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Catalytic Asymmetric Alkynylation and Arylation of Aldehydes by an H_8-Binaphthyl-Based Amino Alcohol Ligand

Jiwu Ruan,[a,b] Gui Lu,[a,b,*] Lijing Xu,[b] Yue-Ming Li,[b] and Albert S. C. Chan[b,*]

[a] School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou, People's Republic of China
[b] Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong SAR, People's Republic of China
Fax: (+852)-2362-2578; e-mail: bcachan@polyu.edu.hk

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Abstract: A novel chiral H_8-1,1′-binaphthyl-based amino alcohol ligand ($1R_a$,2*S*,3*R*)-**2** has been synthesized and applied in the direct nucleophilic addition of organozincs (alkynylzinc and arylzinc prepared *in situ*) to aldehydes, yielding the corresponding optically active propargylic alcohols and diarylmethanols in high yields and good to excellent enantioselectivities. For the asymmetric arylation reaction, one catalyst ($1R_a$,2*S*,3*R*)-**2** can afford both enantiomers of many pharmaceutically interesting diarylmethanols by a proper combination of various arylzinc reagents and aldehydes.

Keywords: alkynylation; amino alcohols; arylation; asymmetric catalysis; H_8-binaphthyl; nucleophilic addition

Introduction

Chiral ligands bearing a binaphthyl framework, such as BINOL and BINAP, have earned a prominent status through their successful applications in a variety of catalytic asymmetric reactions over the last three decades,[1] and the partially hydrogenated binaphthyl scaffold (H_8-binaphthyl) has received more attention in recent years.[2] Positive effects have been observed in some asymmetric catalytic reactions such as asymmetric hydrogenation, alkylation, epoxidation and hetero-Diels–Alder reactions, possibly due to the more preferable electronic and steric effects caused by the electron-rich tetralin unit with more steric bulk and a larger dihedral angle. However, in some cases, some disadvantageous effects were also observed.[2]

Enantiomerically pure propargylic alcohols and diarylmethanols are useful building blocks and important precursors for pharmaceutically and biologically interesting molecules.[3–11] The preparation of these compounds *via* the nucleophilic addition of organozincs (alkynylzinc and arylzinc prepared *in situ*) to aldehydes is of great interest because both the C–C bond and the stereogenic center can be formed in one step.[12]

Bolm and co-workers reported a general protocol for the enantioselective, catalytic synthesis of diarylmethanol compounds from aldehydes by using a nucleophilic arylzinc species generated *in situ* from mixtures of arylboronic acids and diethylzinc.[13] Subsequently, several efficient ligands have been developed in this type of aryl transfer reaction and good results were obtained.[14]

We have recently reported the preparation and application of the new binaphthyl-derived amino alcohol ligand ($1R_a$,2*S*,3*R*)-**1** (Figure 1) in the asymmetric alkynylzinc and arylzinc additions.[12b,14h] Its H_8-analogue ($1R_a$,2*S*,3*R*)-**2** is expected to be more rigid, displaying larger biaryl torsional angles and thus may bestow better performance on the asymmetric alkylation reaction of carbonyl compounds. Herein, we report the synthesis of the partially hydrogenated chiral ligand ($1R_a$,2*S*,3*R*)-**2** and its applications in the asymmetric addition of alkynylzinc and arylzinc reagents (all prepared *in situ*) to various aldehydes. The reactions proceeded readily, giving the corresponding addition products with high stereoselectivity and broad substrate tolerance.

Results and Discussion

Ligand Synthesis

There are two possible approaches for the synthesis of ($1R_a$,2*S*,3*R*)-**2**, one is *via* the bromination of (*R*)-H_8-BINOL, the other is based on the partial hydrogenation of (*R*)-BINOL-CH_2Br (Scheme 1). Compound (*R*)-H_8-BINOL-CH_2Br was a key intermediate for

