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Synthesis of new β-hydroxy amide ligands and their Ti(IV) complex-catalyzed enantioselective alkynylation of aliphatic and vinyl aldehydes

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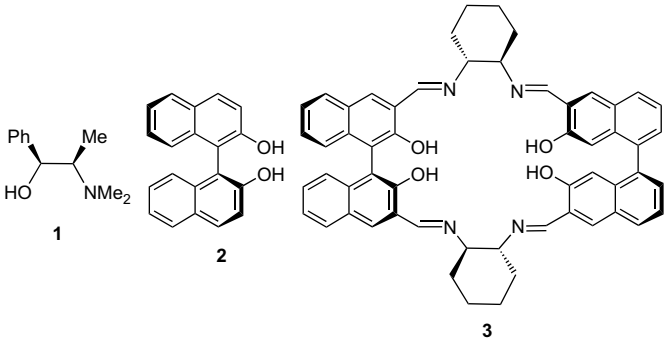
ABSTRACT

Three new chiral β-hydroxy amide ligands were synthesized via the reaction of benzyl chloride and amino alcohols derived from L-tyrosine. The titanium(IV) complex of chiral ligand **8b** was found to be an effective catalyst for the asymmetric alkynylation of aliphatic, vinyl and aromatic aldehydes. The propargyl alcohols were obtained in highly enantiomeric excesses (up to 96% ee) under optimized conditions.

1. Introduction

The alkynylation of aldehydes is one of the most useful carbon–carbon bond-forming reactions because this process can produce the synthetically very useful chiral propargyl alcohols.[1] Since the first efficient asymmetric alkynes addition to aldehydes was demonstrated by Corey and Cimprich[2] using chiral oxazaborolidines, many highly enantioselective catalysts have been developed for this reaction.[3–7] Among the catalytic methods developed, the addition of terminal acetylene to aromatic aldehydes is currently considered to be the most practical. However, fewer excellent chiral ligands have been disclosed in efficiently catalytic asymmetric alkynylation of aliphatic and vinyl aldehydes. Carreira and co-workers reported that a system using $Zn(OTf)_2$ and catalytic amount (+)-*N*-methyl ephedrine (**1**) with triethylamine afforded high yields and enantioselectivities in the addition of terminal acetylide to aliphatic aldehydes.[8] For titanium complex-catalyzed alkynylation reaction, (*S*)-1,1′-bi-2-naphthol (BINOL) (**2**) was demonstrated to be an excellent ligand by Pu's group.[5a] Shibasaki and co-workers developed a new catalytic system for alkynylation of aliphatic and aromatic aldehydes with the combination of indium(III)/(*S*)-BINOL complex and Cy_2NMe.[9] Recently, 1,1′-binaphthyl macrocycle **3** was found to be an excellent catalyst for the alkynes addition to aliphatic and vinyl aldehydes.[10]



In our laboratory, we have developed chiral β-hydroxy amide ligands, and successfully introduced it into the asymmetric addition of phenylacetylene to aromatic aldehydes to obtain excellent enantioselectivities.[11] To further develop efficient catalysts for the asymmetric alkynes addition to aliphatic and vinyl aldehydes, we here report the synthesis of new β-hydroxy amides **8a–c**. The best performed titanium(IV) catalyst of **8b** catalyzes asymmetric phenylacetylene addition to aliphatic and vinyl aldehydes in good yields and excellent enantioselectivities (up to 96% ee).

2. Results and discussion

Recently, we have reported that the C_2-symmetric bis(β-hydroxy amide) **4** in combination with $ZnEt_2$ and $Ti(O\text{-}i\text{-}Pr)_4$ could catalyze the reaction of phenylacetylene with aromatic aldehydes with high enantioselectivities. However, when the C_2-symmetric

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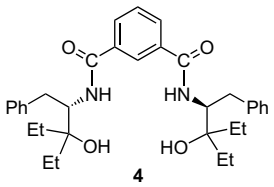
bis(β-hydroxy amide) **4** was used to catalyze the reaction of phenylacetylene with *n*-butylaldehyde at room temperature, only 52% ee was obtained.[11a] To further develop efficient catalysts for the asymmetric alkyne addition to aliphatic and vinyl aldehydes, we chose cheap (*S*)-tyrosine as chiral source and conveniently synthesized new ligands **8a–c** (Scheme 1). Coupling of benzyl chloride with amino alcohols **6a** and **6b**, which were prepared by (*S*)-tyrosine methyl ester hydrochloride with Grignard reagents, in the presence of sodium hydride and DMF gave compounds **7a–c**. Compounds **7a–c** reacted with benzoyl chloride in the presence of triethylamine afforded new β-hydroxy amide ligands **8a–c**.

