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Enantioselective addition of phenylacetylene to aldehydes catalyzed by silica-immobilized titanium(IV) complex of β-hydroxyamide

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Abstract

A chiral β-hydroxyamide was synthesized from L-phenylalanine and successfully grafted onto amorphous silica gel. The silica-immobilized ligand was characterized by FT-IR, solid state NMR and elemental analysis. This is the first example of asymmetric addition of phenylacetylene to aldehydes catalyzed by silica-immobilized titanium(IV) complex of β-hydroxyamide with high yields (up to 95%) and good enantioselectivities (up to 81% ee). The catalyst could be reused up to five times without serious loss of enantioselectivity.

Keywords: Enantioselective addition; Titanium tetraisopropoxide; Silica-immobilized catalyst; Diethylzinc; β-Hydroxyamide

1. Introduction

Optically active propargyl alcohols are important building blocks for the synthesis of many organic compounds [1]. The first effective asymmetric alkynyl addition to aldehydes was demonstrated by Corey and Cimprich [2]. The catalytic enantioselective addition of terminal alkynes to aldehydes has recently generated enormous interest [3–11]. Many chiral ligands, such as *N*-methylephedrine [12–14], BINOL and its derivatives [5,10,15–20] and sulfonamides [21,22] have been used successfully in this reaction. Other chiral ligands, such as amino alcohols [23,24], oxazoline [25,26] and imino alcohol [27], have also been reported to catalyze this reaction.

The heterogeneous asymmetric catalytic systems, which have an inherent advantage of easy handling, separation and facilitation of industrial application, have been used successfully in a lot of reactions [28–30]. However, there have been far fewer reports on asymmetric catalytic reactions [31] using inorganic supported catalysts, which have many advantages over most polymers supported ones for their superior mechanical and thermal stability. In recent years, silica-immobilized ligands have been successfully used for reactions, such as asymmetric addition of diethylzinc to aldehydes [32–36], asymmetric transfer hydrogenation [37], asymmetric Diels–Alder reaction [38–40] and asymmetric Henry reaction [41]. To our knowledge, there is no report of silica-immobilized catalysts for asymmetric alkynylation reactions.

Recently, our group has developed a new β-hydroxyamide chiral ligand **1a**, and successfully introduced it into the asymmetric addition of phenacetylene to aldehydes to obtain excellent enantio-selectivities (up to 97% ee) [42]. With our continuing efforts towards the development of recyclable silica-immobilized ligands [43], we immobilized β-hydroxyamide **1a** on amorphous silica gel to afford silica-immobilized ligand **5**. Enantioselective addition of phenylacetylene to aldehydes

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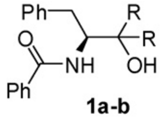
catalyzed by silica-immobilized titanium(IV) complex of β-hydroxyamide **5** was carried out, affording high yields (up to 95%) and good enantioselectivities (up to 81%).



1a-b **1a** R = Et
1b R = Ph

2. Experimental

2.1. General

Melting points were determined using an X-4 melting point apparatus and were uncorrected. Optical rotations were measured with a Perkin-Elmer 341 polarimeter at 18 °C in CH_2Cl_2. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-400 MHz spectrometer with TMS as an internal standard. The solid-state ^{13}C NMR experiment was performed on a Bruker AV400 WB solid-state NMR instrument at 100 MHz. IR spectra were obtained on a Nicollet NEXUS 670 FT-IR spectrometer. HRMS data were measured with ESI techniques (Bruker Apex II). Elemental analyses were performed on an Elementar vario EL appararus. The pore sizes and surface areas were determined on a Micromeritics ASAP 2010 system. Enantiomeric excess values were determined by HPLC with a Chiralcel OD-H column. All catalytic reactions were carried out under nitrogen atmosphere.

2.2. Reagents and solvents

L-Phenylalanine was purchased form Alfa Aesar. 3-Mercaptopropyltrimethoxysilane and phenylacetylene were bought from ABCR GmbH & CoKG and $Ti(O^iPr)_4$ from Acros. Diethylzinc (1 M solution in dichloromethane), trimethylsilylimidazole (TMSIm) and 4-(bromomethyl)benzoyl bromide were synthesized according to literature methods [44–46], respectively. Amorphous silica gel (160–200 mesh) was 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 diethyl ether were freshly distilled from a deep-blue solution of sodium-benzophenone under nitrogen. $Ti(O^iPr)_4$ was distilled under nitrogen prior to use.

2.3. Synthesis of chiral ligands

Compounds **2** and **4** were synthesized according to literature procedures [47,35], respectively.