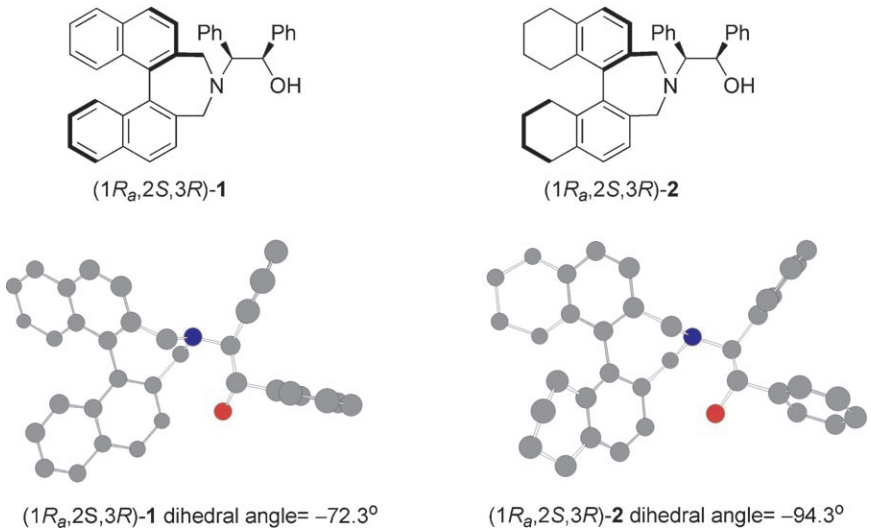
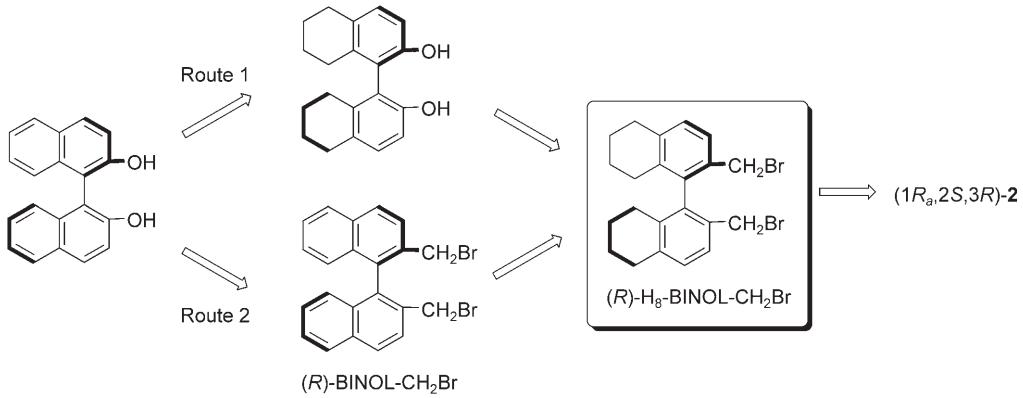
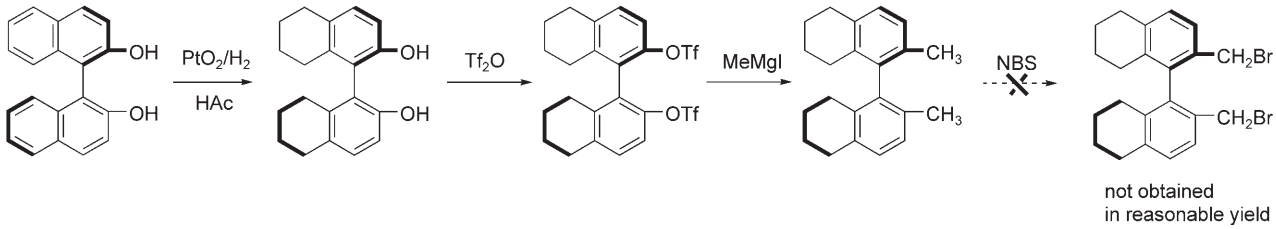


Figure 1. Molecular structures of (1R_a,2*S*,3*R*)-**1** and (1R_a,2*S*,3*R*)-**2**. The hydrogen atoms are omitted for the purpose of clarity. The dihedral angles of the axial biaryl groups were estimated by ChemDraw 3D calculations (MM2). (The minus sign is arbitrarily given by the program.)



Scheme 1. Synthetic analysis of (1R_a,2*S*,3*R*)-**2**.

