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Communications

A Highly General Catalyst for the Enantioselective Reaction of Aldehydes with Diethylzinc

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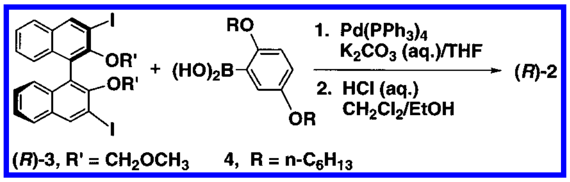
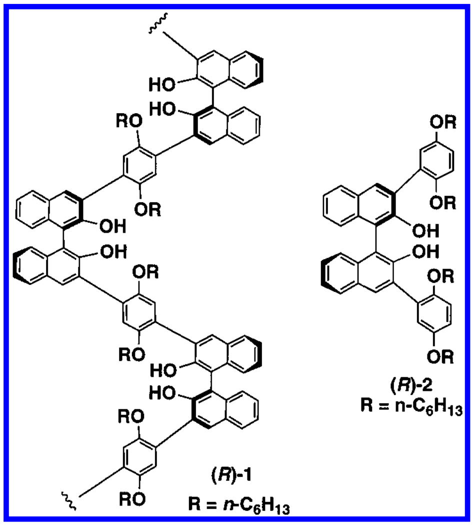
The asymmetric reaction of alkylzinc complexes with aldehydes has been demonstrated as a very useful method for the synthesis of optically active alcohols.[1] Since the first report of a highly enantioselective amino alcohol catalyst by Noyori et al. in 1986,[2] extensive studies have been carried out in this area and many good catalysts have been developed.[1−18] However, the general applicability of these catalysts is still limited because each of these catalysts is good for certain types of aldehyde substrates only. Different catalysts are usually required for the preparation of different chiral alcohols by using this method. Therefore, the search for the ultimate catalyst in this system continues.

Recently, we have reported a highly enantioselective polymeric chiral catalyst (*R*)-**1** for the addition of diethylzinc to certain aldehydes.[19] This polymer catalyzes the reaction of aromatic aldehydes in up to 94% enantiomeric excess (ee) and the reaction of aliphatic aldehydes in up to 83% ee. To further investigate the catalytic activity and stereoselectivity of this novel rigid and sterically regular polymeric chiral catalyst, we have synthesized (*R*)-**2** as the monomeric model compound of (*R*)-**1**. In this paper, we report our exciting discovery that (*R*)-**2** is not only a highly enantioselective catalyst for the reaction of aldehydes with diethylzinc but also the most general one for different types of aldehydes.

Scheme 1. Synthesis of (*R*)-2





(*R*)-**1**
R = *n*-C_6H_{13}

(*R*)-**2**
R = n-C_6H_{13}

A binaphthyl molecule (*R*)-**3** is synthesized in two steps from the optically pure (*R*)-1,1′-bi-2-naphthol[20] by protection of the hydroxyls with methoxymethyl groups[21] and then iodonation at the 3,3′-positions.[22] The Suzuki coupling of (*R*)-**3** with an arylboronic acid **4** followed by hydrolysis gives (*R*)-**2** (Scheme 1). The specific optical rotation of (*R*)-**2** is $[\alpha]_D = 95.0$ ($c = 0.962$, THF).

When this molecule is used to catalyze the reaction of benzaldehyde with diethylzinc, the corresponding alcohol is produced in over 99% ee. We have therefore explored the generality of this catalyst. We are very pleased to discover that (*R*)-**2** exhibits high enantioselectivity for many different substrates including para-, ortho-, or meta-substituted aromatic aldehydes, linear or branched aliphatic aldehydes, and aryl or alkyl substituted α,β-unsaturated aldehydes. These results are summarized in Table 1. All of the reactions are carried out in toluene solution at 0 °C using 5 mol % (*R*)-**2** unless otherwise indicated. The racemic alcohol products are also prepared and their HPLC or GC data are compared with those of the optically active alcohol products in order to determine the enantioselectivity of (*R*)-**2**. The absolute configuration of all of the products is *R* as determined by comparing their optical rotation values or GC data with the literature results.[1−19] (*R*)-**2** can be recovered by column chromatography on silica gel with no change of the structure or activity.

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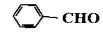
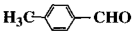
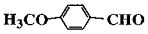
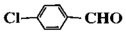
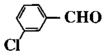
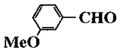
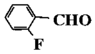
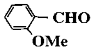
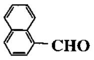
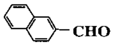
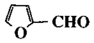
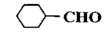
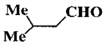
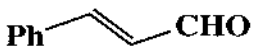
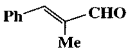
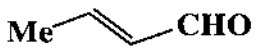
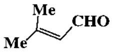
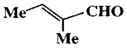
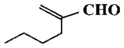
Table 1. Reaction of Aldehydes with Diethylzinc Catalyzed by (*R*)-2

