

A Highly Enantioselective Hetero-Diels–Alder Reaction Catalyzed by Chiral Polybinaphthyl–Aluminum Complexes

Mogens Johannsen and Karl Anker Jørgensen*

Center for Metal Catalyzed Reactions, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Xiao-Fan Zheng, Qiao-Sheng Hu, and Lin Pu*

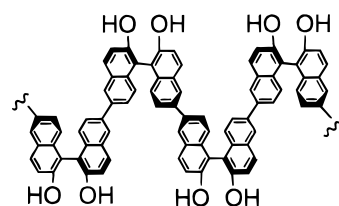
Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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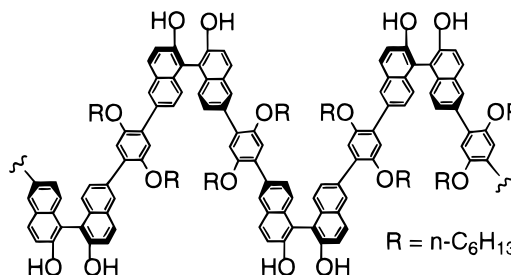
Introduction

Development of enantioselective polymer catalysts is important in the efficient production of optically pure chiral organic compounds including drug molecules.¹ The major advantage that a polymer catalyst offers is the ease of recovery and reuse of the expensive catalyst. The use of polymer catalysts may also enable the reactions to be carried out in flow reactors or flow membrane reactors for continuous production. Recently, we have synthesized optically active binaphthol polymers such as (*R*)-**1** and (*R*)-**2** to build a class of rigid and sterically regular polymeric chiral catalysts.^{2–4} The catalysts based on these polymers are different from the traditional polymeric catalysts prepared by attaching monomeric chiral catalysts to achiral and sterically irregular polymer backbones. The rigid and sterically regular polymer catalysts made from (*R*)-**1** and (*R*)-**2** have a better defined microenvironment at the catalytic sites and have allowed a systematic modification of their catalytic properties. Through such systematic study, we have discovered highly enantioselective polymer catalysts for the reaction of a broad range of aldehydes with diethylzinc.^{3,4}

We have also studied the asymmetric hetero-Diels–Alder (HDA) reaction catalyzed by the chiral polybinaphthyl-based Lewis acid complexes. Scheme 1 shows an example of a HDA reaction where 2,3-dimethyl-1,3-butadiene (**3**) reacts with ethyl glyoxylate (**4**) in the presence of chiral Lewis acid catalysts to give an optically active product **5**. Compound **6** is a side product often observed from the ene reaction of **3** with **4**. The catalytic HDA reaction of aldehydes with conjugated dienes has



(*R*)-**1**



(*R*)-**2**

received considerable attention in recent years as it has been possible to control the chemo-, regio-, diastereo-, and enantioselectivity by using chiral Lewis acid catalysts.⁵ One of the chiral Lewis acid complexes that can control the chemo-, regio-, and enantioselectivities of the HDA reaction of alkyl glyoxylates with simple substituted dienes is the monomeric (*S*)-Al–BINOLate complex **7** (Scheme 2).⁶ The use of **7** as the catalyst for the reaction of **3** with **4** leads to the HDA product **5** as the major product in good yield and with up to 97% ee.⁶ The HDA reaction catalyzed by chiral Al–BINOL complexes containing substituents at the 3,3'-positions as shown in Scheme 2 causes a lowering in both yields and selectivity.⁶ Therefore, development of chiral polymeric BINOL Lewis acids as catalysts for the HDA reaction must take this observation into account, and the polymeric ligands (*R*)-**1** and (*R*)-**2** that are linked at the 6,6'-positions might have properties similar to those of the monomeric BINOL ligand and are therefore tested for the HDA reaction of aldehydes with conjugated dienes. In this paper, we present a highly enantioselective HDA reaction catalyzed by polymeric chiral catalysts.

Results and Discussion

Following the procedure developed earlier in our laboratory, we have prepared the binaphthyl polymer (*S*)-**2** from the Suzuki coupling of (*S*)-**8** with **9** and then hydrolysis (Scheme 3).³ This polymer is a yellowish solid and is soluble in common organic solvents such as CH₂-Cl₂, THF, and CHCl₃. The molecular weight of (*S*)-**2** is

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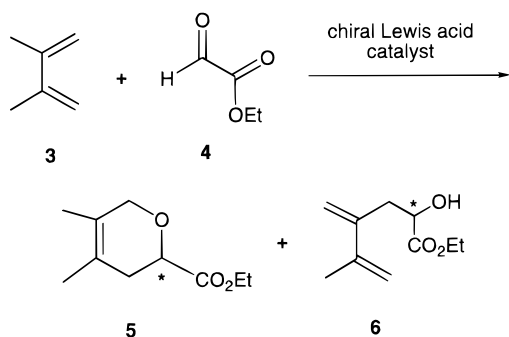
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Table 1. HDA Reactions and Ene Reactions of 3 with 4 in the Presence of 10 Mol % of Aluminum–PolyBINOLates^a