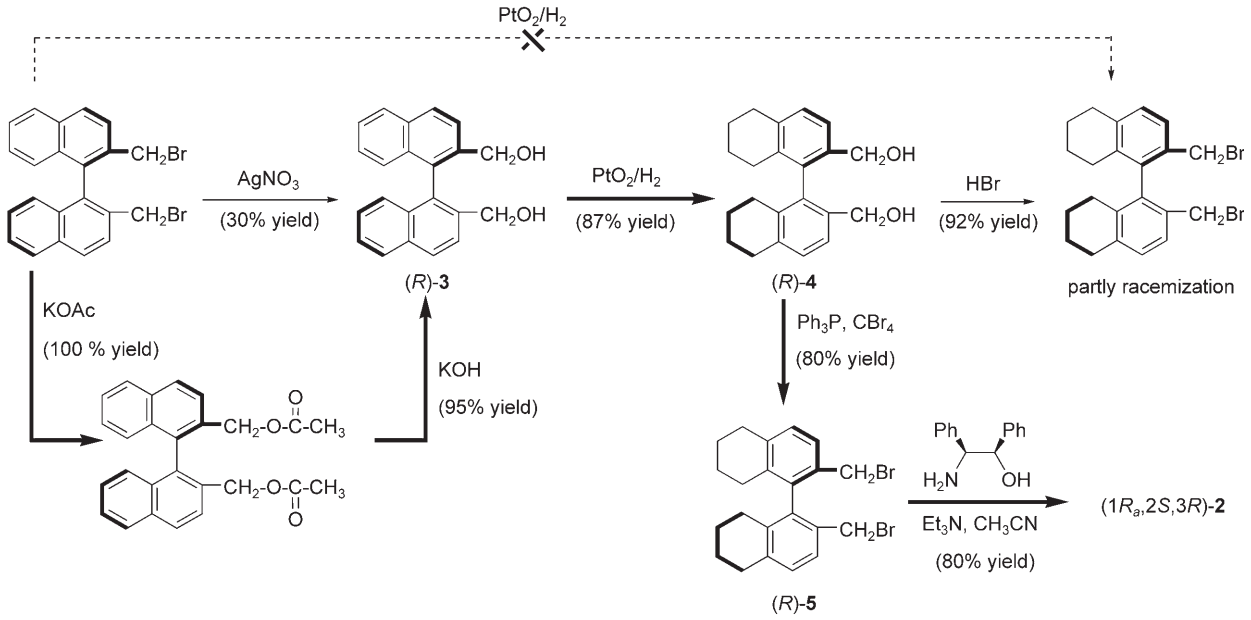


Scheme 2. Synthetic approach from (*R*)-H_8-BINOL.

both routes, therefore our first effort was focused on the synthesis of (*R*)-H_8-BINOL-CH_2Br.

When we tried to access (1R_a,2*S*,3*R*)-**2** from (*R*)-H_8-BINOL, we failed to get (*R*)-H_8-BINOL-CH_2Br in reasonable yield, only mixtures of various substitued bromides were obtained during the bromination of (*R*)-H_8-BINOL-CH_3 with *N*-bromosuccinimide (Scheme 2).

Attempts on the direct partial hydrogenation of (*R*)-BINOL-CH_2Br with PtO_2 also failed to give the desired product. Taking an alternative strategy, we chose diol (*R*)-**3** as a key intermediate. This compound could be obtained from (*R*)-BINOL-CH_2Br either by reaction with $AgNO_3$ or by tandem reaction with KOAc and KOH. The latter approach was superior in chemical yield (Scheme 3). Probably owing to



Scheme 3. Synthetic approach from (*R*)-BINOL-CH_2Br.

the harsh reaction conditions, the bromination of the H_8-diol (*R*)-**4** thus obtained with HBr caused some racemization in the product. Another approach using PPh_3 in CBr_4 was more successful, giving (*R*)-**5** in 80% yield, which can be further converted to (1R_a,2*S*,3*R*)-**2** through the reaction with (1*R*,2*S*)-(+)-2-amino-1,2-diphenylethanol (Scheme 3).

