Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Catalysis A: Chemical 269 (2007) 179–182
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Highly enantioselective addition of phenylacetylene to aldehydes catalyzed by titanium(IV) complexes of β-hydroxy amides

Zhi-Ce Chen [a], Xin-Ping Hui [a,*], Chao Yin [a], Lu-Ning Huang [a], Peng-Fei Xu [a,*], Xiao-Xia Yu [b], Shao-Yi Cheng [b]

[a] *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China*
[b] *Jinchuan Group Limited, Jinchang, Gansu 737104, PR China*

Received 16 October 2006; received in revised form 11 January 2007; accepted 14 January 2007
Available online 19 January 2007

Abstract

A series of chiral β-hydroxy amide ligands was synthesized via the reaction of benzoyl chloride and chiral amino alcohols derived from L-amino acid. Titanium(IV) complexes of these new β-hydroxy amide ligands were used for catalyzing the enantioselective addition of phenylacetylene to aldehydes. We found that the enantioselectivity of the reaction was strongly affected by the amount of titanium tetraisopropoxide and the solvent used. Chiral ligand **2b** synthesized from 2-amino-3-ethyl-1-phenylpentan-3-ol was effective for the asymmetric alkynylation of aldehydes and the propargyl alcohols were obtained in high yields (up to 96%) and high enantiomeric excesses (up to 97%) under optimized conditions. A practical solution for preparing the chiral propargylic alcohol was described.

Keywords: Asymmetric addition; Titanium tetraisopropoxide; Phenylacetylene; Diethylzinc; β-Hydroxy amide

1. Introduction

Asymmetric carbon–carbon bond-forming reactions are of prime importance in modern organic chemistry [1,2]. One of the most powerful methods for the catalytic asymmetric generation of carbon–carbon bonds is the enantioselective addition of organometallic reagents to carbonyl compounds. The catalytic enantioselective addition of terminal alkynes to aldehydes has recently generated enormous interest [3–12]. The addition of acetylides to aldehydes gives access to propargyl alcohols, which are valuable building blocks for fine chemicals, pharmaceuticals, and natural products [13].

Among the catalytic methods developed for alkyne asymmetric addition to aldehydes, several of them are currently considered the most practical. Carreira and co-workers [14–17] reported that a system using $Zn(OTf)_2$ and triethylamine with chiral ligand *N*-methylephedrine gave high yields and enantioselectivities in the addition of terminal acetylide to aliphatic aldehydes. Pu and co-workers [18–23] and Chan and co-workers [24–26] found that titanium complexes of binaphthol (BINOL) catalyzed the asymmetric alkynylation of aldehydes with high enantioselectivities and yields. Wang and co-workers [27–29] reported that sulfonamide alcohol in combination with Ti(O-*i*-Pr)$_4$ could afford high enantioselectivities and yields in this reaction. Other chiral ligands, such as amino alcohols [30,31], oxazoline [32,33], imino alcohol [34] and sulfamide-amino alcohol [35], have also been found to catalyze this reaction.

Although many significant results have been achieved in this field, great efforts to develop new types of efficient chiral catalysts for this important asymmetric reaction are still in great need to probe the relationship between the ligand structure and catalytic activity. For further exploring the chiral ligand effects of titanium(IV) complexes in asymmetric addition of phenylacetylene to aldehydes, we here describe the synthesis of a series of new β-hydroxy amide ligands **2a-2d**. Enantioselective additions of phenylacetylene to aldehydes catalyzed by titanium(IV) complexes of these ligands were investigated, affording excellent enantioselectivities up to 97% enantiomeric excesses (ee).

* Corresponding authors. Tel.: +86 931 8912374; fax: +86 931 8625657.
E-mail addresses: huixp@lzu.edu.cn (X.-P. Hui), xupf@lzu.edu.cn (P.-F. Xu).

1381-1169/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2007.01.025

2. Experimental

2.1. General

All catalytic reactions were carried out under a dry nitrogen atmosphere. Melting points were taken on an X-4 melting point apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 MHz spectrometers with TMS as an internal standard. IR spectra were obtained on a Nicolet NEXUS 670 FT-IR instrument. HRMS data were measured with ESI techniques (Bruker Apex II). Optical rotation was measured on a Perkin-Elmer 341 polarimeter. Enantiomeric excess values were determined by HPLC with a Chiralcel OD-H column. All solvents used were dried and aldehydes were purified by standard methods. Ti(O-*i*-Pr)$_4$ was freshly distilled prior to use. Diethylzinc was prepared from EtI and Zn and then diluted with toluene to 1.0 M. Reactions were monitored by thin layer chromatography (TLC).

2.2. Synthesis of chiral ligands

2.2.1. Amino alcohols

Amino alcohols **1a–c** and **1d** were synthesized according to literature procedures [36,37], respectively.

2.2.2. General procedures for preparation of β-hydroxy amides (*2a–d*)

A solution of benzoyl chloride (5.00 mmol) in CH_2Cl_2 (10 mL) was added to a solution of amino alcohol (5.00 mmol) and Et_3N (2.1 mL, 15 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1N HCl (2 × 5 mL), saturated aqueous $NaHCO_3$ (3 × 10 mL), and brine (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate/hexane to afford the desired β-hydroxy amide.

