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Asymmetric addition of diethylzinc to benzaldehyde catalyzed by silica-immobilized titanium(IV) complexes of *N*-sulfonylated amino alcohols

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Abstract

A chiral (1*R*,2*S*)-2-(*p*-toluenesulfonylamino)-1,3-diphenyl-1-propanol derived catalyst was synthesized and successfully grafted onto amorphous silica gel and mesoporous silica (MCM-41) by a facile approach. This is the first use of silica-immobilized titanium(IV) complexes of *N*-sulfonylated amino alcohols for the asymmetric addition of diethylzinc to benzaldehyde with good enantioselectivity (80% e.e.). Particularly, after readily recoverble procedure, the catalyst was able to be reused in multiple catalytic runs (up to 10 times) without loss of enantioselectivity.

Keywords: Asymmetric addition; Silica-immobilized catalyst; Titanium tetraisopropoxide; *N*-Sulfonylated amino alcohol; Diethylzinc

1. Introduction

The asymmetric addition of dialkylzinc to aldehydes, one of the most important asymmetric catalytic reactions, has been studied extensively in the past decade [1]. In recent years, focus of this reaction has shifted from the homogenous system to the heterogeneous one, which has the advantages of easy handling, separation and facilitation of industrial application. Numerous works have described the synthesis of polymer supported amino alcohols with good results in the reaction of asymmetric addition of dialkylzinc to aldehydes [2]. However, there have been far fewer reports on the uses of inorganic supported catalysts, especially silica gel supported ligands and the reported yields and enantioselectivity were generally poor [3]. Until recently, Pericàs [4a] and Hyeon [4b] reported the use of silica-immobilized chiral amino alcohol for this addition, and both of them treated their immobilized ligands with BuLi to afford the good enantioselectiveity. (75% and 77% e.e.).

It has been reported that Ti(IV) accelerates the asymmetric addition of dialkylzinc to aldehydes with excellent yields and e.e. values [5]. Commonly, Ti(IV) complexes of some chiral ligands, such as chiral diols [6], BINOL [7], disulfonamides [8] and *N*-sulfonylated amino alcohols [9], are effective for this catalytic reaction. Seebach and his co-workers successfully used controlled pore glass-bound Ti-TADDOLates for this addition with excellent e.e. values [10]. In this paper, we describe the synthesis of [(1*R*,2*S*)-2-(*p*-toluenesulfonylamino)-1,3-diphenyl-1-propanol]-derived catalyst **4**, and its successful immobilization on amorphous silica gel and mesoporous silica of MCM-41. To the best of our knowledge, this is the first use of Ti(O-*i*-Pr)$_4$ and the silica immobilized sulfonylated amino alcohol together for the asymmetric addition of diethylzinc to benzaldehyde.

2. Experimental

2.1. Materials and analytical methods

Amorphous silica gel (200–400 mesh) and mesoporous silica (MCM-41) were subjected to heat treatment at 150 °C for 3 h and cooled under nitrogen prior to use. Dichloromethane was freshly distilled from phosphorous pentoxide. Toluene, hexane and tetrahydrofuran were freshly distilled from a deep-blue solution of sodium-benzophenone under nitrogen. Titanium isopropoxide was distilled under nitrogen prior to use. Diethylzinc (1 M solution in hexane) was purchased from Acros and

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diethylzinc (1 M solution in dichloromethane) was synthesized according to the literature method [11]. Benzaldehyde was distilled from magnesium sulfate under nitrogen. All catalytic asymmetric addition reactions were carried out under nitrogen atmosphere. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-plus 400 BB with TMS as internal standard. HRMS data were measured with ESI techniques (Bruker Apex II). FT-IR spectra were performed on Nicolet Nexus 670. Elemental analyses were performed on Elementar Vario EL. The pore sizes and surface areas were determined on a Micromeritics ASAP 2010 system. Optical rotation value was measured on a Perkin-Elmer 341 polarimeter. Enantiomeric excess was determined by HPLC (Hewlett Packard 1090 Series) with a Chiralcel OD-H column.

2.2. Synthesis of ligands

2.2.1. Synthesis of (1R,2S)-4

The compound of (1*R*,2*S*)-**2** (0.341 g, 1.5 mmol) and triethylamine (0.39 mL) were dissolved in CH_2Cl_2 (19.5 mL), and 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilzne (**3**) (0.488 g, 1.5 mmol) in CH_2Cl_2 (19.5 mL) was added dropwise at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 12 h. After washed sequentially with 5% $NaHCO_3$ aqueous solution and saturated brine, respectively, the mixture was dried using anhydrous $MgSO_4$. After filtration, the organic solvent was concentrated under vacuum to afford white solid (1*R*,2*S*)-**4** (0.687 g, 1.3 mmol) in 89% yield. m.p. 53–55 °C. $[\alpha]_D^{14}$-5 (c = 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87–0.92 (m, 2 H), 2.44 (dd, 1 H, J = 14.2, 10.2 Hz), 2.55 (dd, 1 H, J = 14.6, 4.2 Hz), 2.64–2.67 (m, 2 H), 2.91 (br, 1 H), 3.55 (s, 9 H), 3.47–3.58 (m, 1 H), 4.57 (d, 1 H, J = 7.6 Hz), 5.00 (d, 1 H, J = 2.8 Hz), 6.71–7.31 (m, 14 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0, 28.7, 34.6, 50.6, 61.0, 75.0, 126.2, 126.5, 127.0, 127.8, 128.3, 128.4, 128.5, 129.1, 136.8, 136.9, 140.1, 149.4. IR (KBr): 3466, 3293, 3061, 3028, 2938, 2842, 1600, 1496, 1453, 1411, 1327, 1192, 1155, 1089 cm^{-1}. HRMS (ESI)—*m/z* calcd. for $C_{26}H_{33}NO_6SSi$: 538.1690 [M + Na]; found 538.1680 [M + Na]. Anal. calcd. for $C_{26}H_{33}NO_6SSi$ (%): C, 60.56; H, 6.45; N, 2.72. Found: C, 60.92; H, 6.77; N, 2.42.