2.3.1. 4-(Bromomethyl)-N-[(S)-3-ethyl-3-hydroxy-1-phenylpentan-2-yl]benzamide (3)

A solution of 4-(bromomethyl)benzoyl bromide (10 mmol) in CH_2Cl_2 (20 mL) was added to a cold (0 °C) solution of amino alcohol **2** (10 mmol) and *N*,*N*-diisopropylethylamine (DIEA) (10 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After washing sequentially with 1 M HCl, 5% $NaHCO_3$ aqueous solution and saturated brine, the organic layer was dried over anhydrous $MgSO_4$, concentrated under vacuum and recrystallized from ethyl acetate (EA)/hexane to afford benzamide **3** as white solid (yield 82%). m.p. 149–151 °C. $[\alpha]_D^{18} = -141$ (c 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, $J = 7.6$ Hz, 3H, CH_3), 0.97 (t, $J = 7.6$ Hz, 3H, CH_3), 1.53–1.77 (m, 4H, CH_2), 2.84 (dd, $J = 14.2$, 10.2 Hz, 1H, $PhCH_2$), 3.14 (dd, $J = 14.2$, 4.0 Hz, 1H, $PhCH_2$), 4.28–4.34 (m, 1H, CH), 4.45 (s, 2H, $PhCH_2Br$), 6.19 (d, $J = 8.8$ Hz, 1H, NH), 7.15–7.25 (m, 5H, ArH), 7.36 (d, $J = 8.0$ Hz, 2H, ArH), 7.47 (d, $J = 8.8$ Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.66, 8.00, 27.78, 28.11, 32.27, 35.14, 56.58, 126.33, 126.59, 127.28, 128.37, 129.00, 129.11, 134.60, 138.74, 140.84, 167.35. IR (KBr): 3455, 3355, 2962, 2928, 2876, 1627, 1536, 1450, 1259, 1130, 983, 931, 741, 693 cm^{-1}. HRMS (ESI): $M+Na^+$, 426.1039; found: 426.1039. Anal. calculated for $C_{21}H_{26}BrNO_2$: C, 62.38; H, 6.48; N, 3.46. Found: C, 62.56; H, 6.58; N, 3.12.

2.3.2. Synthesis of silica-immobilized ligand 5

Compound **4** (7.5 g) was suspended in dry toluene (30 mL) under nitrogen. DIEA (1.51 mL, 15 mmol) and benzamide **3** (6.07 g, 15 mmol) were added and the mixture was stirred at 70 °C for 12 h. After washing with toluene (100 mL) and the mixture of CH_2Cl_2 and CH_3OH (1:1, 100 mL), the solid was suspended in the mixture solvent (CH_2Cl_2:CH_3OH = 1:1, 50 mL) and stirred for 12 h. After filtration and thorough wash with CH_2Cl_2 (50 mL), hexane (50 mL), CH_3OH (50 mL), acetone (50 mL) and CH_2Cl_2 (50 mL), the solid was dried at 110 °C in vacuum for 48 h to give the immobilized ligand **5** as a yellowish powder. IR (KBr): 3436, 2967, 2859, 1630, 1608, 1501, 1449, 1187, 1099, 952, 845, 805, 759, 697, 468 cm^{-1}. Anal. found: C, 12.26; H, 2.09; N, 0.29. Average pore diameter: 6.3 nm. S_{BET}: 282 m^2/g.

2.4. General procedure for the asymmetric addition of phenylacetylene to aldehydes

Method A: Under dry nitrogen, the silica-immobilized ligand (0.04 mmol) and $Ti(O^iPr)_4$ (0.12 mmol) were mixed in solvent (1.0 mL) at room temperature and stirred for 1 h. Then a solution of $ZnEt_2$ (1.0 M in CH_2Cl_2) was added. After the mixture was stirred at room temperature for 2 h, phenylacetylene was added and stirred for another 1 h and the solution was treated with aldehyde (0.2 mmol). After the reaction was completed (TLC), the reaction solution was cooled to 0 °C and quenched by 0.5 M aqueous HCl. The mixture was extracted with diethyl ether (3 × 10 mL), washed with brine (3 × 15 mL), dried with anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, petroleum ether (PE:EA = 8:1) to give the propargyl alcohol.

Method B: According to a modified procedure of Pu's [17], phenylacetylene (0.6 mmol) and diethylzinc (0.6 mmol, 1 M in CH_2Cl_2) were added to a flask containing dry toluene (1 mL). The solution was refluxed for 5 h. It was then transferred into the suspension of silica-immobilized ligand **5** (0.04 mmol) in