Asymmetric Alkynylation Reaction

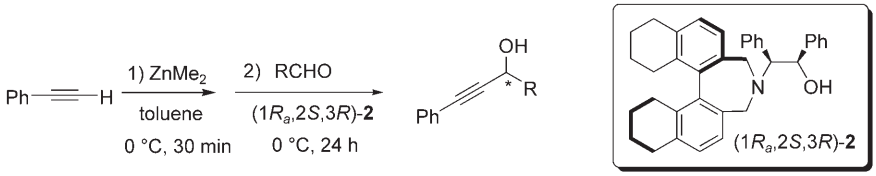
The newly prepared ligand (1R_a,2*S*,3*R*)-**2** induced a comparable enantioselectivity with (1R_a,2*S*,3*R*)-**1** in the asymmetric alkynylation reactions. Table 1 summarizes the results of asymmetric additions of alkynylzinc (prepared *in situ*) to various aldehydes using ligand (1R_a,2*S*,3*R*)-**2**, yielding the corresponding optically active propargylic alcohols in high yields and good to excellent enantioselectivities. The results from entries 4 and 5 demonstrate that this catalyst is applicable to both aromatic and aliphatic acetylenes. Substituted benzaldehydes gave better enantioselectivities than benzaldehyde, while aliphatic aldehydes such as cyclohexanecarboxaldehyde gave low enantioselectivities (34% *ee*, entry 8), possibly due to the unfavorable electronic effect of the aldehyde. For benzaldehydes with electron-donating substituents such as 2-methylbenzaldehyde and 2-methoxybenzaldehyde, (1R_a,2*S*,3*R*)-**2** offered better *ee*s (84% and 76%, respectively) than its parent compound (1R_a,2*S*,3*R*)-**1** (entries 6 and 7).

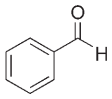
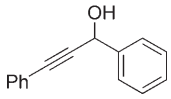
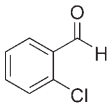
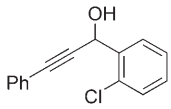
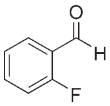
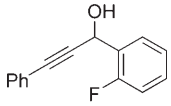
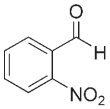
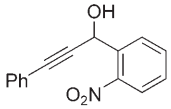
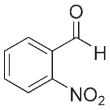
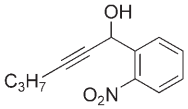
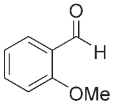
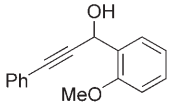
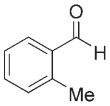
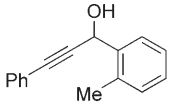
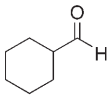
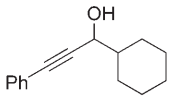
Asymmetric Arylation Reaction

The direct addition of arylzinc (prepared *in situ*) to aldehydes afforded optically active diarylmethanols in high yields and excellent enantioselectivities (up to 96% *ee*) using H_8-ligand (1R_a,2*S*,3*R*)-**2** (Table 2). High *ee*s were obtained even in the case of the sterically hindered 1-naphthaldehyde (entry 9). Reactions also worked well when different arylboronic acids were used as aryl sources, except for the case of 2-bromophenylboronic acid which gave the racemic arylation product (entry 12). Using the same ligand (1R_a,2*S*,3*R*)-**2**, both enantiomers of the corresponding diarylmethanols could be obtained in good yields and high enantiomeric excesses by proper combination of arylboronic acids and aromatic aldehydes (entries 1 and 10).[14h] Most results induced by chiral ligand (1R_a,2*S*,3*R*)-**2** were comparable with those of its parent ligand (1R_a,2*S*,3*R*)-**1**. Particularly noteworthy are *o*-methylbenzhydrol (entry 6), *p*-methylbenzhydrol (entry 11) and *p*-chlorobenzhydrol (entries 1 and 10), which are useful precursor for some pharmaceuticals.

It is quite interesting to note that using 2-bromophenylboronic acid gave the racemic arylation product (entry 12), while combining phenylboronic acid and 2-bromobenzaldehyde afforded 91% *ee* for the arylation product (entry 7). Although the mechanism of the reaction is still not clear, it may be helpful to explain the influence of chiral ligands by speculating on possible transition states of the aryl transfer step. Generally the major enantiomer is produced from the *anti-trans* path, in which the aldehyde coordinates to the catalytic Zn center through the *trans* lone pair,

Table 1. Asymmetric alkynylation of aldehydes catalyzed by ($1R_a$,2*S*,3*R*)-**2**.[a]



Entry	RCHO	Product	Time [h]	Yield [%]	*ee* [%][b]	*ee* [%][c]
1			24	87	72 (*S*)	70 (–)(*S*)
2			24	86	82 (*S*)	85 (+)
3			24	83	77 (+)	87 (+)
4			24	90	85 (+)	87 (+)
5			24	88	83 (+)	85 (+)
6			24	87	76 (S)	71 (+)
7			24	85	84 (*S*)	71 (+)
8			24	81	34 (*S*)	--