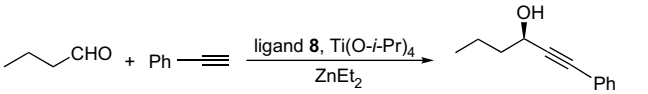


4

The addition of phenylacetylene to *n*-butyraldehyde was first examined in the presence of 0.2 equiv chiral ligands **8a** and **8b**, $ZnEt_2$ and Ti(O-*i*-Pr)$_4$ in toluene and the results are summarized in Table 1. Ligand **8a**, which has two benzyl substituents at the hydroxyl-bearing carbon atom, resulted in a lower enantioselectivity (Table 1, entry 1). To our delight, when **8b** was used and the corresponding propargyl alcohol was given in 85% yield and 91% ee (Table 1, entry 2). It is obviously that ligand **8a**, which has the bulkier, less flexible benzyl substituents at the hydroxy-bearing carbon atom, resulted in a lower enantioselectivity than ligand **8b**, which has the more flexible ethyl substituents. For further exploring the chiral ligand effect of titanium(IV) complex in asymmetric addition reactions of phenylacetylene to *n*-butyraldehyde, ligand **8c**, which having 4-methoxybenzyl group instead of benzyl group in **8b**, was synthesized. For ligand **8c**, the propargyl alcohol was obtained in a slightly lower selectivity than **8b** (Table 1, entry 3). So, ligand **8b** was chosen to be the best overall chiral ligand to facilitate this alkynyl addition reaction.

Further optimization studies were carried out using ligand **8b** in combination with $ZnEt_2$ and Ti(O-*i*-Pr)$_4$. The enantioselectivities of the reaction were strongly affected by different conditions. Increasing the amount of Ti(O-*i*-Pr)$_4$ from 2:1 to 3:1 relative to chiral ligand **8b** afforded obviously increased enantioselectivity (Table 1, entries 2 and 4). Further increase in the amount of Ti(O-*i*-Pr)$_4$ resulted in decrease in enantioselectivity (Table 1, entry 5). The amount of diethylzinc was also important. When the amount of $ZnEt_2$ was increased, the ee value decreased from 91 to 84% (Table 1, entry 7). Four solvents were also examined and toluene was found to be the best choice (Table 1, entries 8–11). The ee value of propargyl alcohol decreased when the amount of chiral ligand **8b** was reduced from 20 to 10% (Table 1, entry 13). To further improve the enantioselectivity in this reaction, temperature effect was observed. The result showed that temperature effect was obvious and only 72% ee was obtained under 0 °C (Table 1, entry 14). Thus, entry 2 in Table 1 was identified as the optimized reaction procedure.

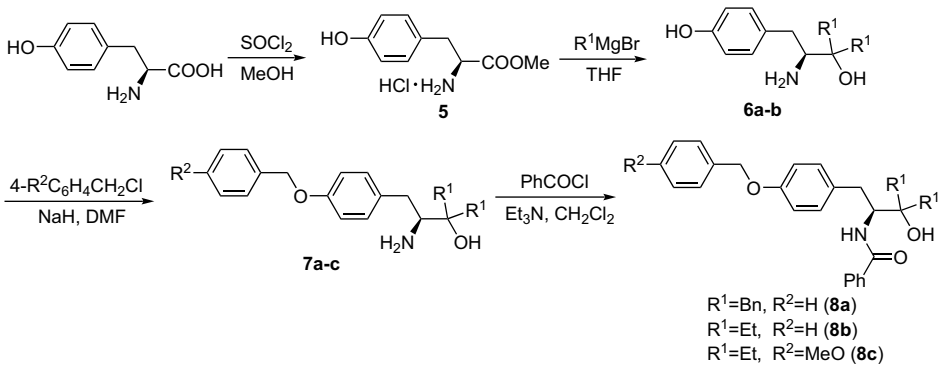
Table 1
Optimization of reaction conditions[a]



