Full paper

Applied Organometallic Chemistry

Received: 1 September 2015 Revised: 22 November 2015 Accepted: 29 November 2015 Published online in Wiley Online Library: 26 January 2016

(wileyonlinelibrary.com) DOI 10.1002/aoc.3423

Asymmetric addition of phenylacetylene to aldehydes catalyzed by complex of *O*-sulfonyl camphor derivatives and titanium

Dong-Sheng Lee*, Chang-Weu Gau, Yu-Yang Chen and Ta-Jung Lu

Several novel ligands that are based on the camphor skeleton or contain the *O*-sulfonyl group were synthesized and used in the asymmetric addition of phenylacetylene to aldehydes. This enantioselective reaction afforded chiral propargylic alcohols in high yields and with good to excellent levels of enantiopurity (up to 99% enantiomeric excess). Copyright © 2016 John Wiley & Sons, Ltd.

Additional supporting information may be found in the online version of this article at the publisher's web site.

Keywords: asymmetric alkynylation; *O*-sulfonyl ligand; propargylic alcohol; titanium catalysis

Introduction

Efficient methods for the preparation of optically active propargylic alcohols are of particular interest because of the significance of these intermediates in the manufacturing of pharmaceuticals. For instance, (−)-virginiamycin M_2,[1] adociacetylene B[2] and asteriscunolide D[3] (Fig. 1) are all physiologically active compounds. Additionally, optically active propargylic alcohols are precursors for many chiral materials such as optically active allenes and vinylsilanes.[4]

The enantioselective alkynylation of aldehydes is one of the most effective methods for preparing optically active propargylic alcohols.[5] Several chiral ligands, such as 1,1′-bi-2-naphthol derivatives,[6] amino alcohols,[7] oxazolines,[8] (−)-2-*exo*-morpholinoisobornane-10-thiol[9] and imino alcohols,[10] have been used in the enantioselective addition of alkynes to aldehydes. In 2004, Wang and co-workers[7c] reported the asymmetric addition of phenylacetylene to aldehydes using a camphorsulfonamide titanium complex as a catalyst. The reactions were performed at room temperature for 12 h in the presence of 10 mol% of camphorsulfonamide and gave the products with high yields and high enantiomeric excess (ee). However, diethylzinc (3.0 equiv.) and phenylacetylene (3.0 equiv.) were used and the reaction time was long (12 h). To the best of our knowledge, ligands that contain the *O*-sulfonyl group have not yet been examined in this context. Therefore, in the work reported here, an effective and stable chiral catalyst system was developed for catalyzing the addition of alkynes to aldehydes. New classes of camphor-based ligands that bear the *O*-sulfonyl moiety, and their application to the catalytic asymmetric alkynylation of aldehydes, are presented.

Results and discussion

A series of ligands **3** can be obtained from salicylaldehyde or its derivatives **1** and corresponding amino alcohols **2** with good yields (63–92%; Scheme 1). Derivatives **1** were prepared easily via the esterification of salicyladehyde with sulfonyl chloride.[11a] The absolute configuration of **3c** was confirmed as (1*R*,2*S*,3*R*,4*S*) using single-crystal X-ray diffraction (Fig. 2).[11b]

The addition of phenylacetylene to benzaldehyde (**5a**) catalyzed with ligands **3a–3f** and $Ti(O^iPr)_4$ was firstly studied to investigate the optimal reaction conditions. Various reaction parameters, such as ligand loading, amount of titanium, solvent and temperature, were examined (Table 1). The *ortho*-substituted ligand **3b** exhibits a slightly greater reaction activity and enantioselectivity than ligand **3a** (entries 1 and 2). The enantioselectivity slightly increases as the ratio of ligand to $Ti(O^iPr)_4$ decreases from 1:3 to 1:2 (entry 3). *n*-Hexane is the best solvent in this reaction (entry 4, 51% ee). To improve the enantioselectivity of this reaction, *O*-sulfonyl ligands **3c–3f** were synthesized and utilized in the asymmetric addition. Experimental results reveal that the ee value is thus significantly improved to 73% (entries 9 and 10). A low reaction temperature (−20 °C) increases ee further from 73 to 85% (entry 12 versus 10). Ligand **3d** provides better enantioselectivity than ligands **3e** and **3f** in the asymmetric addition of phenylacetylene to benzaldehyde (entries 12–14), indicating that the camphor backbone is crucial for high enantioselectivity. The alkynylation product **6a** favors the (*R*) configuration based on comparison with reported optical rotation values.[12]