2.2.2. General procedure for the synthesis of immobilized ligands 5a and 5b

The compound (1*R*,2*S*)-**4** (0.8 mmol) in CH_2Cl_2 (4 mL) was added to the suspension of pre-dried silica (1.3 g) in anhydrous toluene by syringe under nitrogen. The resulting suspension was heated under refluxing for 6 h and a tolene/methanol mixture (about 10 mL) was distilled off. The same volume of toluene was added and the heating and distillation were repeated twice. After filtration, the white solid was washed using toluene (50 mL) and the mixture of CH_2Cl_2 and CH_3OH (1:1, 50 mL). Then the solid was suspended in the mixture solvent (CH_2Cl_2:CH_3OH = 1:1, 50 mL) and stirred for 2 h. After filtration and thorough wash with the mixture solvent (CH_2Cl_2:CH_3OH = 1:1, 50 mL) and CH_3OH (50 mL), the solid was dried at 50 °C in vacuo for 24 h to give the immobilized ligands **5a** and **5b**.

- Ligand **5a**—IR (KBr): 3442, 2941, 2844, 1633, 1494, 1098, 959, 808, 703, 469 cm^{-1}. Anal. found: C 11.16, H 1.46, N 0.48. Average pore diameter: 8.01 nm. S_{BET}: 301 m^2/g.
- Ligand **5b**—IR (KBr): 3434, 2981, 2933, 2844, 1634, 1454, 1075, 955, 805, 703, 561, 460 cm^{-1}. Anal. found: C 16.65, H 2.00, N 0.39. Average pore diameter: 1.99 nm. S_{BET}: 1056 m^2/g.

2.2.3. Synthesis of compound 6

2-(4-Chlorosulfonylphenyl)ethyltrimethoxysilane (**3**) (0.4 mmol) in CH_2Cl_2 (2 mL) was added to the suspension of pre-dried amorphous silica (0.618 g) in anhydrous toluene by syringe under nitrogen. The resulting suspension was heated under refluxing for 6 h and a tolene/methanol mixture (about 5 mL) was distilled off. The same volume of toluene was added and the heating and distillation were repeated twice. After filtration, the white solid was washed with toluene (50 mL), mixture solvent of CH_2Cl_2 and CH_3OH (1:1, 50 mL). Then the solid was suspended in the mixture solvent (CH_2Cl_2:CH_3OH = 1:1, 50 mL) and stirred for 2 h. After filtration and thorough wash with the mixture solvent (CH_2Cl_2:CH_3OH = 1:1, 50 mL) and CH_3OH (50 mL), the solid was dried at 50 °C in vacuo for 24 h to give the immobilized compound **6**. IR (KBr): 3431, 2919, 1623, 1101, 804, 577, 468 cm^{-1}. Anal. found: C 6.04, H 0.88.

2.2.4. Synthesis of compound 7

The suspension of compound **6** (0.702 g) in HMDS (30 mL) under nitrogen was heated under rufluxing for 12 h. After filtration, the whitish-brown solid was washed with toluene (25 mL) and CH_2Cl_2:CH_3OH (1:1, 50 mL). Then the solid was suspended in CH_2Cl_2:CH_3OH (1:1, 30 mL) and stirred for 2 h. After filtration and thorough wash with CH_3OH (50 mL), the solid was dried at 50 °C in vacuo for 24 h to give the immobilized compound **7**. IR (KBr): 3424, 2934, 2852, 1622, 1542, 1446, 1397, 1102, 802, 628, 470 cm^{-1}. Anal. found: C 9.10, H 1.43.

2.2.5. Synthesis of ligand 8

(1*R*,2*S*)-**2** (0.36 mmol) and triethylamine (1 mL) in CH_2Cl_2 (10 mL) was added to the suspension of compound **7** in CH_2Cl_2 (10 mL) by a syringe under nitrogen. The resulting suspension was heated under refluxing for 12 h. After filtration and thorough wash with CH_2Cl_2 (100 mL) and CH_3OH (100 mL), the whitish-brown solid was dried at 50 °C in vacuo for 24 h to give the immobilized ligand **8**. IR (KBr): 3440, 2964, 1631, 1099, 847, 808, 760, 701, 468 cm^{-1}. Anal. found: C 11.23, H 1.47, N 0.16. Average pore diameter: 7.40 nm. S_{BET}: 279 m^2/g.

2.2.6. General procedure for asymmetric addition of diethylzinc to benzaldehyde

To a suspension of the ligand (required amount for 0.05 mmol sulfonylated amino alcohol) in anhydrous dichloromethane (1.5 mL) under nitroden at room temperature, was added Ti(O-*i*-Pr)$_4$ (Fig. 1) and the mixture was stirred for 0.5 h. After removal the solvent under vacuo for 2.5 h, fresh dichloromethane (1.5 mL) was added and stirred for 10 min. Another part of Ti(O-*i*-Pr)$_4$ (150 μL, 0.5 mmol) was added and stirred for 1 h. Then diethylzinc (1.0 M solution in hexane or 1.0 M solution in