Entry	Catalyst	L (mol %)	Solvent	L/Ti(O-*i*-Pr)$_4$	Yield[b] (%)	ee[c] (%) (Config.)
1	**8a**	20	Toluene	1/3	78	39 (*R*)
2	**8b**	20	Toluene	1/3	85	91
3	**8c**	20	Toluene	1/3	87	81
4	**8b**	20	Toluene	1/2	64	80
5	**8b**	20	Toluene	1/4	79	86
6[d]	**8b**	20	Toluene	1/3	80	87
7[e]	**8b**	20	Toluene	1/3	83	84
8	**8b**	20	Hexane	1/3	77	82
9	**8b**	20	CH_2Cl_2	1/3	79	80
10	**8b**	20	THF	1/3	71	65
11	**8b**	20	Et_2O	1/3	74	82
12	**8b**	30	Toluene	1/3	85	91
13	**8b**	10	Toluene	1/3	80	73
14[f]	**8b**	20	Toluene	1/3	76	72

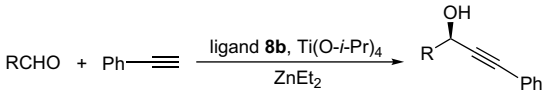
[a] Phenylacetylene/$ZnEt_2$/*n*-butyraldehyde=3:3:1 (molar ratio); reaction time: 18 h; reaction temperature: rt.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiralcel OD-H column.
[d] Phenylacetylene/$ZnEt_2$/*n*-butyraldehyde=2:2:1 (molar ratio).
[e] Phenylacetylene/$ZnEt_2$/*n*-butyraldehyde=4:4:1 (molar ratio).
[f] Reaction temperature: 0 °C.

The generality of this catalytic system for phenylacetylene asymmetric addition to aliphatic and vinyl aldehydes was examined using the titanium complex of ligand **8b** under the optimized reaction conditions and the results are summarized in Table 2. The chiral propargyl alcohols could be obtained in 88–96% ee for aliphatic and vinyl aldehydes (Table 2, entries 1–11). For aliphatic aldehydes, the one with bulky group gave a slightly lower enantioselectivities (Table 2, entries 6 and 7). It is worth noting that for 2-phenylacetaldehyde, excellent enantioselectivity of 94% ee was obtained (Table 2, entry 8). For vinyl aldehydes, *trans*-cinnamaldehyde afforded excellent enantioselectivity of 96% ee (Table 2, entry 9). Furthermore, the optimized conditions were also applicable to benzaldehyde. The addition of phenylacetylene to benzaldehyde proceeded smoothly to give the product in 85% yield and 92% ee (Table 2, entry 12). It is noteworthy that this catalytic system has broad generality for both aliphatic, vinyl and aromatic aldehydes.



Scheme 1. Synthesis of chiral ligands **8a–c**.

Table 2
Asymmetric addition of phenylacetylene to aliphatic and vinyl aldehydes promoted by ligand **8b**[a]



Entry	Aldehydes	Yield[b] (%)	ee[c] (%)	Config.[d]
1	Propionaldehyde	75	90	(*R*)
2	*n*-Butyraldehyde	85	91	(*R*)
3	Isobutyraldehyde	87	92	(*R*)
4	3-Methylbutanal	83	90	(*R*)
5	*n*-Heptanal	80	91	(*R*)
6	Pivalaldehyde	81	88	(*R*)
7	Cyclohexanecarbaldehyde	81	88	(*R*)
8	2-Phenylacetaldehyde	79	94	(−)
9	*trans*-Cinnamaldehyde	83	96	(*R*)
10	Acrylaldehyde	71	90	(*R*)
11	(*E*)-But-2-enal	86	90	(*R*)
12	Benzaldehyde	85	92	(*R*)

[a] Phenylacetylene/$ZnEt_2$/aldehyde/Ti(O-*i*-Pr)$_4$/**8b**=3:3:1:0.6:0.2 (molar ratio); reaction time: 18 h; reaction temperature: rt.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiralcel OD-H column.
[d] Absolute configuration of the products was based on measurement of the optical rotation and comparison with the literature values.[4a,5a,7b,10]

3. Conclusions

In conclusion, the new chiral β-hydroxy amide ligands were synthesized and used in the reaction of catalytic asymmetric addition of phenylacetylene to aliphatic, vinyl and aromatic aldehydes. Ligand **8b** was found to be an effective catalyst for this reaction and the propargyl alcohols were obtained in highly enantiomeric excesses (up to 96% ee). The application of these ligands supported by cross-linked polystyrene backbone in this asymmetric addition is ongoing.