The scope of the alkynylation reaction was then examined using various aldehydes **5** and phenylacetylene (Table 2). *Ortho*-substituted benzaldehyde exhibits slightly higher enantioselectivity than *meta* and *para* substitutions (entries 2–4). Furthermore, all other *ortho*-substituted aromatic aldehydes react with phenylacetylene to produce propargylic alcohols **6** with good enantioselectivities (86–92% ee) and excellent yields (87–96%). In

* *Correspondence to: Dong-Sheng Lee, Department of Chemistry, National Chung-Hsing University, Taichung, 40227, Taiwan. E-mail: dslee@mail.nchu.edu.tw*

Department of Chemistry, National Chung-Hsing University, Taichung, 40227, Taiwan

Applied Organometallic Chemistry

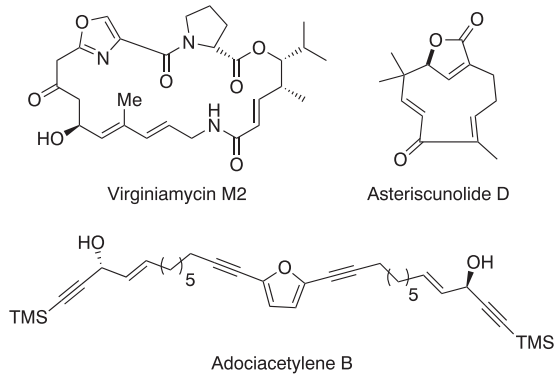
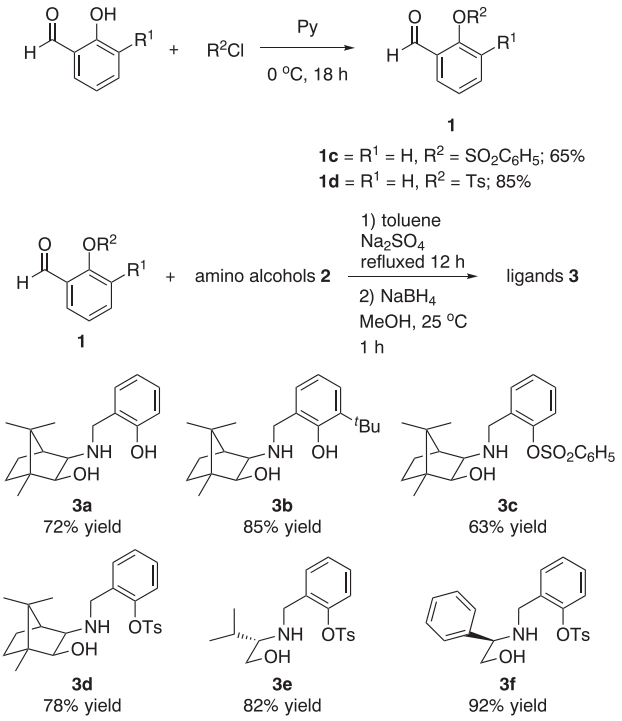


Figure 1. Examples of manufactured pharmaceuticals.



Scheme 1. Synthesis of novel camphor-based ligands and amino alcohol ligands **3**.

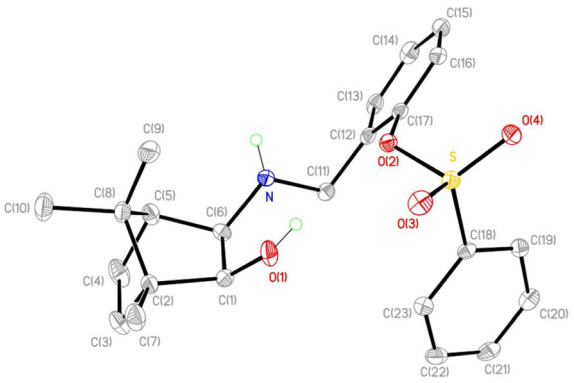


Figure 2. X-ray crystal structure of **3c**.

Table 1. Alkynylation of benzaldehyde with phenylacetylene in the presence of ligands **3a–f**[a]

Entry	Ligand (equiv.)	$Ti(O^iPr)_4$ (equiv.)	Solvent	Temp. (°C)	Yield (%)	ee (%)[b]
1	**3a** (0.20)	0.60	Toluene	25	90	40 (*R*)
2	**3b** (0.20)	0.60	Toluene	25	93	46 (*S*)
3	**3b** (0.20)	0.40	Toluene	25	90	48 (*S*)
4	**3b** (0.20)	0.40	*n*-Hexane	25	88	51 (*S*)
5	**3b** (0.20)	0.40	CH_2Cl_2	25	90	48 (*S*)
6	**3b** (0.20)	0.40	Tetrahydrofuran	25	43	41 (*S*)
7	**3b** (0.10)	0.20	*n*-Hexane	25	9	16 (*S*)
8	**3b** (0.30)	0.60	*n*-Hexane	25	93	48 (*S*)
9	**3c** (0.20)	0.40	*n*-Hexane	25	90	73 (*R*)
10	**3d** (0.20)	0.40	*n*-Hexane	25	90	73 (*R*)
11[c]	**3d** (0.20)	0.40	*n*-Hexane	0	92	80 (*R*)
12[d]	**3d** (0.20)	0.40	*n*-Hexane	−20	87	85 (*R*)
13	**3e** (0.20)	0.40	*n*-Hexane	−20	33	7 (*S*)
14	**3f** (0.20)	0.40	*n*-Hexane	−20	53	13 (*R*)

[a]All reactions performed at 25 °C for 3 h.
[b]Values of ee obtained using HPLC with a chiral OD-H column.
[c]Reaction performed at 0 °C over 5 h.
[d]Reaction performed at −20 °C over 5 h.

particular, 4-anisaldehyde yields the chiral alcohol **6j** with the highest enantioselectivity (99%; entry 10). Heteroaromatic aldehydes result in high ee values, as can be seen for substrates thiophene and furan (entries 11 and 12). Aliphatic aldehydes also give propargylic alcohols with good ee values in excellent yields (entries 13 and 14).

Conclusions

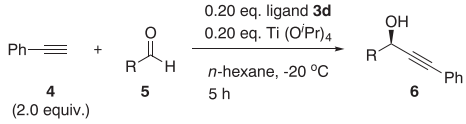
Several novel ligands based on the camphor skeleton or containing sulfonyl moieties were easily developed, and applied to the enantioselective addition of phenylacetylene to aldehydes. This catalytic reaction is completed within a short reaction time (5 h) at −20 °C. Two equivalent amounts of dimethylzinc and acetylene were used in the catalytic system. A promising system for the preparation of chiral propargylic alcohols in high yield and good to excellent ee (up to 99%) was thus established. The properties of the *O*-sulfonyl moiety in the ligands with respect to the titanium-catalyzed asymmetric alkynylation reaction were elucidated for the first time. Further study of the use of these ligands in other asymmetric reactions is ongoing. The catalyst system is suitable for use in the preparation of pharmaceutically important molecules and natural products.

Experimental

Materials and methods

Reactions were analyzed using pre-coated silica gel 60 (F-254) plates (0.2 mm layer thickness), using a solution of 0.5%

Table 2. Alkynylation of phenylacetylene with aldehydes **5** catalyzed by **3d**



Entry	R	Product	Yield (%)[a]	ee (%)[b]	Entry	R	Product	Yield (%)[a]	ee (%)[b]
1	Ph	**6a**	90	85 (*R*)	8	*o*-BrC_6H_4	**6 h**	(91)	92 (*R*)
2	*o*-MeC_6H_4	**6b**	87	90 (*R*)	9	1-Naphthyl	**6i**	(91)	88 (*R*)
3	*m*-MeC_6H_4	**6c**	90	86 (*R*)	10	*p*-$MeOC_6H_4$	**6j**	(92)	99 (*R*)
4	*p*-MeC_6H_4	**6d**	88	86 (*R*)	11	2-Thiophenyl	**6 k**	(93)	92 (*R*)
5	*o*-$MeOC_6H_4$	**6e**	96	86 (*R*)	12[c]	Furanyl	**6 l**	(95)	82 (*R*)
6	*o*-FC_6H_4	**6f**	89	86 (*R*)	13	Cyclohexyl	**6 m**	(93)	88 (*R*)
7	*o*-ClC_6H_4	**6 g**	96	88 (*R*)	14	*t*-Butyl	**6n**	(91)	86 (*R*)

[a]Isolated yield.
[b]Values of ee were determined using HPLC with a chiral OD-H column.
[c]Reaction performed at −20 °C over 10 h.

phosphomolybdic acid in 95% ethanol as the detector. All products were purified by column chromatography (silica gel, 0.040–0.063 mm) using hexane–ethyl acetate as eluent unless otherwise indicated. Melting points were determined using a Mel-Temp 1001D (Barnstead/Thermo) digital melting point apparatus and were uncorrected. Optical rotations were recorded with an Autopol® IV automatic polarimeter (Rudolph Research Analytical) using a 1.0 dm cell at specific temperatures. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian Mercury 400 spectrometer in $CDCl_3$ with chemical shifts (δ) recorded relative to tetramethylsilane. The central peak of $CDCl_3$ ($\delta = 77.0$ ppm) was used as internal standard for ^{13}C NMR spectra. High-resolution mass spectra (HRMS) were recorded using a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Mass spectra were obtained using either the electron impact (EI) or electrospray ionization method. Enantiomeric excess of secondary alcohols was determined using HPLC with chiral columns, using a mixture of isopropanol and *n*-hexane as the mobile phase.

Compounds **1** were synthesized according to similar literature procedures.[11a]

General procedure for preparation of ligands 3

Salicylaldehyde or derivative (3.00 mmol) in dry toluene (3 ml) was added to a solution of amino alcohol (3.90 mmol) in toluene (7 ml) and stirred in the presence of anhydrous Na_2SO_4 (6.00 mmol) at room temperature and then refluxed for 12 h. Then, it was filtered through an anhydrous Na_2SO_4 plug and the filtrate was evaporated to afford a Schiff base. The Schiff base was dissolved in methanol (10 ml) and $NaBH_4$ (6.00 mmol) was added. After stirring for 1 h, methanol was removed and the residue was extracted using EtOAc (3 × 10 ml) and dried over Na_2SO_4. The liquid was filtered and solvent removed to afford the product that was purified using chromatography (ethyl acetate–*n*-hexane = 1:15–1:5) to give ligand **3**.

*(1R,2S,3R,4S)-3-[(2-hydroxybenzyl)amino)]-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**3a**)*

Yield 72% (0.599 g); white solid; $[\alpha]_D^{25} = +24.9$ ($c = 1.00$, $CHCl_3$); m.p. 91–94 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 7.16 (t, $J = 7.6$ Hz, 1H, C_{15}-*H*), 7.00 (d, $J = 7.6$ Hz, 1H, C_{13}-*H*), 6.83 (d, $J = 7.6$ Hz, 1H, C_{16}-*H*), 6.77 (t, $J = 7.6$ Hz, 1H, C_{14}-*H*), 4.00 (d, $J = 13.6$ Hz, 1H, C_{11}-*H*, NCH_2Ph), 3.94 (d, $J = 13.6$ Hz, 1H, C_{11}-*H*, NCH_2Ph), 3.77 (d, $J = 7.6$ Hz, 1H, C_2-*H*, *CH*OH), 2.79 (d, $J = 7.6$ Hz, 1H, C_3-*H*, N*CH*), 1.78 (d, $J = 4.4$ Hz, 1H, C_4-*H*, *CH*), 1.72–1.65 (m, 1H, C_5-*H*, CH_2), 1.51–1.45 (m, 1H, C_6-*H*, CH_2), 1.15 (s, 3H, C_{10}-*H*, CH_3), 1.03–0.95 (m, 2H, C_5-*H* and C_5-*H*, CH_2), 0.93 (s, 3H, C_8-*H*, CH_3), 0.81 (s, 3H, C_9-*H*, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 158.1 (C_{17}), 128.7 (C_{13}), 128.3 (C_{15}), 123.3 (C_{12}), 118.9 (C_{14}), 116.3 (C_{16}), 80.1 (C_2, OCH), 66.1 (C_3, NCH), 53.1 (C_4, CH), 50.1 (C_1, CCH_3), 49.1 (C_7, CMe_2), 46.7 (C_{11}, NCH_2), 33.1 (C_6, CH_2), 26.7 (C_5, CH_2), 21.7 (C_8, CH_3), 21.0 (C_9, CH_3), 11.3 (C_{10}, CH_3). HRMS-EI (*m/z*) $[M]^+$ Calcd for $C_{17}H_{25}NO_2$: 275.1885; found: 275.1877. Anal. Calcd for $C_{17}H_{25}NO_2$ (%): C, 74.14; H, 9.15; N, 5.09; found (%): C, 73.59; H, 9.35; N, 4.86.

*(1R,2S,3R,4S)-3-[(2-hydroxy-3-tert-butylbenzyl)amino]-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**3b**)*

Yield 85% (0.845 g); white solid; $[\alpha]_D^{25} = +28.5$ ($c = 1.00$, $CHCl_3$); m.p. 118–119 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 7.19 (dd, $J = 7.6$, 1.2 Hz, 1H, C_{15}-*H*), 6.88 (d, $J = 7.6$ Hz, 1H, C_{13}-*H*), 6.71 (t, $J = 7.6$ Hz, 1H, C_{14}-*H*), 4.04 (d, $J = 13.6$ Hz, 1H, C_{11}-*H*, NCH_2Ph), 3.90 (d, $J = 13.6$ Hz, 1H, C_{11}-*H*, NCH_2Ph), 3.76 (d, $J = 7.6$ Hz, 1H, C_2-*H*, *CH*OH), 2.77 (d, $J = 7.6$ Hz, 1H, C_3-*H*, N*CH*), 1.75 (d, $J = 4.4$ Hz, 1H, C_4-*H*, *CH*), 1.69–1.61 (m, 1H, C_5-*H*, CH_2), 1.50–1.44 (m, 1H, C_6-*H*, CH_2), 1.42 (s, 9H, $C(CH_3)_3$), 1.15 (s, 3H, C_{10}-*H*, CH_3), 1.02–0.96 (m, 2H, C_5-*H* and C_5-*H*, CH_2), 0.93 (s, 3H, C_8-*H*, CH_3), 0.80 (s, 3, C_9-*H*, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 157.2 (C_{17}), 136.7 (C_{12}), 126.5 (C_{13}), 125.8 (C_{15}), 123.6 (C_{16}), 118.1 (C_{14}), 80.1 (C_2, OCH), 66.2 (C_3, NCH), 53.6 (C_4, CH), 49.9 (C_1, CMe), 49.0 (C_7, CMe_2), 46.7 (C_{11}, NCH_2), 34.6 (C_{18}, CMe_3), 33.2 (C_6, CH_2), 29.5 ($C(CH_3)_3$), 26.6 (C_5, CH_2), 21.7 (C_8, CH_3), 21.0 (C_9, CH_3), 11.3 (C_{10}, CH_3). HRMS-EI (*m/z*) $[M]^+$ Calcd for $C_{21}H_{33}NO_2$: 331.2511; found: 331.2504. Anal. Calcd for $C_{21}H_{33}NO_2$(%): C, 76.09; H, 10.03; N, 4.23; found (%): C, 76.10; H, 9.83; N, 4.03.

*(1R,2S,3R,4S)-3-[(2-benzenesulfonylbenzyl)amino]-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**3c**)*

Yield 63% (0.785 g); white solid; $[\alpha]_D^{24.0} = +27.3$ ($c = 1.22$, $CHCl_3$); m.p. 62–64 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 7.91 (dd, $J = 8.4$, 1.2 Hz, 2H, C_{19}-*H* and C_{23}-*H*), 7.72 (tt, $J = 8.4$, 1.2 Hz, 1H, C_{21}-*H*), 7.58, (t, $J = 8.4$ Hz, 2H, C_{20}-*H* and C_{22}-*H*), 7.40 (dd, $J = 7.6$, 1.6 Hz, 1H, C_{13}-*H*), 7.25 (td, $J = 7.6$ Hz, 1.2 Hz, 1H, C_{15}-*H*), 7.19 (td, $J = 7.6$ Hz, 1.6 Hz, 1H,

C_{14}-*H*), 6.89 (dd, *J* = 7.6, 1.2 Hz, 1H, C_{16}-*H*), 3.79 (d, *J* = 13.6 Hz, 1H, C_{11}-*H*, NCH_2Ph), 3.55 (d, *J* = 13.6 Hz, 1H, C_{11}-*H*, NCH_2Ph), 3.41 (d, *J* = 7.6 Hz, 1H, C_2-*H*, *C*HOH), 2.70 (d, *J* = 7.6 Hz, 1H, C_3-*H*, NC*H*), 1.70–1.64 (m, 1H, C_5-*H*, CH_2), 1.55 (d, *J* = 4.8 Hz, 1H, C_4-*H*, *C*H), 1.43–1.38 (m, 1H, C_6-*H*, CH_2), 1.01 (s, 3H, C_{10}-*H*, CH_3), 0.98 (d, *J* = 8.4 Hz, 2H, C_5-*H* and C_6-*H*, CH_2), 0.93 (s, 3H, C_8-*H*, CH_3), 0.75 (s, 3H, C_9-*H*, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 147.8 (C_{17}), 135.8 (C_{18}), 134.4 (C_{21}), 133.4 (C_{12}), 130.7 (C_{13}), 129.3 (C_{20} and C_{22}), 128.4 (C_{19} and C_{23}), 128.3 (C_{15}), 127.4 (C_{14}), 122.2 (C_{16}), 78.7 (C_2, OCH), 65.7 (C_3, NCH), 51.4 (C_4, *C*H), 48.9 (C_1, *C*Me), 48.8 (C_7, *C*Me_2), 46.6 (C_{11}, NCH_2), 32.9 (C_6, CH_2), 27.1 (C_5, CH_2), 21.9 (C_8, CH_3), 21.2 (C_9, CH_3), 11.3 (C_{10}, CH_3). HRMS-EI (*m/z*) $[M]^+$ Calcd for $C_{23}H_{29}NO_4S$: 415.1823; found: 415.1820. Anal. Calcd for $C_{23}H_{29}NO_4S$ (%): C, 66.48; H, 7.03; N, 3.37; found (%): C, 66.50; H, 7.19; N, 3.19.

*(1R,2S,3R,4S)-3-[(2-p-tolylsulfonylbenzyl)amino]-2-hydroxy-1,7,7-trimethylbicyclo [2.2.1]heptane (**3d**)*

Yield 78% (1.01 g); white solid; $[\alpha]_D^{25.8}$ = +33.6 (*c* = 1.25, $CHCl_3$); m.p. 72–74 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 7.78 (d, *J* = 8.4 Hz, 2H, C_{19}-*H* and C_{23}-*H*), 7.40 (dd, *J* = 7.6, 1.6 Hz, 1H, C_{13}-*H*), 7.35, (d, *J* = 8.4 Hz, 2H, C_{20}-*H* and C_{22}-*H*), 7.24 (td, *J* = 7.6, 1.6 Hz, 1H, C_{15}-*H*), 7.19 (td, *J* = 7.6, 1.6 Hz, 1H, C_{14}-*H*), 6.90 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H, C_{16}-*H*), 3.79 (d, *J* = 14.0 Hz, 1H, C_{11}-*H*, NCH_2Ph), 3.55 (d, *J* = 14.0 Hz, 1H, C_{11}-*H*, NCH_2Ph), 3.40 (d, *J* = 7.6 Hz, 1H, C_2-*H*, *C*HOH), 2.77 (d, *J* = 7.6 Hz, 1H, C_3-*H*, NC*H*), 2.47 (s, 3H, C_{24}-*H*, CH_3), 1.69–1.64 (m, 1H, C_5-*H*, CH_2), 1.54 (d, *J* = 4.8 Hz, 1H, C_4-*H*, *C*H), 1.43–1.38 (m, 1H, C_6-*H*, CH_2), 1.01 (s, 3H, C_{10}-*H*, CH_3), 0.97 (d, *J* = 8.4 Hz, C_5-*H* and C_6-*H*, 2H), 0.97 (s, 3H, C_8-*H*, CH_3), 0.75 (s, 3H, C_9-*H*, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 147.9 (C_{17}), 145.6 (C_{21}), 133.3 (C_{12}), 132.8 (C_{18}), 130.7 (C_{13}), 129.9 (C_{20} and C_{22}), 128.4 (C_{19} and C_{23}), 128.3 (C_{15}), 127.3 (C_{14}), 122.2 (C_{16}), 78.7 (C_2, OCH), 65.7 (C_3, NCH), 51.4 (C_4, *C*H), 49.0 (C_1, *C*Me), 48.8 (C_7, *C*Me_2), 46.6 (C_{11}, NCH_2), 32.9 (C_6, CH_2), 27.1 (C_5, CH_2), 21.9 (C_8, CH_3), 21.7 (C_{24}, CH_3), 21.2 (C_9, CH_3), 11.3 (C_{10}, CH_3). HRMS-EI (*m/z*) $[M]^+$ Calcd for $C_{24}H_{31}NO_4S$: 429.1960; found: 429.1967. Anal. Calcd for $C_{24}H_{31}NO_4S$ (%): C, 67.10; H, 7.27; N, 3.26; found (%): C, 67.23; H, 7.55; N, 3.20.

*(S)-2-(((1-hydroxy-3-methylbutan-2-yl)amino)methyl)phenyl-4-methylbenzene-sulfonate (**3e**)*

Yield 82% (1.50 g); colorless liquid; $[\alpha]_D^{24.2}$ = +94.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 7.74 (d, *J* = 8.0 Hz, 2H, C_{14}-*H* and C_{18}-*H*), 7.42 (d, *J* = 7.6 Hz, 1H, C_8-*H*), 7.33 (d, *J* = 8.0 Hz, 2H, C_{15}-*H* and C_{17}-*H*), 7.22 (t, *J* = 8.0 Hz, 1H, C_{10}-*H*), 7.16 (t, *J* = 7.6 Hz, 1H, C_9-*H*), 6.88 (d, *J* = 8.0 Hz, 1H, C_{11}-*H*), 3.73 (d, *J* = 13.6 Hz, 1H, C_6-*H*, NCH_2), 3.59 (d, *J* = 10.8 Hz, 1H, C_1-*H*, CH_2OH), 3.55 (d, *J* = 13.6 Hz, 1H, C_6-*H*, NCH_2), 3.33 (d, *J* = 10.8 Hz, 1H, C_1-*H*, CH_2OH), 2.45 (s, 3H, C_{19}-*H*, CH_3), 2.39–2.33 (m, 1H, C_2-*H*, NC*H*), 2.35 (br, 2H, N*H* and O*H*), 1.85–1.73 (m, 1H, C_3-*H*, NC*H*Me_2), 0.93 (d, *J* = 6.8 Hz, 3H, C_4-*H*, CH_3), 0.87 (d, *J* = 6.8 Hz, 3H, C_5-*H*, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 147.9 (C_{12}), 145.6 (C_{16}), 133.4 (C_7), 132.8 (C_{13}), 130.9 (C_8), 129.9 (C_{15} and C_{17}), 128.42 (C_{14} and C_{18}), 128.40 (C_{10}), 127.4 (C_9), 122.2 (C_{11}), 64.4 (C_1, OCH_2), 60.2 (C_2, NCH), 45.6 (C_6, NCH_2), 28.8 (C_3, *C*Me_2), 21.7 (C_{19}, CH_3), 19.5 (C_4, CH_3), 18.4 (C_5, CH_3). HRMS-ESI (*m/z*) for $C_{19}H_{26}NO_4S$ calcd 364.1577 (M + H^+); found 364.1574. Anal. Calcd for $C_{19}H_{25}NO_4S$ (%): N, 3.85; C, 62.78; H, 6.93; O, 17.61; found (%): N, 3.60; C, 59.88; H, 6.72; O, 17.61.

*(R)-2-(((2-hydroxy-1-phenylethyl)amino)methyl)phenyl-4-methylbenzene-sulfonate (**3f**)*

Yield 92% (1.80 g); white solid; $[\alpha]_D^{24.4}$ = 95.1 (*c* = 1.0, $CHCl_3$); m.p. 99–100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 7.61 (d, *J* = 8.4 Hz, 2H, C_{17}-*H* and C_{21}-*H*), 7.38–7.28 (m, 6H, C_4-*H*, C_5-*H*, C_6-*H*, C_7-*H*, C_8-*H*, and C_{11}-*H*), 7.24–7.17 (m, 4H, C_{12}-*H*, C_{13}-*H*, C_{18}-*H*, and C_{20}-*H*), 6.98 (dd, *J* = 7.6, 1.6 Hz, 1H, C_{14}-*H*), 3.74–3.65 (m, 2H, C_1-*H*, CH_2OH), 3.55–2.49 (m, 2H, C_2-*H* and C_9-*H*, NHC*H*Ph and NCH_2Ph), 3.40 (d, *J* = 13.6 Hz, 1H, C_9-*H*, NCH_2Ph), 2.41 (s, 3H, C_{22}-*H*, CH_3), 2.00 (br, 2H, N*H* and O*H*). ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 147.8 (C_{15}), 145.4 (C_{19}), 140.2 (C_3), 133.4 (C_{10}), 132.7 (C_{16}), 130.9 (C_{11}), 129.8 (C_{18} and C_{20}), 128.7 (C_{17} and C_{21}), 128.31 (C_5 and C_7), 128.27 (C_{13}), 127.7 (C_{12}), 127.3 (C_4 and C_8), 127.2 (C_6), 122.4 (C_{14}), 66.7 (C_1, OCH_2), 66.4 (C_2, NCH), 45.7 (C_9, NCH_2), 21.7 (C_{22}, CH_3). HRMS-EI (*m/z*) for $C_{22}H_{23}NO_4S$ calcd 397.1312 (M^+); found 397.1314. Anal. Calcd for $C_{22}H_{23}NO_4S$ (%): N, 3.52; C, 66.48; H, 5.83; O, 16.10; found (%): N, 3.60; C, 66.40; H, 5.89; O, 15.99.