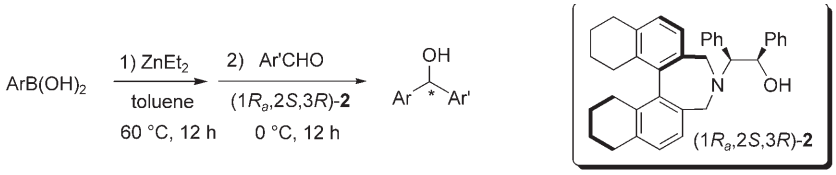
[a] Aldehyde:alkyne:ligand:$ZnMe_2$ = 1:2.4:0.1:2.2 (molar ratio).
[b] The *ee*s were determined by HPLC. Absolute configurations were determined by comparison of the order of the peaks observed from HPLC with literature values.
[c] The *ee*s were obtained by using ($1R_a$,2*S*,3*R*)-**1** under identical reaction conditions.[12b]

and the R group *anti* to the ligand is transferring.[14i] In the presence of ($1R_a$,2*S*,3*R*)-**2**, the *syn-trans* TS is higher in energy than the *anti-trans* TS, and hence good selectivities result for substituted benzaldehydes (Figure 2, a). An exception is the arylation of *in situ* prepared 2-bromophenylzinc, which experiences a severe steric clash that only slightly disfavors the *syn-trans* pathway, and it leads to racemic product (Figure 2, b).

Conclusions

In summary, we have prepared an H_8-1,1′-binaphthyl-derived amino alcohol ligand ($1R_a$,2*S*,3*R*)-**2**, and successfully applied it in the asymmetric addition of alkynylzinc and arylzinc (prepared *in situ*) to various aldehydes. The ligand showed good enantioselectivities (up to 85% *ee*) in the asymmetric alkynylation and excellent enantioselectivities (up to 96% *ee*) in the asymmetric arylation of aromatic aldehydes. A diverse array of optically active diarylmethanols, which

Table 2. Asymmetric aryl transfer to aromatic aldehydes catalyzed by ($1R_a$,2*S*,3*R*)-**2**.[a]



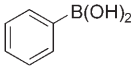
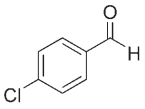
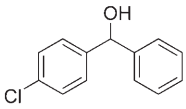
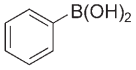
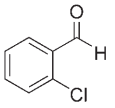
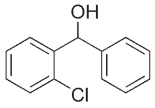
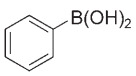
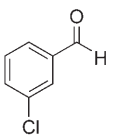
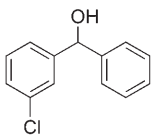
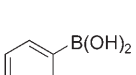
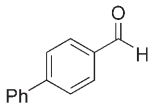
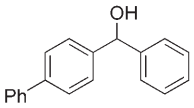
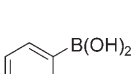
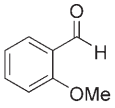
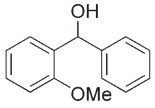
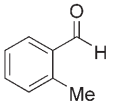
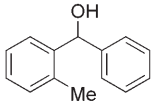
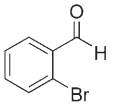
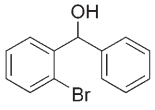
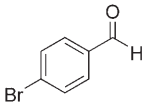
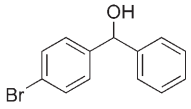
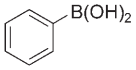
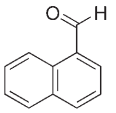
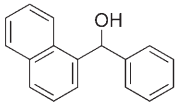
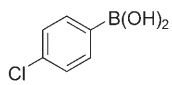
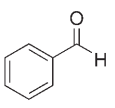
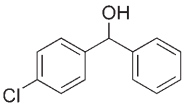
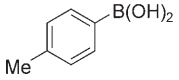
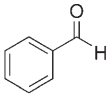
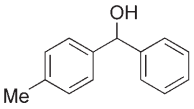
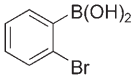
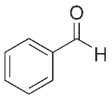
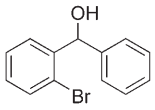
Entry	$ArB(OH)_2$	Ar'CHO	Product	Yield [%]	*ee* [%][b]	*ee* [%][c]
1				95	96 (*R*)	96 (*R*)
2				92	95 (*R*)	90 (*R*)[d]
3				93	95 (*R*)	94 (*R*)
4				93	92 (*R*)	99 (*R*)[d]
5				89	86 (*R*)	93 (*R*)
6				92	95 (*R*)	98 (*R*)
7				90	91 (*R*)	
8				95	91 (*R*)	96 (*R*)[d]
9				95	93 (*R*)	95 (*R*)
10				95	92 (*S*)	87 (*S*)