4. Experimental

4.1. General

All reactions were carried out under nitrogen atmosphere. All solvents used were dried and aldehydes were purified by standard methods. Ti(O-*i*-Pr)$_4$ was freshly distilled prior to use. Reactions were monitored by thin layer chromatography (TLC). Melting points were taken on an X-4 melting point apparatus and are 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 NEXUS 670 FT-IR spectrometer in KBr disc. HRMS data were measured with ESI techniques (Bruker Apex II). Optical rotation value was measured on Perkin–Elmer 341 polarimeter. Enantiomeric excess values were determined by HPLC with Chiralcel OD-H column on Waters 600 Delta.

Diethylzinc (1.0 M solution in CH_2Cl_2) was prepared according to the literature method.[12] (*S*)-Tyrosine methyl ester hydrochloride (**5**) was synthesized according to the literature method.[13]

4.2. Synthesis of chiral ligands

*4.2.1. Preparation of amino alcohols **6a** and **6b***

(*S*)-Tyrosine methyl ester hydrochloride (2.8 g, 12.0 mmol) was added portion wise to a THF solution of ethylmagnesium bromide (96.0 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. After the reaction was completed, the reaction solution was cooled to 0 °C and quenched by saturated aqueous NH_4Cl. The organic layer was separated, the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), then dried with anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the crude product was obtained. The crude product was dissolved in dichloromethane, dry hydrogen chloride was bubbled. The solvent was removed and the solid was recrystallized from ethyl acetate–petroleum ether to give a white solid. The white solid was neutralized by ammonia, extracted with chloroform, and the solvent was removed to give pure **6a** and **6b**.

4.2.1.1. 4-[(S)-2-Amino-3-ethyl-3-hydroxypentyl]phenol hydrochloride. Mp 166–170 °C. $[\alpha]_D^{20}$ −42 (*c* 1.0, H_2O). ^{1}H NMR (400 MHz, D_2O) δ: 0.74–0.86 (m, 6H), 1.48–1.59 (m, 4H), 2.48 (t, *J*=12.9 Hz, 1H), 2.95 (d, *J*=8.0 Hz, 1H), 3.35 (dd, *J*=3.0, 12.0 Hz, 1H), 6.75 (d, *J*=8.4 Hz, 2H), 7.06 (d, *J*=8.4 Hz, 2H). IR (KBr): 3399, 3101, 2968, 2684, 2571, 1619, 1515, 1448, 1249, 1136, 969 cm^{-1}.

4.2.1.2. 4-[(S)-2-Amino-3-benzyl-3-hydroxy-4-phenylbutyl]phenol hydrochloride. Mp 168–170 °C. $[\alpha]_D^{20}$ −4 (*c* 1.0, H_2O). ^{1}H NMR (300 MHz, D_2O) δ: 2.77 (dd, *J*=12.3, 14.7 Hz, 1H, CH_2), 2.93–3.04 (m, 3H, CH, CH_2), 3.17 (dd, *J*=2.1, 12.6 Hz, 2H, CH_2), 3.34 (dd, *J*=3.6, 14.7 Hz, 1H, CH_2), 6.84 (d, *J*=8.7 Hz, 2H, ArH), 7.01 (d, *J*=8.7 Hz, 2H, ArH), 7.31–7.48 (m, 10H, ArH). ^{13}C NMR (75 MHz, D_2O) δ: 32.73, 40.46, 41.81, 59.45, 74.16, 116.07, 127.40, 127.47, 128.75, 128.83, 130.51, 130.70, 131.52, 135.12, 135.60, 155.04.

*4.2.2. Preparation of amino alcohols **7a–c***

A solution of **6a** or **6b** (10 mmol) in dry DMF (15 mL) was added dropwise at room temperature to NaH (60%, 0.40 g, 10 mmol). After the evolution of hydrogen was complete, benzyl chloride/4-methoxybenzyl chloride (10 mmol) was added dropwise. The resulting mixture was stirred at room temperature under nitrogen for 10 h. The solution was then poured into a mixture of water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic fractions were washed with water (20 mL) and brine (20 mL), then dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was recrystallized from ethyl acetate/petroleum ether to afford amino alcohols **7a–c**.