General procedure for addition of phenylacetylene to aldehydes

All reactions were carried out under nitrogen using dried and degassed solvent. Ligand **3** (0.100 mmol) and Ti(O^{i}Pr)$_4$ (60.0 µl, 0.200 mmol) were mixed in dry *n*-hexane (1.15 ml) at room temperature for 1 h. Then, a solution of $ZnMe_2$ (0.85 ml, 1.2 M in toluene) was added. After the mixture was stirred at room temperature for 1 h, phenylacetylene (110 µl, 1.00 mmol) was added and stirred for 1 h. The solution was cooled to −20 °C, and aldehyde **5** (0.500 mmol) was added. The resulting mixture was allowed to stir for 5–10 h. After the reaction completed, checked using TLC, it was quenched by NH_4Cl (aq.). The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to give product **6**. The ee values of all propargylic alcohols were determined using chiral HPLC (conditions for all propargylic alcohols: Chiralcel OD-H, 10% 2-propanol–*n*-hexane, 1 ml min^{-1}, 254 nm; except 1-(2-bromophenyl)-3-phenylprop-2-yn-1-ol: 0.25 ml min^{-1}).

Acknowledgements

We thank the National Science Council of the Republic of China for financial support under grant no. 102WFA0500216. Ted Knoy is appreciated for his editorial assistance.

References

[1] J. Wu, J. S. Panek, *Angew. Chem. Int. Ed.* **2010**, *49*, 616.
[2] B. M. Trost, A. H. Weiss, *Org. Lett.* **2006**, *8*, 4461.
[3] B. M. Trost, A. C. Burns, M. J. Bartlett, T. Tautz, A. H. Weiss, *J. Am. Chem. Soc.* **2012**, *134*, 1474.
[4] B. M. Trost, Z. T. Ball, *Synthesis* **2005**, *6*, 853.
[5] a) L. Pu, *Tetrahedron* **2003**, *59*, 9873; b) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095; c) G. Lu, Y.-M. Li, X.-S. Li, A. S. C. Chan, *Coord. Chem. Rev.* **2005**, *249*, 1736; d) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963.
[6] a) L. Pu, D. Moore, *Org. Lett.* **2002**, *4*, 1855; b) G. Gao, D. Moore, R.-G. Xie, L. Pu, *Org. Lett.* **2002**, *4*, 4143; c) M.-H. Xu, L. Pu, *Org. Lett.* **2002**, *4*, 4555; d) C. Chen, Q. Huang, S. Zou, L. Wang, B. Luan, J. Zhu, Q. Wang, L. Pu, *Tetrahedron: Asymm.* **2014**, *25*, 199; e) X. Li, G. Lu, W. H. Kwok, A. S. C. Chan, *J. Am. Chem. Soc.* **2002**, *124*, 12636; f) G. Lu, X. Li, W. L. Chan, A. S. C. Chan, *Chem. Commun.* **2002**, *2*, 172.
[7] a) B. Jiang, Z. Chen, W. Xiong, *Chem. Commun.* **2002**, *14*, 1524; b) G. Lu, X. Li, Z. Zhou, W.-L. Chan, A. S. C. Chan, *Tetrahedron: Asymm.* **2001**, *12*, 2147; c) Z. Xu, C. Chen, J. Xu, M. Miao, W. Yan, R. Wang, *Org. Lett.* **2004**, *6*, 1193; d) Z.-Q. Xu, R. Wang, J.-K. Xu, C.-S. Da, W.-J. Yan, C. Chen, *Angew. Chem. Int. Ed.* **2003**, *42*, 5747; e) S. Gou, Z. Ye, Z. Huang, X. Ma, *Appl.*

Organometal. Chem. **2010**, *24*, 374; f) H. Koyuncu, O. Dogan, *Org. Lett.* **2007**, *9*, 3477.

[8] a) M. Li, X.-Z. Zhu, K. Yuan, B.-X. Cao, X.-L. Hou, *Tetrahedron: Asymm.* **2004**, *15*, 219; b) A. L. Braga, H. R. Appelt, C. C. Silveria, L. A. Wessjohann, P. H. Schneider, *Tetrahedron* **2002**, *58*, 10413.

[9] P.-Y. Wu, H.-L. Wu, Y.-Y. Shen, B.-J. Uang, *Tetrahedron: Asymm.* **2009**, *20*, 1837.

[10] a) S. Dahmen, *Org. Lett.* **2004**, *6*, 2113; b) R. Boobalan, C. Chen, G.-H. Lee, *Org. Biomol. Chem.* **2012**, *10*, 1625; c) J. Sun, X. Pan, Z. Dai, C. Zhu, *Tetrahedron: Asymm.* **2008**, *19*, 2451.

[11] a) E. M. Chen, P. J. Lu, A. Y. Shaw, J. Heterocyclic, *Chem.* **2012**, *49*, 792; b) Details of the X-ray structure of **3c** can be obtained from the Cambridge Crystallographic Data Centre (CCDC 984375).

[12] R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site.