*2.2.2.1. N-[(S)-1-hydroxy-1,1,3-triphenylpropan-2-yl]benzamide (**2a**).* White powder, yield 42%, mp 242–244 °C. $[\alpha]_D^{17} = -130°$ (c 1.00, DMSO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.97 (d, J = 9.9 Hz, 1H, NH), 7.69–7.59 (m, 4H, ArH), 7.45–7.24 (m, 7H, ArH), 7.21–7.03 (m, 9H, ArH), 6.14 (s, 1H, OH), 5.40–5.34 (m, 1H, CH), 2.87 (dd, J = 14.1, 11.1 Hz, 1H, $PhCH_2$), 2.62 (d, J = 11.7 Hz, 1H, $PhCH_2$). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 166.29, 146.87, 146.00, 139.29, 134.96, 130.91, 129.11, 128.29, 128.12, 127.88, 127.62, 126.86, 126.29, 125.80, 125.62, 125.25, 80.27, 57.75, 35.91. IR (KBr): 3358, 3026, 2930, 1635, 1529, 1490, 1447, 1283, 1062 cm^{-1}. HRMS (ESI): $M + Na^+$, 430.1778; Found, 430.1771.

*2.2.2.2. N-[(S)-3-ethyl-3-hydroxy-1-phenylpentan-2-yl]benzamide (**2b**).* Colorless needle crystal, yield 47%, mp 164–166 °C. $[\alpha]_D^{17} = -125°$ (c 1.00, DMSO). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50–7.12 (m, 10H, ArH), 6.40 (d, J = 8.7 Hz, 1H, NH), 4.37–4.29 (m, 1H, CH), 3.13 (dd, J = 14.1, 3.9 Hz, 1H, $PhCH_2$), 3.02 (br, 1H, OH), 2.87 (dd, J = 14.1, 10.5 Hz, 1H, $PhCH_2$), 1.79–1.54 (m, 4H, CH_2), 1.00–0.89 (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.10, 138.84, 134.57, 131.22, 129.11, 128.56, 128.34, 126.77, 126.27, 76.58, 56.75, 35.04, 28.06, 27.72, 8.02, 7.67. IR (KBr): 3359, 3030, 2964, 1629, 1577, 1541, 1452, 1268, 1036 cm^{-1}. HRMS (ESI): $M + Na^+$, 334.1778; Found, 334.1771.

*2.2.2.3. N-[(S)-5-ethyl-5-hydroxy-2-methylheptan-4-yl]benzamide (**2c**).* Colorless needle crystal, yield 54%, mp 97–98 °C. $[\alpha]_D^{20} = -52°$ (c 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (d, J = 6.9 Hz, 2H, ArH), 7.52–7.40 (m, 3H, ArH), 6.26 (d, J = 9.3 Hz, 1H, NH), 4.30–4.22 (m, 1H, CH), 2.07 (br, 1H, OH), 1.69–1.33 (m, 7H, CH_2, CH), 1.00–0.87 (m, 12H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.78, 134.58, 131.23, 128.35, 126.89, 52.84, 38.39, 27.80, 27.57, 24.89, 24.09, 21.56, 7.83, 7.47. IR (KBr): 3369, 2962, 1631, 1576, 1535, 1463, 1267, 1023 cm^{-1}. HRMS (ESI): $M + H^+$, 278.2115; Found, 278.2115.

*2.2.2.4. N-[(1R,2S)-1-hydroxy-1,3-diphenylpropan-2-yl]benzamide (**2d**).* Colorless needle crystal, yield 85%, mp 228–230 °C. $[\alpha]_D^{17} = -21°$ (c 1.00, DMSO). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29 (d, J = 8.7 Hz, 1H, NH), 7.67–7.06 (m, 15H, ArH), 5.66 (d, J = 5.1 Hz, 1H, OH), 4.79 (t, J = 5.4 Hz, 1H, *CH*OH), 4.37–4.4.28 (m, 1H, CH), 2.97–2.87 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.83, 113.54, 109.80, 104.80, 100.85, 98.95, 98.04, 97.96, 97.78, 97.12, 96.78, 96.36, 95.71, 44.64, 27.29, 4.24. IR (KBr): 3304, 3029, 1640, 1543, 1492, 1448, 1288, 1024 cm^{-1}. HRMS (ESI): $M + Na^+$, 354.1465; Found, 354.1467.

2.3. General procedure for asymmetric addition of phenylacetylene to aldehydes

Under a dry nitrogen atmosphere, phenylacetylene (82.4 μL, 0.75 mmol) and diethylzinc (0.75 mL, 1.0 M solution in toluene, 0.75 mmol) were added to a 25 mL flask containing toluene (2 mL). This solution was heated under reflux for 5 h during which a white precipitate was generated. It was then combined with ligand **2** (0.05 mmol) and CH_2Cl_2 (1 mL). After the mixture was stirred at room temperature for 15 min, Ti(O-*i*-Pr)$_4$ (45 μL, 0.15 mmol) was added and the stirring continued for another 1 h. Aldehyde (0.25 mmol) was then added, and the reaction mixture was stirred at room temperature for 12 h. Aqueous HCl (5%) was added to quench the reaction, and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 12.5% EtOAc in petroleum ether) to give the desired product.

3. Results and discussion

Reaction of benzoyl chloride with amino alcohol (**1a–c**) or (1*R*,2*S*)-2-amino-1,3-diphenyl-1-propanol (**1d**), which were synthesized from (L)-amino acids by literature methods [36,37], in the presence of triethylamine afforded the new β-hydroxy amides **2a–c** and **2d**, respectively (Scheme 1).