*4.2.2.1. (S)-3-Amino-2-benzyl-4-(4-(benzyloxy)phenyl)-1-phenylbutan-2-ol (**7a**).* White powder, yield 45%; mp 119–120 °C. $[\alpha]_D^{20}$ −11 (*c* 1.00, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.34–2.42 (m, 1H), 2.63–2.83 (m, 3H), 2.97 (dd, *J*=3.9, 12.9 Hz, 2H), 3.21 (d, *J*=13.5 Hz, 1H), 3.85 (br, 1H), 5.01 (s, 2H), 6.84–6.92 (m, 4H), 7.24–7.40 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 38.25, 42.03, 42.66, 58.22, 69.93, 75.05, 114.86, 126.32, 127.38, 127.90, 127.96, 128.08, 128.53, 129.88, 130.69, 130.87, 131.75, 136.96, 137.58, 137.64, 157.32. HRMS (ESI) calcd for $C_{30}H_{31}NO_2$ (M+H): 438.2428; found: 438.2431.

*4.2.2.2. (S)-2-Amino-1-(4-(benzyloxy)phenyl)-3-ethylpentan-3-ol (**7b**).* Light yellow powder, yield 47%; mp 63–65 °C. $[\alpha]_D^{20}$ −27 (*c* 1.00, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92–0.98 (m, 6H), 1.39–1.69 (m, 4H), 2.26 (dd, *J*=13.5, 3.4 Hz, 1H), 2.90–2.94 (m, 2H), 5.05 (s, 2H), 6.94 (d, *J*=8.1 Hz, 2H), 7.11 (d, *J*=8.1 Hz, 2H), 7.31–7.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.60, 7.64, 26.39, 27.76, 36.92, 57.15, 69.87, 74.22, 114.85, 127.37, 127.86, 128.47, 129.96, 132.09, 136.89, 157.24. HRMS (ESI) calcd for $C_{20}H_{27}NO_2$ (M+H): 314.2115; found: 314.2119.

*4.2.2.3. (S)-1-(4-(4-Methoxybenzyloxy)phenyl)-2-amino-3-ethylpentan-3-ol (**7c**).* Light yellow powder, yield 54%; mp 81–83 °C. $[\alpha]_D^{20}$ −20 (*c* 1.00, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.85–0.98 (m, 6H), 1.39–1.69 (m, 4H), 2.25 (dd, *J*=14.1, 11.7 Hz, 1H), 2.89–2.93

(m, 2H), 3.82 (s, 3H), 4.97 (s, 2H), 6.91 (d, *J*=1.8 Hz, 2H), 6.94 (d, *J*=1.8 Hz, 2H), 7.10 (d, *J*=8.4 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.59, 7.62, 26.40, 27.77, 36.96, 55.14, 57.17, 69.66, 74.18, 113.84, 114.86, 128.89, 129.12, 129.92, 132.02, 157.30, 159.29. HRMS (ESI) calcd for $C_{21}H_{29}NO_3$ (M+H): 344.2220; found: 344.2223.

*4.2.3. General procedures for preparation of β-hydroxy amides **8a–c***

A solution of benzoyl chloride (5.5 mmol) in CH_2Cl_2 (20 mL) was added to a cold (0 °C) solution of amino alcohol **7** (5.00 mmol) and Et_3N (0.77 mL, 5.5 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with 1 N HCl (2×10 mL), saturated aqueous $NaHCO_3$ (2×10 mL), and brine (2×10 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated under vacuum. The yellow residue was purified by column chromatography to afford β-hydroxy amides.