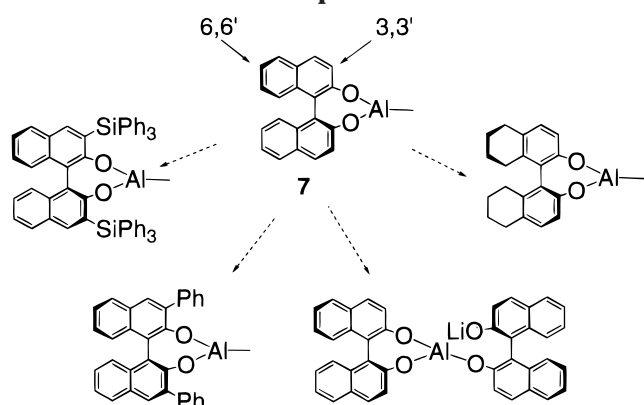
entry	polymer	Me ₂ AlX X	solvent	T/°C	total yield/%	HDA product 5 ee ^b /%	ene product 6 ee ^b /%	5:6 ratio
1	(<i>R</i>)-1	Me	CH ₂ Cl ₂	rt	49	27 (<i>S</i>)	7	2:1
2	(<i>R</i>)-1	Me	CH ₂ Cl ₂	−40	45	46 (<i>S</i>)	7	3:1
3	(<i>S</i>)-2	Me	CH ₂ Cl ₂	−40	10 ^e	84 (<i>R</i>)	nd ^c	nd ^c
4	(<i>S</i>)-2	Me	Et ₂ O	rt	69	89 (<i>R</i>)	46	5:1
5 ^d	(<i>S</i>)-2	Me	Et ₂ O	rt	80	88 (<i>R</i>)	38	5:1
6	(<i>S</i>)-2	Me	Et ₂ O	−40 to −10	10	95 (<i>R</i>)	42	nd ^c
7	(<i>S</i>)-2	Cl	Et ₂ O	rt	10	42 (<i>R</i>)	4	2:1
8	(<i>S</i>)-2	Cl	Et ₂ O	−78 to rt	<10	76 (<i>R</i>)	18	3:1
9	(<i>S</i>)-2 ^f	Me	Et ₂ O	rt	63	85 (<i>R</i>)	39	5:1

^a All reactions were run for 20 h. ^b Absolute configuration in parentheses was determined by comparison of optical rotation to reported values (see ref 5 g). ^c Not determined. ^d 20 mol % catalyst. ^e Isolated yield of HDA adduct. ^f Recovered polymer (second run).

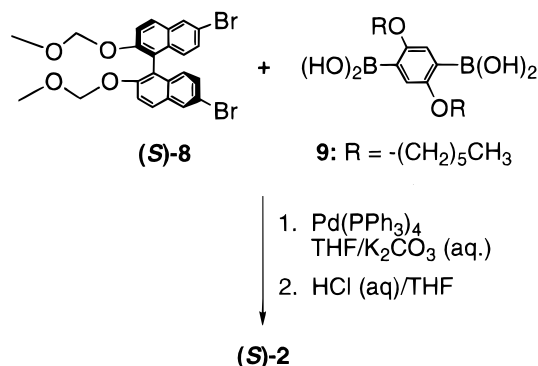
Scheme 1. Hetero-Diels–Alder Reaction of 2,3-Dimethyl-1,3-butadiene (3) with Ethyl Glyoxylate (4)



Scheme 2. BINOL-Based Chiral Aluminum Complexes



Scheme 3. Synthesis of the Optically Active Polybinaphthyl (S)-2



$M_w = 10\,800$ and $M_n = 6400$ (PDI = 1.7) as determined by gel permeation chromatography relative to polystyrene standards. Its specific optical rotation is $[\alpha]_D = 390.9$ ($c = 1$, CH₂Cl₂).

We have studied the use of polymers (*R*)-1² and (*S*)-2 to react with Me₃Al or Me₂AlCl to generate the corresponding polymeric chiral aluminum catalysts in situ for the HDA reaction of 3 with 4 (Scheme 1) under various reaction conditions. These results are listed in Table 1.

The use of the insoluble chiral polymer (*R*)-1 and Me₃Al as the catalyst for the reaction leads to a reasonable yield of the HDA product 5, but the ee is only 27% (Table 1, entry 1). Reducing the reaction temperature to −40 °C leads to an increase in the ee to 46% and a 45% total yield of 5 and the ene product 6 (entry 2). The ratio of 5 versus 6 is 3:1. When the soluble polymer (*S*)-2 is used in place of (*R*)-1 for this reaction with Me₃Al as the Lewis acid and CH₂Cl₂ as the solvent, the ee of 5 is increased to 84%. However only a total yield of 10% is observed at −40 °C (entry 3). Changing the solvent to Et₂O causes a significant improvement in the yield and chemoselectivity. The ee of 5 is obtained as high as 89% at room temperature, while the ee of the ene product 6 is 46% (entry 4). Increasing the amount of catalyst leads to a small increase in the yield, without affecting the selectivity of the reaction (entry 5). Lowering the reaction temperature to −40 °C and allowing the temperature to raise to −10 °C during the reaction leads to an increase of the ee to 95%, and at the same time the yield is lowered to around 10% (entry 6). The results presented in entries 4–6 have demonstrated the excellent enantioselective properties of the polymeric (*S*)-2–AlMe catalyst. It is notable that changing the solvent from Et₂O to the more coordinative THF almost completely inhibits the catalytic activity of the catalyst. The Lewis acid Me₂AlCl has also been tested with (*S*)-2 as the polymeric chiral ligand, and the results are presented in entries 7 and 8. The results for the polymeric (*S*)-2–AlCl catalyst show that an exchange of the methyl substituent with chloride reduces both the yield and the enantioselectivity of the HDA product dramatically.

The most important aspect of the use of the chiral polymeric (*S*)-2–AlMe catalyst is that the chiral ligand can be easily recovered by simple precipitation with methanol and is reused without significant change in yield and chemo- and enantioselectivity. Application of the recovered chiral polymer (*S*)-2 with Me₃Al as the Lewis acid under the same reaction conditions as in entry 4 (Table 1) leads to the formation of the HDA product 5 in 85% ee in a total yield of 63% and with a HDA/ene ratio of 5:1 (entry 9).

The HDA reaction of 3 with 4 catalyzed by the chiral polymeric (*S*)-2–AlMe catalyst (Table 1, entries 4–6) is similar to the reaction catalyzed by the monomeric (*S*)-Al–BINOLate complex 7.⁶ The use of 7 as the catalyst

for this reaction gave 97% ee at $-78\text{ }^{\circ}\text{C}$ and a HDA/ene ratio of 7:1, which are comparable to the present results. The polymer (*S*)-**2** has the advantage of easy recovery and reuse. The similar enantioselectivity of (*S*)-**2** with **7** also indicates that in the HDA reaction catalyzed by **7** the monobinaphthyl form should be catalytically active even though this complex may exist mainly in an oligomeric form through the formation of Al–O–Al bridging bonds.

As shown above, (*S*)-**2** demonstrates very high enantioselectivity in the HDA reaction. Very few studies have been carried out on polymer-supported asymmetric Diels–Alder reactions.⁷ The work described here represents the first example of highly enantioselective HDA reactions catalyzed by chiral polymer catalysts.

Experimental Section

General Methods. All reactions were carried out using anhydrous solvents and under N_2 in flame-dried Schlenk tubes. CH_2Cl_2 were dried over CaH_2 , distilled, and stored over 4 Å MS. Tetrahydrofuran (THF) and Et_2O were dried and distilled from sodium benzophenone prior to use. 2,3-Dimethyl-1,3-butadiene from Aldrich was used as received without any purification. Ethyl glyoxylate was prepared according to literature procedures,⁸ stored at $-20\text{ }^{\circ}\text{C}$, and distilled prior to use. TLC was performed on Merck analytical silica gel 60 F₂₅₄ plates and visualized with a basic KMnO_4 solution. Merck silica gel (230–400 mesh) was used for flash chromatography (FC). Enantiomeric excess (ee) was determined by GC using a Chrompack Chirasil-DEX CB column.

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General Procedure for the Catalytic HDA Reaction and Ene Reaction: Preparation of (*R*)-(+)-Ethyl 4,5-Dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylate (5**) and Ethyl 2-hydroxy-5-methyl-4-methylene-5-hexenoate (**6**).** To a flame-dried Schlenk flask were added (*S*)-**2** (31 mg, 0.055 mmol based on the binaphthyl unit) and dry Et_2O (1–2 mL) under an inert atmosphere. A 2 M solution of AlMe_3 in toluene was added (25 μL , 0.05 mmol), and the resulting heterogeneous solution was stirred for 1 h at room temperature. Freshly distilled **4**⁸ (51 mg, 0.5 mmol) dissolved in Et_2O (0.2 mL) was added to the catalyst solution followed by **3** (565 μL , 5 mmol). The mixture was stirred at room temperature for 20 h before MeOH (5 mL) was added to precipitate the polymer. The polymer was collected by filtration or better by centrifugation and washed with MeOH. The combined organic phases were evaporated, and the crude product was purified by flash chromatography (18 cm \times 1.5 cm silica gel, 2:8 Et_2O /light petroleum) to give the HDA adduct **5** (56 mg, 58%) with 88% ee and the ene product **6** (11 mg, 11%) with 46% ee.^{5g,6} The ee was measured by using a GC–HP 5890 Series II with He as the carrier gas and the products dissolved in diethyl ether. The chiral column was isothermal at $115\text{ }^{\circ}\text{C}$. The GC retention times are 18.2 min (minor) and 18.5 min (major) for **5** and 17.2 min (major) and 18.6 min (minor) for **6**. Before reuse of the polymer, it was washed with 1 N HCl and MeOH and then dissolved in toluene, filtered to remove inorganic solids, and dried under vacuum for 1–2 h.

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Supporting Information Available: NMR spectra for compounds **5** and **6** (4 pages). See any current masthead page for ordering and Internet access information.

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