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

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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.
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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).

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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$_2$Cl$_2$ (10 mL) was added to a solution of amino alcohol (5.00 mmol) and Et$_3$N (2.1 mL, 15 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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. [α]$_D^{17}$ = −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. [α]$_D^{17}$ = −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. [α]$_D^{20}$ = −52° (c 1.00, CH$_2$Cl$_2$). ^{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.
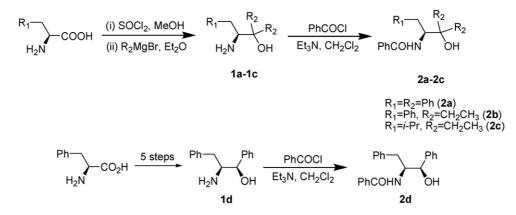
2.2.2.4. N-[(1R,2S)-1-hydroxy-1,3-diphenylpropan-2-yl]benzamide (2d).
Colorless needle crystal, yield 85%, mp 228–230 °C. [α]$_D^{17}$ = −21° (c 1.00, DMSO). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.29 (d, J = 8.7 Hz, 1H, NH), 7.67–7.06 (m, 15H, ArH), 5.66 (d, J = 5.1 Hz, 1H, OH), 4.79 (t, J = 5.4 Hz, 1H, CHOH), 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$_2$Cl$_2$ (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 (1R,2S)-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).

Scheme 1. Synthesis of chiral ligands **2a–d**.

The addition of phenylacetylene to benzaldehyde in the presence of chiral ligands **2a–d**, Et_2Zn and $Ti(O-i-Pr)_4$ in CH_2Cl_2 were first examined and the results are summarized in Table 1. The zinc phenylacetylide, a white precipitate, was obtained using the method developed by Pu et al. [20]. Ligand **2a**, which has bulky, less flexible phenyl substituents at the hydroxy-bearing carbon atom, resulted in a low enantioselectivity (Table 1, entry 1). However, the corresponding propargyl alcohol was given in 94% yield and 97% ee when **2b** was used, which possesses small and more flexible ethyl substituents (Table 1, entry 2). For ligand **2c**, having an isopropyl group at α-position of amino-containing carbon instead of the phenyl group, the yield of the desired propargyl alcohol decreased to 71% and the enantioselectivity dropped substantially to 47% ee (Table 1, entry 3). When 20 mol% of ligand **2d** was used, the propargyl alcohol was only obtained in 54% yield and 16% ee (Table 1, entry 4).

In this study, we found that the enantioselectivity of the reaction was strongly affected by the amount of titanium tetraisopropoxide and the solvent. Decreasing the amount of $Ti(O-i-Pr)_4$ from 3:1 to 1:1 relative to the chiral ligand **2b** decreased the enantioselectivity (Table 1, entries 2, 5 and 6). On the other hand, when the ratio of the chiral ligand **2b** to $Ti(O-i-Pr)_4$ was increased to 1:4, the enantioselectivity decreased dramatically (Table 1, entry 7). So the ratio in entry 2 was found to be the best. When the reaction was carried out in other solvents such as toluene, THF and diethyl ether, it was found that CH_2Cl_2 was still the best choice of the solvent (Table 1, entries 2, 8, 9 and 10). The ee values decreased slightly when the amount of the chiral ligand **2b** was reduced from 20% to 10% (Table 1, entries 2, 11 and 12).

To demonstrate the generality of the ligand for phenylacetylene asymmetric addition to aldehydes, various aldehydes were examined using the titanium complex of the ligand **2b** under

Table 1

Asymmetric addition of phenylacetylene to benzaldehyde using **2a–d** as the ligand[a]

Entry	Ligand	mol%	Solvent	L/Ti(O-i-Pr)₄	Yield (%)[b]	ee (%)[c]
1	**2a**	20	CH_2Cl_2	1/3	95	3
2	**2b**	20	CH_2Cl_2	1/3	94	97
3	**2c**	20	CH_2Cl_2	1/3	71	47
4	**2d**	20	CH_2Cl_2	1/3	54	16
5	**2b**	20	CH_2Cl_2	1/2	90	86
6	**2b**	20	CH_2Cl_2	1/1	93	70
7	**2b**	20	CH_2Cl_2	1/4	89	23
8	**2b**	20	Toluene	1/3	67	57
9	**2b**	20	THF	1/3	67	64
10	**2b**	20	Et_2O	1/3	75	25
11	**2b**	15	CH_2Cl_2	1/3	97	95
12	**2b**	10	CH_2Cl_2	1/3	96	94

[a] Phenylacetylene/Et₂Zn/benzaldehyde = 3:3:1; reaction temperature: r.t.; reaction time: 8 h; Et₂Zn (1 M solution in toluene).
[b] Isolated yield.
[c] Determined by HPLC with a Chiralcel OD-H column.

Table 2

Asymmetric addition of phenylacetylene to aldehydes promoted by the ligand **2b**[a]

Entry	Aldehyde	Yield (%)[b]	ee (%)[c]
1	Benzaldehyde	96	97
2	2-Anisaldehyde	94	92
3	4-Anisaldehyde	92	89
4	4-Tolualdehyde	96	97
5	2-Chlorobenzaldehyde	95	93
6	3-Chlorobenzaldehyde	96	90
7	4-Chlorobenzaldehyde	84	95
8	1-Naphthaldehyde	95	93
9	2-Naphthaldehyde	85	92
10	4-Nitrobenzaldehyde	78	77
11	Cinnamaldehyde	91	89
12	Cyclohexanecarbaldehyde	80	63

[a] Et₂Zn/phenylacetylene/aldehyde/Ti(O-i-Pr)₄/**2b** = 3:3:1:0.6:0.2; reaction temperature: r.t.; reaction time: 12 h.
[b] Isolated yield.
[c] Determined by HPLC with a Chiralcel OD-H column.

the optimized reaction conditions and the results are listed in Table 2. The chiral propargyl alcohols could be obtained in good isolated yields of 84–96% and excellent enantioselectivities of 89–97% ee for aromatic aldehydes (Table 2, entries 1–9) except 4-nitrobenzaldehyde (Table 2, entry 10). 4-Nitrobenzaldehyde gave moderate enantioselectivity maybe due to its coordination with Ti(O-i-Pr)$_4$ by the 4-nitro group. α,β-Unsaturated *trans*-cinnamaldehyde afforded high enantioselectivity (Table 2, entry 11). However, aliphatic cyclohexanecarbaldehyde gave the product in low enantioselectivity of only 63% ee (Table 2, entry 12).

For *para*-substituted benzaldehydes, the strong electron-withdrawing and electron-donating substituents reduced the enantiomeric excesses (Table 2, entry 8, p-NO$_2$, ee 77%; entry 3, p-CH$_3$O, ee 89%), while the moderate electron-withdrawing and electron-donating substituents favored the enantiomeric excesses (Table 2, entry 4, p-CH$_3$, ee 97%; entry 7, p-Cl, ee 95%).

4. Conclusions

In summary, four new β-hydroxy amide ligands were synthesized from L-amino acids. The enantioselective addition of phenylacetylene to aldehydes catalyzed by the **2b**/Ti(O-i-Pr)$_4$ catalytic system was demonstrated with excellent enantioselectivity up to 97% ee. The application of these ligands in other asymmetric reaction is underway.

Acknowledgements

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