0 °C and decomposes to the corresponding diene and metallic zinc.4 When 2 mol % of ligand 5 in toluene was added to the solution of the alkenylzinc at -78 °C and the mixture was slowly warmed to 0 °C followed by the addition of benzaldehyde, only a trace amount of the product was observed. The color of the solution began to

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was warmed to 0 °C, the allylic alcohol product was obtained. The temperature was set to 0 °C to achieve the desired rate and small rate difference between the catalyzed and uncatalyzed reactions, probably because of the slow alkenylation process. The temperature was controlled with a low temperature bath with internal magnetic stirrer (Table 1).

Turn into black at -30 °C and severe decomposition of the aldehyde at 0 °C was observed. When benzaldehyde was added at -78 °C without ligand 5, the reaction mixture was warmed to 0 °C, and the aliphatic alcohol product was obtained in low yield (entry 1, Table 1). Since the alkenylation process was very sensitive to reaction temperature, we added the ligand 5 at -60 °C to the alkenylzinc solution followed by the addition of benzaldehyde. We studied the effect of temperature on the reaction after the addition of benzaldehyde (entries 2 and 3). Reactions under the temperature lower than 0 °C provided poor results both in reaction yields and enantioselectivity, probably because of the slow alkenylation rate and small rate difference between the catalyzed and uncatalyzed background reaction. Better results were obtained with the use of 3 mol % of 5 and 0 °C alkenylation temperature (entry 5). Higher reaction temperature (entry 6) or the use of Me₂Zn instead of Et₂Zn decreased the selectivity (entry 7). Enantioselectivity of the reaction could be further improved by using 10 mol % of ligand 5 (entry 8).

With the conditions optimized for the 1-0ctenylation of benzaldehyde, several terminal alkynes were used for the asymmetric alkenylation of aromatic and aliphatic aldehydes with the use of 3 mol % 5 (Table 2). Similar enantioselectivity was observed with aromatic aldehydes, and low enantioselectivity with aliphatic aldehydes. Alkenylation with 4-buty lacetylene was much faster than the use of other alkynes probably because of the unfavorable formation of less reactive aggregates due to steric reasons (entries 4 and 5). Many unidentified byproducts were formed with the use of phenylacetylene and caused much decreased reaction yields (entries 6 and 7). Alkenylation of benzaldehyde using a symmetric internal alkene, 3-hexyne, produced the corresponding allylic alcohol with moderate enantioselectivity. In conclusion, we demonstrated the first application of binaphthyl-based amino alcohol ligand for the catalytic asymmetric alkenylation of aldehyde. This ligand is successfully applied to the asymmetric synthesis of allylic alcohols from aromatic aldehydes, and unsatisfactory results were obtained with aliphatic aldehydes. Further study to improve the enantioselectivity of the alkenylation using the ligands having binaphthyl backbone is currently in progress.

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**References**

1. Reviews on enantioselective diorganozinc additions to aldehydes: