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Synthesis of new C_2-symmetric bis(β-hydroxy amide) ligands and their applications in the enantioselective addition of alkynylzinc to aldehydes

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Abstract

A series of chiral C_2-symmetric bis(β-hydroxy amide) ligands was synthesized via the reaction of isophthaloyl dichloride and amino alcohols derived from L-amino acid. The titanium(IV) complex of C_2-symmetric chiral ligand **3b** was effective for the asymmetric alkynylation of aldehydes and the propargyl alcohols were obtained in high yields (up to 94%) and high enantiomeric excesses (up to 98%) under optimized conditions. The results obtained using ligand **3h** support that the two β-hydroxy amide moieties in these ligands behave as two independent ligands in the catalytic system.

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

1. Introduction

The asymmetric alkyne addition to carbonyl compounds is very useful for the synthesis of chiral propargyl alcohols, which are valuable building blocks for fine chemicals, pharmaceuticals, and natural products.[1] Since the first efficient asymmetric alkyne addition to aldehydes was demonstrated by Corey and Cimprich[2] using chiral oxazaborolidines, the development of new and efficient catalysts for alkynylation of aldehydes is of current interest and many highly enantioselective catalysts have been disclosed to this reaction.[3,4] Among the catalytic methods developed, several of them are currently considered to be the most practical. Carreira and coworkers[5] reported that a system using $Zn(OTf)_2$ and chiral ephedrine with triethylamine afforded high yields and enantioselectivities in the addition of terminal acetylide to aliphatic aldehydes. For titanium complex-catalyzed alkynylation reaction, BINOLs and H_8-BINOLs were demonstrated to be excellent ligands by Chan et al.,[6] Pu et al.,[7] and Gong et al..[8] Wang et al.[9] described a highly enantioselective addition of phenylacetylene to aldehydes catalyzed by β-sulfonamide alcohols in combination with $Ti(O\text{-}i\text{-}Pr)_4$.

C_2-Symmetry is interesting in chemistry, and compounds with C_2-symmetry have also received much attention for their utilities as asymmetric ligands in stereoselective reactions.[10] Development of new types of C_2-symmetric ligands for asymmetric reaction is an intriguing research area. Recently, we have developed a new β-hydroxy amide chiral ligand **1b**, which was successfully used in the asymmetric addition of phenylacetylene to aldehydes with excellent enantioselectivities (up to 97% ee).[11] For further exploring chiral ligand effects of titanium(IV) complexes in this addition, we herein describe the synthesis of a series of new C_2-symmetric β-hydroxy amide ligands **3a–f** and their applications in enantioselective additions of phenylacetylene to aldehydes.

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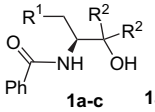


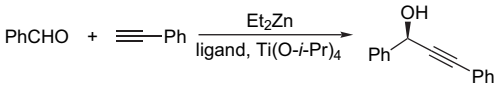
1a-c **1a** $R^1 = R^2 = Ph$
1b $R^1 = Ph$, $R^2 = Et$
1c $R^1 = i\text{-Pr}$, $R^2 = Et$

2. Results and discussion

Reaction of isophthalyl chloride with amino alcohols **2a–f**[12–14] in the presence of triethylamine afforded new C_2-symmetric bis(β-hydroxy amide) ligands **3a–f** (Scheme 1). The addition of phenylacetylene to benzaldehyde in the presence of chiral ligands **3a–f**, Et_2Zn, and Ti(O-*i*-Pr)$_4$ in toluene was first examined and the results are summarized in Table 1. Ligand **3a**, which has two benzyl substituents at the hydroxy-bearing carbon atom, resulted in a low enantioselectivity (Table 1, entry 1). When **3b** was used, which possesses small and more flexible ethyl substituents, the corresponding propargyl alcohol was given in 92% yield and 95% ee (Table 1, entry 2). For ligands **3c** and **3d**, having α-phenylethyl or isobutyl group instead of benzyl group, the enantioselectivity dropped to 88 and 62% ee, respectively (Table 1, entries 3 and 4). When ligands **3e** and **3f** were used, the propargyl alcohol was only obtained in 26 and 23% ee, respectively (Table 1, entries 5 and 6). The ee value decreased when the amount of chiral ligand **3b** was reduced from 10 to 7.5% (Table 1, entry 7).

To improve the enantioselectivity, the reaction conditions were optimized with ligand **3b**. The results are summarized in Table 2. The enantioselectivity of the reaction was strongly affected by different conditions. Increasing the amount of Ti(O-*i*-Pr)$_4$ from 2:1 to 3:1 relative to chiral ligand **3b** increased the enantioselectivity (Table 2, entries 1 and 2). However, the enantioselectivity decreased obviously when the ratio of Ti(O-*i*-Pr)$_4$ to chiral ligand **3b** was increased to 4:1 (Table 2, entry 3). So the ratio in entry 2 was found to be the best. The amount of diethylzinc is also important. When the amount of $ZnEt_2$ was increased, the ee value decreased from 95 to 84% (Table 2, entry 5). When the reaction was carried out in various solvents, such as *n*-hexane, dichloromethane, diethyl ether, and THF, lower ee values were obtained (Table 2, entries 6–9). So toluene is the best choice of the solvent.

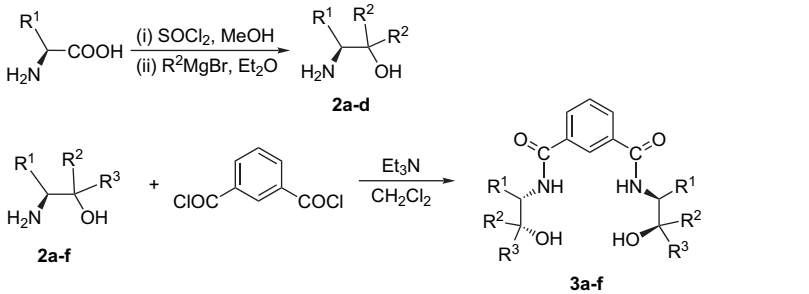
Table 1
Asymmetric addition of phenylacetylene to benzaldehyde catalyzed by ligands **3a–h**[a]



Entry	Ligand	Ligand/Ti(O-*i*-Pr)$_4$	Yield[b] (%)	ee[c] (%)
1	**3a**	1:3	88	56
2	**3b**	1:3	92	95
3	**3c**	1:3	89	88
4	**3d**	1:3	88	62
5	**3e**	1:3	87	26
6	**3f**	1:3	86	23
7[d]	**3b**	1:3	87	85
8	**3g**	1:3	85	11
9	**3h**	1:1.5	83	74
10	**3h**	1:3	89	78
11	**3h**	1:4	93	94
12	**3h**	1:5	91	81

[a] $ZnEt_2$/phenylacetylene/PhCHO/ligand=3:3:1:0.1; solvent: toluene; reaction time: 18 h; reaction temperature: rt.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiracel OD-H column.
[d] Ligand was 7.5 mol %.

In this study, ligand **3b** contains two β-hydroxy amide moieties and each β-hydroxy amide moiety resembles a bidentate ligand. In order to support our proposal, a ligand with one β-hydroxy amide moiety blocked is required to demonstrate that the remaining unblocked β-hydroxy amide moiety is still an effective ligand for this addition reaction. Thus, β-hydroxy amide **2b** was first converted to **4**. Compound **4** was deprotonated with *n*-BuLi followed by the addition of 1.0 equiv of isophthalyl chloride to give a mixture of **5** and **3g**. Without purification, the mixture was treated with 1.65 equiv of **2b** in the presence of NEt_3 and a catalytic amount of DMAP to afford the target compound **3h** (Scheme 2). Both compounds **3g** and **3h** were examined for alkynylzinc addition to benzaldehyde. For ligand **3g**, the desired product was obtained in 85% yield and only 11% ee (Table 1, entry 8). For ligand



2a-d

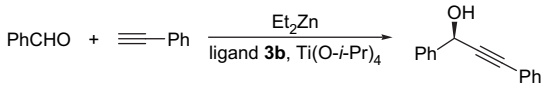
2a-f

3a-f

$R^1 = R^2 = R^3 = PhCH_2$ (**3a**)
$R^1 = PhCH_2$, $R^2 = R^3 = CH_2CH_3$ (**3b**)
$R^1 = PhCH_2CH_2$, $R^2 = R^3 = CH_2CH_3$ (**3c**)
$R^1 = i\text{-Bu}$, $R^2 = R^3 = CH_2CH_3$ (**3d**)
$R^1 = PhCH_2$, $R^2 = R^3 = H$ (**3e**)
$R^1 = PhCH_2$, $R^2 = H$, R^3=Ph (**3f**)

Scheme 1. Synthesis of chiral ligands **3a–f**.