Table 2. (Continued)

Entry	$ArB(OH)_2$	Ar'CHO	Product	Yield [%]	*ee* [%][b]	*ee* [%][c]
11				92	95 (*S*)	93 (*S*)
12				92	*rac*	*rac*

[a] Ar′CHO:ligand:$ArB(OH)_2$:$ZnEt_2$ = 0.5:0.05:1.2:3.6 (molar ratio).
[b] The *ee*s were determined by HPLC. Absolute configurations were determined by comparison of the order of the peaks observed from HPLC with literature values.
[c] The *ee*s were obtained by using (1R_a,2*S*,3*R*)-**1** under identical reaction conditions.[14h]
[d] Data were obtained at −20 °C.[14h]

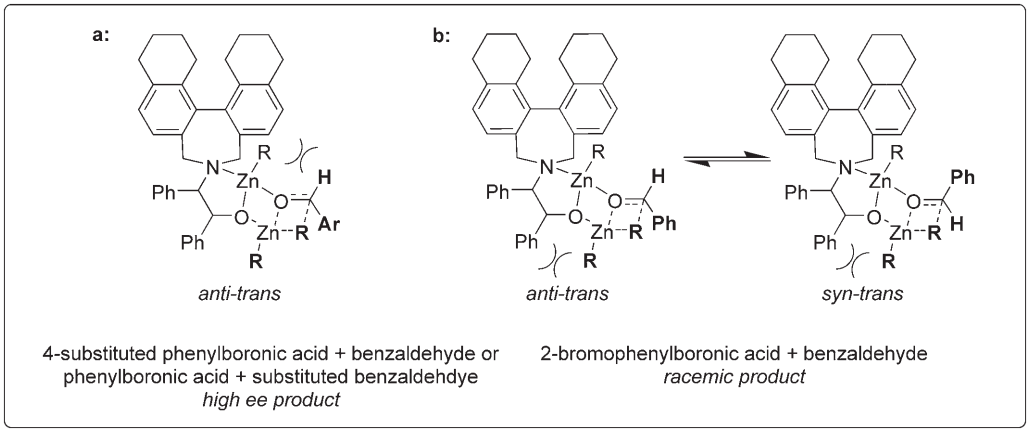


Figure 2. Proposed transition states for the asymmetric arylation of aldehydes.

are of high interest in biological and pharmaceutical sciences, can be obtained in one step by alternating the nucleophiles and the aldehydes. Mechanistic studies, synthetic applications of these transformations as well as the extension of our catalyst to other organic transformations are currently being investigated in our laboratory.

Experimental Section

All experiments were carried out under a nitrogen atmosphere. Unless otherwise stated, commercial reagents were used as received without further purification. The reactions were carried out in solvents distilled from standard drying agents. Toluene and tetrahydrofuran (THF) were freshly distilled from sodium and benzophenone under nitrogen. Aldehydes were freshly distilled under reduced pressure before use. ^{1}H NMR spectra were recorded on a Varian (500 MHz) spectrometer. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ ($\delta = 7.26$ ppm), or with tetramethylsilane (TMS, $\delta = 0.00$ ppm) as the internal standard. Chemical shifts (δ) were reported as parts per million (ppm) in the δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a Varian 500 spectrometer and referenced to $CDCl_3$ ($\delta = 77.0$ ppm). Mass spectra were obtained on a Finnigan Model Mat 95 ST mass spectrometer. HPLC analyses were carried out with a Waters 600 model instrument using a Daicel Chiralcel OD column. The products were eluted with 10% *i*-PrOH in hexane at a flow rate of 1.0 mL min^{-1} unless otherwise indicated, and were detected at 254 nm with a Waters 486 detector. Optical rotations were measured with a Perkin–Elmer Model 341 polarimeter at 20 °C. The absolute configurations of products were deduced based on the comparison of HPLC patterns and/or the direction of optical rotation with known compounds.