*4.2.3.1. N-((S)-3-Benzyl-1-(4-(benzyloxy)phenyl)-3-hydroxy-4-phenylbutan-2-yl)benzamide (**8a**).* White needle solid, yield 72%; mp 169–170 °C. $[\alpha]_D^{20}$ −48 (*c* 1.00, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.83 (dd, *J*=11.4, 14.4 Hz, 1H), 2.95 (dd, *J*=8.7, 13.8 Hz, 2H), 3.05 (dd, *J*=6.6, 13.8 Hz, 2H), 3.33 (dd, *J*=3.3, 14.4 Hz, 1H), 3.77 (s, 1H), 4.25–4.33 (m, 1H), 4.96 (s, 2H), 5.53 (d, *J*=8.7 Hz, 1H), 6.81 (d, *J*=8.7 Hz, 2H), 6.95 (d, *J*=8.7 Hz, 2H), 7.13–7.44 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.35, 42.71, 45.10, 58.28, 69.83, 77.49, 114.90, 126.54, 126.63, 126.73, 127.36, 127.84, 128.18, 128.32, 128.41, 128.47, 129.59, 130.04, 130.61, 130.64, 131.39, 133.59, 136.74, 136.86, 137.66, 157.39, 168.70. IR (KBr): 3414, 3373, 3028, 2940, 1630, 1531, 1514, 1490, 1450, 1247, 1024, 709 cm^{-1}. HRMS (ESI) calcd for $C_{37}H_{35}NO_3$ (M+Na): 564.2509; found: 564.2504.

*4.2.3.2. N-((S)-1-(4-(Benzyloxy)phenyl)-3-ethyl-3-hydroxypentan-2-yl)benzamide (**8b**).* White needle solid, yield 76%; mp 156–157 °C. $[\alpha]_D^{20}$ −139 (*c* 1.00, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90–1.00 (m, 6H), 1.57–1.78 (m, 4H), 2.56 (br, 1H), 2.79 (dd, *J*=14.1, 10.5 Hz, 1H), 3.08 (dd, *J*=14.1, 3.6 Hz, 1H), 4.23–4.30 (m, 1H), 4.99 (s, 2H), 6.17 (d, *J*=9.3 Hz, 1H), 6.84 (d, *J*=8.7 Hz, 2H), 7.12 (d, *J*=8.7 Hz, 2H), 7.28–7.55 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.62, 7.98, 27.72, 28.07, 34.21, 56.67, 69.83, 76.89, 114.74, 126.77, 127.35, 127.76, 128.32, 128.41, 130.04, 131.15, 134.64, 136.99, 157.24, 168.03. IR (KBr): 3446, 3352, 2967, 1630, 1540, 1511, 1237, 1012, 694 cm^{-1}. HRMS (ESI) calcd for $C_{27}H_{31}NO_3$ (M+Na): 440.2196; found: 440.2192.

*4.2.3.3. N-((S)-1-(4-(4-Methoxybenzyloxy)phenyl)-3-ethyl-3-hydroxypentan-2-yl)benzamide (**8c**).* White needle solid, yield 79%; mp 167–168 °C. $[\alpha]_D^{20}$ −128 (*c* 1.00, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90–1.00 (m, 6H), 1.56–1.76 (m, 4H), 2.69 (br, 1H), 2.80 (dd, *J*=14.1, 10.5 Hz, 1H), 3.08 (dd, *J*=14.1, 3.6 Hz, 1H), 3.80 (s, 3H), 4.25–4.30 (m, 1H), 4.91 (s, 2H), 6.22 (d, *J*=6.9 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 7.14 (d, *J*=8.1 Hz, 2H), 7.30–7.48 (m, 4H), 7.54 (d, *J*=8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.65, 8.02, 27.76, 28.08, 34.16, 55.21, 56.76, 69.62, 76.92, 113.85, 114.75, 126.78, 128.37, 128.96, 129.18, 130.02, 130.93, 131.24, 134.60, 157.29, 159.28, 168.05. IR (KBr): 3403, 3364, 3033, 2964, 1623, 1535, 1516, 1491, 1244, 1176, 1033, 692 cm^{-1}. HRMS (ESI) calcd for $C_{28}H_{33}NO_4$ (M+Na): 470.2302; found: 470.2302.

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

Under dry nitrogen, the ligand **8b** (0.05 mmol) and Ti(O-*i*-Pr)$_4$ (45 μL, 0.15 mmol) were mixed in anhydrous toluene (1.5 mL) at room temperature and stirred for 1 h. Then a solution of $ZnEt_2$ (0.75 mL, 1.0 M in CH_2Cl_2, 0.75 mmol) was added. After the mixture was stirred at room temperature for 2 h, phenylacetylene (82.4 μL, 0.75 mmol) was added and stirred for another 1 h. Aldehyde (0.25 mmol) was then added, and the reaction mixture was stirred at room temperature for 18 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 with anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, 12.5% EtOAc in petroleum ether) to give the propargyl alcohol.

Acknowledgements

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