Aldehyde	Time (h)	Isolated Yield (%)	*ee* (%)	Enantiomeric Ratio (*er*)
	4	95	>99[a]	>200:1
	4	91	98[b]	99:1
	6	92	97[c]	66:1
	4	96	>99[a]	>200:1
	4	97	98[d]	99:1
	6	95	99[a]	200:1
	4	93	94[b]	32:1
	8	90	94[b]	32:1
	6	92	>99[a]	>200:1
	5	94	99[a]	200:1
	6	90	91[d]	21:1
n-$C_5H_{11}CHO$	40	89	98[d]	99:1
n-$C_6H_{13}CHO$	24	86	98[d]	99:1
n-$C_8H_{17}CHO$	45	91	98[d]	99:1
	40	90	98[d]	99:1
	30	73	98[e]	99:1
	24	91	92[a]	24:1
	27	86	98[d]	99:1
	18	66	91[b,f]	21:1
	40	62	93[b,f,g]	28:1
	18	64	97[b]	66:1
	18	90	98[d]	99:1
	15	90	93[a,h]	28:1

[a] Determined by HPLC-Chiracel OD column. [b] Determined by chiral GC (*β*-Dex capillary column). [c] Determined by HPLC-Chiracel AD column. [d] Determined by analyzing the acetate derivative of the product on the GC-*β*-Dex capillary column. [e] Determined by analyzing the benzoate derivative of the product on the GC-*β*-Dex capillary column. [f] Et_2O was used as the solvent. [g] At −40 °C. 0.3 equiv of catalyst was used. [h] 0.2 equiv of catalyst was used. The reaction was carried out in THF at −10 °C, and the aldehyde was distilled before use.

A typical experimental procedure for these reactions is described below. Under nitrogen, to a Schlenk flask containing toluene (10 mL, dried with Na) were added (*R*)-**2** (42 mg, 0.05 mmol) and diethylzinc (0.21 mL, 2.0 mmol) at room temperature. After the colorless solution was stirred for ca. 15 min, the flask was cooled to 0 °C and benzaldehyde (0.1 mL, 1.0 mmol) was added dropwise. The solution turned yellow, which then faded in 4 h, indicating the completion of the reaction. HCl (1N) was added to quench the reaction at 0 °C, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine until pH = 7 and then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel with EtOAc/hexanes (1:5) to give (*R*)-1-phenylpropanol as a colorless liquid (129 mg, 95%). HPLC analysis on Chiracel-OD column (eluent: 2-propanol/hexane = 1/9; 1 mL/min) showed an ee of over 99%. When 0.5 mol % of (*R*)-**2** was used, although the high enantioselectivity was maintained, the reaction became much slower.

The previously reported catalysts that have shown good results for the asymmetric reaction of certain aldehydes with diethylzinc are cited in refs 2−18. Most of these catalysts are good for aromatic aldehydes and few are good for aliphatic aldehydes. Although the addition to α,*β*-unsaturated aldehydes is particularly useful since the resulting chiral allylic alcohols are important precursors to many organic compounds, it is very rare to find an enantioselective catalyst for the reaction of alkyl-substituted α,*β*-unsaturated aldehydes. Catalysts prepared by Katsuki *et al.*[8] are also made of the chiral binaphthyl structure. Although these catalysts show good enantioselectivity for the reaction of aromatic aldehydes, their catalytic properties for simple aliphatic aldehydes and alkyl-substituted α,*β*-unsaturated aldehydes have not been studied. Among all of the previously reported catalysts, the chiral titanium complexes developed by Seebach et al.[17] represent the most enantioselective catalyst system. However, the use of these catalysts normally requires the addition of a stoichiometric amount of $Ti(OiPr)_4$. In the work we report here, a catalytic amount of (*R*)-**2** can carry out the highly enantioselective reaction of different types of substrates including aromatic, aliphatic, and α,*β*-unsaturated aldehydes with diethylzinc. This unusually general enantioselectivity makes (*R*)-**2** superior to all of the currently known catalysts for this reaction.

The study of (*R*)-**2** not only provides a highly enantioselective and practical catalyst but also sheds new light on improving the enantioselectivity of the polymeric catalyst (*R*)-**1**. The work described here demonstrates that (*R*)-**2** has greater enantioselectivity as well as catalytic activity than the polymer (*R*)-**1** especially for the reaction of *ortho*-substituted benzaldehydes and aliphatic aldehydes. We attribute the differences in the catalytic properties between the monomer and the polymer to their differences in structure. In (*R*)-**1**, the dialkoxy phenylene linker can serve as a dual ligand for both of the adjacent binaphthyl units, which makes this polymeric catalyst structurally different from the monomer (*R*)-**2**. On the basis of this analysis, we have modified the structure of the polymeric catalyst and have greatly improved its catalytic properties. These results will be reported shortly.

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Supporting Information Available: Detailed experimental procedures and characterizations involving (*R*)-**2** and **4** in the catalytic reaction and the HPLC and GC analysis results of the chiral alcohol products (4 pages).

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