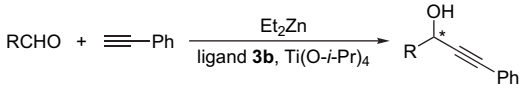
Table 2
Asymmetric addition of phenylacetylene to benzaldehyde catalyzed by ligand **3b**[a]



Entry	Solvent	Ligand/Ti(O-*i*-Pr)$_4$	$ZnEt_2$ (mmol)	Yield[b] (%)	ee[c] (%)
1	Toluene	1:2	0.75	84	81
2	Toluene	1:3	0.75	92	95
3	Toluene	1:4	0.75	92	82
4	Toluene	1:3	0.50	80	74
5	Toluene	1:3	1.00	85	84
6	*n*-Hexane	1:3	0.75	88	87
7	CH_2Cl_2	1:3	0.75	84	87
8	Et_2O	1:3	0.75	79	58
9	THF	1:3	0.75	86	29
10[d]	Toluene	1:3	0.75	81	89

[a] PhCHO/ligand=1: 0.1; reaction time: 18 h; reaction temperature: rt.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiracel OD-H column.
[d] Reaction was performed under 0 °C.

Table 3
Asymmetric addition of phenylacetylene to aldehydes promoted by ligand **3b**[a]

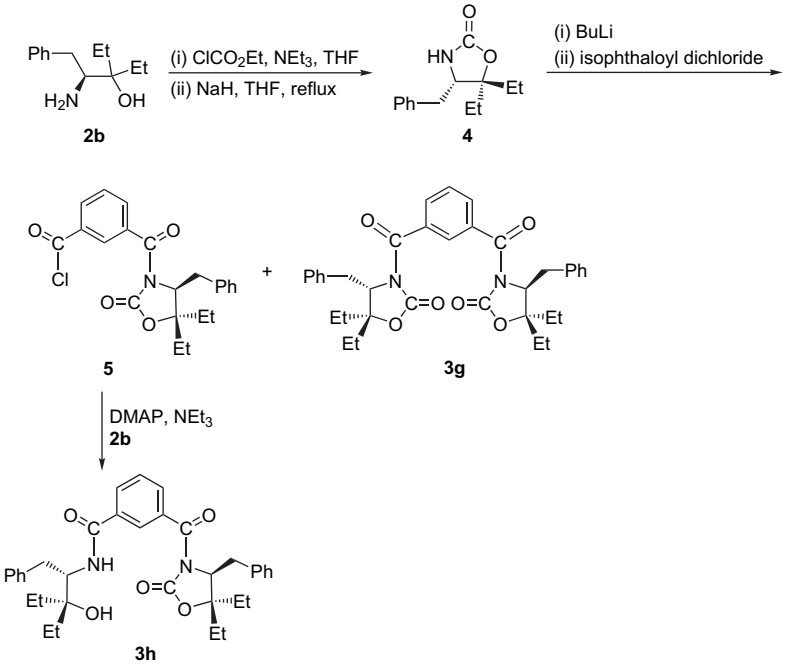


Entry	Aldehyde	Yield[b] (%)	ee[c] (%)
1	Benzaldehyde	92	95
2	2-Anisaldehyde	93	88
3	4-Anisaldehyde	90	93
4	2-Tolualdehyde	91	90
5	4-Tolualdehyde	94	98
6	2-Chlorobenzaldehyde	89	93
7	2-Flourobenzaldehyde	93	92
8	3-Chlorobenzaldehyde	89	94
9	4-Chlorobenzaldehyde	91	96
10	1-Naphthaldehyde	87	89
11	2-Naphthaldehyde	82	94
12	Cinnamaldehyde	85	87
13	*n*-Butylaldehyde	83	52
14	Cyclohexanecarbaldehyde	87	67

[a] Aldehyde/phenylacetylene/$ZnEt_2$/Ti(O-*i*-Pr)$_4$/**3b**=1:3:3:0.3:0.1; solvent: toluene; reaction time: 18 h; reaction temperature: rt.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiracel OD-H column.

3h with one β-hydroxy amide moiety blocked, a half-amount of Ti(O-*i*-Pr)$_4$ is expected to be enough to catalyze the reaction with comparable enantioselectivity which was obtained from the catalytic system of ligand **3b**. In fact, ligand **3h** gave the desired propargylic alcohol in good yield and 78% ee (Table 1, entry 10) in the same conditions.

To demonstrate the generality of the ligand for phenylacetylene asymmetric addition to aldehydes, various aldehydes were examined using the titanium complex of ligand **3b** under the optimized reaction conditions and the results are listed in Table 3. The chiral propargyl alcohols could be obtained in good isolated yields of 82–94% and excellent enantioselectivities of 88–98% ee for aromatic aldehydes (Table 3, entries 1–11). For *para*-substituted benzaldehydes, the one with strong electron-donating group gave a slightly lower enantioselectivity (Table 3, entry 3, *p*-CH_3O, ee 93%), while the aldehydes with moderate electron-withdrawing and electron-donating groups gave a little higher enatioselectivities (Table 3, entry 5, *p*-CH_3, ee 98%; entry 9, *p*-Cl, ee 96%). α,β-Unsaturated *trans*-cinnamaldehyde afforded 87% enantioselectivity (Table 3, entry 12). However, aliphatic *n*-butylaldehyde and cyclohexanecarbaldehyde gave the products in low



Scheme 2. Synthesis of chiral ligands **3g–h**.

enantioselectivities of only 52 and 67% ee, respectively (Table 3, entries 13 and 14).

3. Conclusions

We have described new C_2-symmetric chiral bis(β-hydroxy amide) ligands, which could be prepared easily from isophthalyl chloride and chiral amino alcohols. The enantioselective addition of phenylacetylene to aldehydes catalyzed by **3b**/Ti(O-*i*-Pr)$_4$ was demonstrated with excellent enantioselectivity (up to 98% ee). The reaction catalyzed by blocked ligand **3h**/Ti(O-*i*-Pr)$_4$ system supports that the two β-hydroxy amide moieties in these C_2-symmetrical ligands behave as two independent ligands in the catalytic system. The application of these ligands supported by cross-linked polystyrene backbone in this asymmetric addition is currently under the way and will be reported in due course.

4. Experimental

4.1. General information

All the reactions were carried out under a dry nitrogen atmosphere. Melting points were taken on an X-4 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-400 or 300 MHz spectrometer with TMS as an internal standard. IR spectra were obtained on a Nicolet NEXUS 670 FT-IR instrument. Mass spectra were performed on Thermo DSQ mass instrument (EI at 70 eV). Optical rotation was measured on a Perkin–Elmer 341 polarimeter. Elemental analyses were determined by Elemental vario EL instrument. Enantiomeric excess values were determined by HPLC with a Chiralcel OD-H column. Ti(O-*i*-Pr)$_4$ was freshly distilled prior to use. Triethylamine was distilled over KOH pellets and stored in a sealed flask. All solvents used were dried by heating under reflux for at least 12 h over P_2O_5 (dichloromethane) or sodium/benzophenone (diethyl ether, THF, toluene or *n*-hexane), and were freshly distilled prior to use. Aldehydes were purchased from Aldrich and used directly. Reactions were monitored by thin layer chromatography (TLC). Diethylzinc (1.0 M solution in CH_2Cl_2) was prepared following the literature method[15] and then diluted with CH_2Cl_2 to 1.0 M.

4.2. Synthesis of chiral ligands

4.2.1. Amino alcohols

Amino alcohols **2a–d**, **2e**, and **2f** were synthesized according to literature procedures,[12–14] respectively.

4.2.2. General procedures for preparation of C_2-symmetrical β-hydroxy amides (*3a–f*)

A solution of isophthalyl chloride (5.00 mmol) in CH_2Cl_2 (10 mL) was added to a solution of the corresponding amino alcohol (10.0 mmol) and Et_3N (4.18 mL, 30 mmol) in CH_2Cl_2 (20 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 1 M HCl (2×10 mL), saturated aqueous $NaHCO_3$ (3×10 mL), and brine (3×10 mL). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to give a yellow residue. The crude product was purified by flash column chromatography to give **3a–f**.

*4.2.2.1. N_1,N_3-Bis[(S)-3-benzyl-3-hydroxy-1,4-diphenylbutan-2-yl]isophthalamide (**3a**).* White powder, yield 55%, mp 150–151 °C. $[\alpha]_D^{25}$ −16 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.42–7.00 (m, 34H, ArH), 5.57 (d, *J*=8.8 Hz, 2H, NH), 4.38–4.30 (m, 2H, CH), 3.54 (br, 2H, OH), 3.38 (d, *J*=14.4 Hz, 2H, CH), 3.06–2.84 (m, 10H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.63, 137.78, 137.33, 136.62, 133.80, 130.61, 129.47, 128.63, 128.53, 128.44, 128.37, 128.18, 126.79, 126.74, 126.56, 124.99, 77.37, 58.24, 44.81, 42.65, 36.09. IR (KBr): 3409, 3344, 3060, 3027, 2941, 1641, 1541, 1496, 1451, 733 cm^{-1}. Anal. Calcd for $C_{54}H_{52}N_2O_4$ (%): C, 81.79; H, 6.61; N, 3.53. Found: C, 81.58; H, 6.63; N, 3.55.

*4.2.2.2. N_1,N_3-Bis[(S)-3-ethyl-3-hydroxy-1-phenylpentan-2-yl]-isophthalamide (**3b**).* White powder, yield 57%, mp 144–145 °C. $[\alpha]_D^{25}$ −126 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.60 (s, 1H, ArH), 7.43 (d, *J*=8.4 Hz, 2H, ArH), 7.26–7.11 (m, 11H, ArH), 6.35 (d, *J*=8.7 Hz, 2H, NH), 4.37–4.29 (m, 2H, CH), 3.13 (dd, *J*=14.1, 3.6 Hz, 2H, $PhCH_2$), 2.83 (dd, *J*=14.1, 11.1 Hz, 2H, $PhCH_2$), 2.63 (br, 2H, OH), 1.79–1.52 (m, 8H, CH_2), 1.00–0.92 (m, 12H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 167.36, 138.82, 134.76, 129.48, 129.15, 128.43, 128.28, 126.23, 124.99, 56.52, 35.04, 28.02, 27.62, 7.97, 7.67. IR (KBr): 3403, 2967, 2940, 1639, 1541, 1452, 741 cm^{-1}. Anal. Calcd for $C_{34}H_{44}N_2O_4$: C, 74.97; H, 8.14; N, 5.14. Found: C, 74.69; H, 7.94; N, 5.32.

*4.2.2.3. N_1,N_3-Bis[(S)-4-ethyl-4-hydroxy-1-phenylhexan-3-yl]-isophthalamide (**3c**).* White powder, yield 58%, mp 81–82 °C. $[\alpha]_D^{25}$ −40 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 8.28 (s, 1H, ArH), 7.91 (d, *J*=7.8 Hz, 2H, ArH), 7.48 (t, *J*=7.5 Hz, 1H, ArH), 7.27–7.12 (m, 10H, ArH), 6.64 (d, *J*=9.6 Hz, 2H, NH), 4.30–4.23 (m, 2H, CH), 2.78–2.65 (m, 4H, CH_2), 2.09 (br, 2H, OH), 2.02–1.82 (m, 4H, CH_2), 1.66–1.47 (m, 8H, CH_2), 0.85 (t, *J*=7.2 Hz, 12H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 166.95, 141.87, 134.80, 129.88, 128.80, 128.34, 128.31, 125.81, 125.58, 77.06, 54.60, 32.80, 31.30, 27.86, 27.70, 7.77, 7.57. IR (KBr): 3419, 3062, 2967, 2939, 2882, 1644, 1519, 1454, 728 cm^{-1}. Anal. Calcd for $C_{36}H_{48}N_2O_4$: C, 75.49; H, 8.45; N, 4.89. Found: C, 75.42; H, 8.15; N, 4.83.

*4.2.2.4. N_1,N_3-Bis[(S)-5-ethyl-5-hydroxy-2-methylheptan-4-yl]-isophthalamide (**3d**).* White powder, yield 53%, mp 206–208 °C. $[\alpha]_D^{25}$ −43 (*c* 1.00, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.23 (s, 1H, ArH), 7.91 (d, *J*=8.0 Hz, 2H, ArH), 7.49 (t, *J*=7.6 Hz, 1H, ArH), 6.40 (d, *J*=9.2 Hz, 2H, NH), 4.27 (t, *J*=9.6 Hz, 2H, CH), 1.95 (br, 2H, OH), 1.68–1.47 (m, 12H, CH_2, CH), 1.39–1.33 (m, 2H, CH), 0.99–0.87 (m,

24H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.85, 134.89, 129.83, 128.74, 125.52, 77.16, 52.94, 38.37, 27.86, 27.71, 24.96, 24.14, 21.55, 7.85, 7.51. IR (KBr): 3432, 3315, 2964, 2878, 1640, 1583, 1531, 1467, 718 cm^{-1}. Anal. Calcd for $C_{28}H_{48}N_2O_4$: C, 70.55; H, 10.15; N, 5.88. Found: C, 70.31; H, 9.83; N, 5.58.

*4.2.2.5. N_1,N_3-Bis[(S)-1-hydroxy-3-phenylpropan-2-yl]isophthalamide (**3e**).* White powder, yield 53%, mp 151–152 °C. $[\alpha]_D^{25}$ −129 (*c* 1.00, DMSO). ^1H NMR (300 MHz, DMSO-d_6) δ: 8.29 (d, *J*=9.0 Hz, 2H, NH), 8.16 (s, 1H, ArH), 7.85 (d, *J*=7.5 Hz, 2H, ArH), 7.48 (t, *J*=7.5 Hz, 1H, ArH), 7.24–7.12 (m, 10H, ArH), 4.89 (t, *J*=5.7 Hz, 2H, OH), 4.16–4.14 (m, 2H, CH), 3.55–3.28 (m, 4H, CH_2), 2.93 (dd, *J*=13.5, 4.8 Hz, 2H, $PhCH_2$), 2.77 (dd, *J*=13.5, 8.7 Hz, 2H, $PhCH_2$). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 166.63, 139.84, 135.42, 130.28, 129.73, 128.83, 126.99, 126.68, 63.49, 53.96, 37.10. IR (KBr): 3414, 3343, 2958, 1633, 1547, 1452, 730 cm^{-1}. Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.01; H, 6.84; N, 6.48.

*4.2.2.6. N_1,N_3-Bis[(1R,2S)-1-hydroxy-1,3-diphenylpropan-2-yl]isophthalamide (**3f**).* White powder, yield 84%, mp 110–111 °C. $[\alpha]_D^{25}$ −91 (*c* 1.00, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.69 (s, 1H, ArH), 7.39–7.01 (m, 23H, ArH), 6.38 (d, *J*=8.1 Hz, 2H, NH), 5.06 (d, *J*=2.7 Hz, 2H, CH), 4.60–4.52 (m, 2H, CH), 2.80–2.77 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.74, 141.27, 138.70, 134.35, 129.27, 129.11, 128.66, 128.37, 127.74, 126.60, 126.34, 125.90, 75.29, 57.68, 33.15. IR (KBr): 3409, 3061, 3028, 1643, 1519, 1450, 749 cm^{-1}. Anal. Calcd for $C_{38}H_{36}N_2O_4$: C, 78.06; H, 6.21; N, 4.79. Found: C, 77.77; H, 6.31; N, 4.72.

*4.2.3. Preparation of (S)-4-benzyl-5,5-diethyloxazolidin-2-one (**4**)*

To a solution of **2b** (1.03 g, 5.0 mmol) and triethylamine (3.48 mL, 25 mmol) in THF (25 mL), ethyl chloroformate (0.48 mL, 5.0 mmol) was added at room temperature and the mixture was allowed to react for 3 h. The solution was then added slowly to a suspension of NaH (1.20 g, 50 mmol) in THF (25 mL) during a period of 0.5 h and the resulting mixture was refluxed for 12 h. The solution was cooled down and washed with 1 M HCl (3×50 mL) and brine (3×50 mL), then the organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed to give yellowish oil **4** in 88% yield. $[\alpha]_D^{25}$ −66 (*c* 1.00, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.37–7.16 (m, 5H, ArH), 4.96 (br, 1H, NH), 3.76 (dd, *J*=11.1, 3.6 Hz, 1H, CH), 2.86 (dd, *J*=3.0, 14.4 Hz, 1H, $PhCH_2$), 2.70 (dd, *J*=14.4, 12.9 Hz, 1H, $PhCH_2$), 1.98–1.91 (m, 1H, CH_2), 1.84–1.68 (m, 3H, CH_2), 1.06 (t, *J*=7.5 Hz, 3H, CH_3), 0.97 (t, *J*=7.5 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.99, 137.10, 128.88, 128.74, 126.95, 87.22, 60.86, 37.08, 28.99, 24.89, 7.65, 7.37. IR (KBr): 3272, 2973, 1747, 1604, 1495, 1457, 1388, 739 cm^{-1}. MS (EI) *m/z*: 234.0 (47.5), 141.8 (72.7), 97.8 (100), 90.8 (63.1).

*4.2.4. Synthesis of chiral ligands **3g** and **3h***

To a solution of **4** (1.03 g, 4.41 mmol) in CH_2Cl_2 (25 mL) at −78 °C, *n*-butyllithium solution (2.5 M, 2.11 mL, 5.3 mmol) was added and the mixture was stirred for 0.5 h. A solution of isophthalyl chloride (0.90 g, 4.41 mmol) in CH_2Cl_2 (25 mL) was added to the above solution. The resulting solution was allowed to warm to room temperature and stirred for 18 h. This mixture was added slowly in 0.5 h to a solution of NEt_3 (1.85 mL, 13.2 mmol), a catalytic amount of DMAP, and amino alcohol **2b** (1.09 g, 5.29 mmol) in CH_2Cl_2 (20 mL) at room temperature. The solution was stirred overnight and then washed with 1 M HCl (3×25 mL), and brine (3×25 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to give a yellow residue. The crude product was purified by flash column chromatography to afford **3g** and **3h**.

*4.2.4.1. 1,3-Bis[(S)-4-benzyl-5,5-diethyloxooxazolidin-3-formyl]-benzene (**3g**).* White powder, yield 21%, mp 61–62 °C. $[\alpha]_D^{25}$ +29 (*c* 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.90 (s, 1H, ArH), 7.73 (d, *J*=8.0 Hz, 2H, ArH), 7.39 (t, *J*=8.0 Hz, 1H, ArH), 7.27–7.13 (m, 10H, ArH), 4.77–4.74 (m, 2H, CH), 3.23 (dd, *J*=14.0, 5.2 Hz, 2H, $PhCH_2$), 2.91 (dd, *J*=14.0, 8.4 Hz, 2H, $PhCH_2$), 1.98–1.92 (m, 2H, CH_2), 1.66–1.58 (m, 4H, CH_2), 1.50–1.43 (m, 2H, CH_2), 0.95 (t, *J*=7.6 Hz, 6H, CH_3), 0.75 (t, *J*=7.6 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.71, 152.40, 136.49, 133.12, 132.77, 130.63, 129.07, 128.64, 127.00, 126.90, 86.67, 61.75, 34.62, 29.12, 25.65, 7.74, 7.24. IR (KBr): 2975, 2944, 2885, 1781, 1683, 1458, 1356, 1301, 724 cm^{-1}. Anal. Calcd for $C_{36}H_{40}N_2O_6$: C, 72.46; H, 6.76; N, 4.69. Found: C, 72.27; H, 6.81; N, 4.74.

*4.2.4.2. 3-[(S)-4-Benzyl-5,5-diethyloxooxazolidin-3-formyl]-N-[(S)-3-ethyl-3-hydroxy-1-phenylpentan-2-yl]-benzamide (**3h**).* White powder, yield 25%, mp 63–64 °C. $[\alpha]_D^{25}$ −54 (*c* 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.76 (s, 1H, ArH), 7.66 (d, *J*=8.0 Hz, 2H, ArH), 7.39 (t, *J*=8.0, 1H, ArH), 7.34–7.14 (m, 10H, ArH), 6.22 (d, *J*=9.2 Hz, 1H, NH), 4.83–4.79 (m, 1H, CH), 4.33–4.29 (m, 1H, CH), 3.27 (dd, *J*=5.2, 14.0 Hz, 1H, $PhCH_2$), 3.14 (dd, *J*=14.0, 3.6 Hz, 1H, $PhCH_2$), 2.98 (dd, *J*=14.0, 8.8 Hz, 1H, $PhCH_2$), 2.87 (dd, *J*=14.0, 10.4 Hz, 1H, $PhCH_2$), 2.51 (br, 1H, OH), 1.79–1.50 (m, 8H, CH_2), 1.04–0.80 (m, 12H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.01, 166.89, 152.48, 138.73, 136.48, 134.47, 133.52, 131.77, 130.55, 129.17, 129.13, 128.68, 128.46, 127.89, 127.59, 126.99, 126.37, 86.90, 76.95, 61.65, 56.82, 35.11, 34.67, 29.12, 28.11, 27.82, 25.57, 8.03, 7.77, 7.67, 7.28. IR (KBr): 3383, 2970, 2941, 2882, 1781, 1684, 1642, 1536, 1357, 729 cm^{-1}. Anal. Calcd for $C_{35}H_{42}N_2O_5$: C, 73.66; H, 7.42; N, 4.91. Found: C, 73.63; H, 7.38; N, 4.80.

4.3. General procedure for asymmetric addition of phenylacetylene to aldehydes

Under dry nitrogen, the ligand (0.025 mmol) and Ti(O-*i*-Pr)$_4$ (0.075 mmol) were mixed in the solvent (1.5 mL)

at room temperature. Then diethylzinc (0.75 mL, 1.0 M solution in CH_2Cl_2) was added. After the mixture was stirred at room temperature for 2 h, phenylacetylene (82.4 μL, 0.75 mmol) was added and the mixture was stirred for 1 h. Then the solution was treated with aldehyde (0.25 mmol). After the reaction was completed (TLC), the reaction solution was cooled to 0 °C and quenched by 5% aqueous HCl. The mixture was extracted with diethyl ether (3×10 mL). The extract was washed with brine (3×15 mL), dried over anhydrous Na_2SO_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.

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References and notes

1. (a) Guillarme, S.; Plé, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* **2006**, *106*, 2355; (b) Trost, B.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131; (c) Evans, D. A.; Halstead, D. P.; Allison, B. D. *Tetrahedron Lett.* **1999**, *40*, 4461.
2. Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.
3. For reviews: (a) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757; (b) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373; (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873.
4. (a) Li, Z.-B.; Liu, T.-D.; Pu, L. *J. Org. Chem.* **2007**, *72*, 4340; (b) Lin, L.; Jiang, X.; Liu, W.; Qiu, L.; Xu, Z.; Xu, J.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2007**, *9*, 2329; (c) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew Chem., Int. Ed.* **2006**, *45*, 122; (d) Wolf, C.; Liu, S. *J. Am. Chem. Soc.* **2006**, *128*, 10996; (e) Trost, B. M.; Weiss, A. H.; Jacobi von Wangelin, A. *J. Am. Chem. Soc.* **2006**, *128*, 8; (f) Hsieh, S.-H.; Gau, H.-M. *Synlett* **2006**, 1871; (g) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760; (h) Fang, T.; Du, D.-M.; Lu, S.-F.; Xu, J.-X. *Org. Lett.* **2005**, *7*, 2081; (i) Yamashita, M.; Yamada, K.; Tomioka, K. *Adv. Synth. Catal.* **2005**, *347*, 1649; (j) Li, M.; Zhu, X. Z.; Yuan, K.; Cao, B. X.; Hou, X. L. *Tetrahedron: Asymmetry* **2004**, *15*, 219; (k) Dahmen, S. *Org. Lett.* **2004**, *6*, 2113.
5. (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687; (b) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605; (c) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.
6. (a) Lu, G.; Li, X.; Chen, G.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 449; (b) Li, X. S.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636; (c) Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002**, 172.
7. (a) Li, Z.-B.; Pu, L. *Org. Lett.* **2004**, *6*, 1065; (b) Gao, G.; Moore, D.; Xie, R. G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143; (c) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855.
8. Liu, Q.-Z.; Xie, N.-S.; Luo, Z.-B.; Cui, X.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *J. Org. Chem.* **2003**, *68*, 7921.
9. (a) Xu, Z.; Wang, R.; Xu, J.; Da, C.-S.; Chen, W.-J.; Chen, C. *Angew Chem., Int. Ed.* **2003**, *42*, 5747; (b) Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193.
10. (a) Jiang, B.; Feng, Y. *Tetrahedron Lett.* **2002**, *43*, 2975; (b) Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 1573; (c) Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1103; (d) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584; (e) Ni, M.; Wang, R.; Han, Z.; Mao, B.; Da, C.; Liu, L.; Chen, C. *Adv. Synth. Catal.* **2005**, *347*, 1659; (f) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321; (g) Hsieh, S.-H.; Gau, H.-M. *Chirality* **2006**, *18*, 569.
11. (a) Chen, Z.-C.; Hui, X.-P.; Yin, C.; Huang, L.-N.; Xu, P.-F.; Yu, X.-X.; Cheng, S.-Y. *J. Mol. Catal. A: Chem.* **2007**, *269*, 179; (b) Huang, L.-N.; Hui, X.-P.; Chen, Z.-C.; Yin, C.; Xu, P.-F.; Yu, X.-X.; Cheng, S.-Y. *J. Mol. Catal. A: Chem.* **2007**, *275*, 9.
12. Wu, Y.-J.; Yun, H.-Y.; Wu, Y.-S.; Ding, K.-L.; Zhou, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 3543.
13. Mckennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.
14. Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.
15. Noller, C. R. *Org. Synth. Coll.* **1951**, *2*, 184–186.