Synthesis of Compound (*R*)-4[15]

The diol (*R*)-**3** (944 mg, 3 mmol), which was prepared according to a literature method,[12b,16] was dissolved in 20 mL of glacial acetic acid. Platinum oxide (68 mg, 0.3 mmol) was

added and the mixture was stirred under 500 psi of H_2 for 10 h at 40 °C. The solution was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was washed with aqueous $NaHCO_3$. After drying with Na_2SO_4 and evaporation of solvents, the crude product was purified *via* column chromatography (silica gel, hexane:ethyl acetate = 5:1) to give octahydrodiol (*R*)-**4** as a white solid; yield: 842 mg (87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.0 Hz, 2H, ArH), 7.09 (d, J = 8.0 Hz, 2H, ArH), 4.15 (d, J = 11.0 Hz, 2H, CH_2), 4.09 (s, 2H, OH), 3.97 (d, J = 11.0 Hz, 2H, CH_2), 2.83–2.81 (m, 4H, CH_2), 2.09–1.98 (m, 4H, CH_2), 1.77–1.62 (m, 8H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 137.7, 135.8, 134.9, 129.1, 127.5, 63.1, 30.2, 28.00, 23.6, 23.1; HR-MS (ESI): m/z = 323.1991, calcd. for $C_{22}H_{27}O_2$ $[M+H]^+$: 323.2011; $[\alpha]_D^{20}$: +91.6 (*c* 1.0, CH_2Cl_2).

Synthesis of Compound (*R*)-5

The octahydrodiol (*R*)-**4** (807 mg, 2.5 mmol) was dissolved in 100 mL of dried CH_2Cl_2. PPh_3 (2.62 g, 10 mmol) and CBr_4 (4.98 g, 15 mmol) were added, and the mixture was stirred at 25 °C for 36 h. 40 mL of saturated aqueous $NaHCO_3$ were added and the mixture was stirred for another 15 min. The organic layer was separated and the water layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined and dried with Na_2SO_4. After evaporation of the solvent, the residue was purified via column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give octahydrodibromide (*R*)-**5** as a white solid; yield: 897 mg (80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.15 (d, J = 8.0 Hz, 2H, ArH), 4.15 (q, J = 10.0 Hz, 4H, CH_2), 2.86–2.84 (m, 4H, CH_2), 2.40–2.34 (m, 2H, CH_2), 2.14–2.08 (m, 2H, CH_2), 1.84–1.67 (m, 8H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.6, 137.9, 135.6, 132.4, 129.6, 128.1, 33.1, 30.1, 27.7, 23.2, 22.8; HR-MS (ESI): m/z = 447.0305, calcd. for $C_{22}H_{25}Br_2$ $[M+H]^+$: 447.0323; $[\alpha]_D^{20}$: +36.5 (*c* 1.0, CH_2Cl_2).

Synthesis of Ligand (1R_a,2*S*,3*R*)-2[12b]

The octahydrodibromide (*R*)-**5** (897 mg, 2 mmol) was dissolved in 100 mL of CH_3CN. Et_3N (510 mg, 5 mmol) and (1*R*, 2*S*)-(+)-2-amino-1,2-diphenylethanol (534 mg, 2.5 mmol) were added and the mixture was refluxed for 24 h. The solvent was removed, and the residue was purified *via* column chromatography (silica gel, hexane:ethyl acetate = 5: 1) to give (1R_a,2*S*,3*R*)-**2** as a white solid; yield: 800 mg (80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.13 (m, 3H, ArH), 7.10 (d, J = 7.5 Hz, 2H, ArH), 7.06–7.04 (m, 3H, ArH), 6.99–6.96 (m, 2H, ArH), 6.93 (d, J = 7.5 Hz, 2H, ArH), 6.83–6.81 (m, 2H, ArH), 5.30 (s, 1H, CH), 3.80 (d, J = 12.0 Hz, 2H, CH_2), 3.40 (s, 1H, CH), 3.05 (d, J = 12.0 Hz, 2H, CH_2), 2.90–2.85 (m, 4H, CH_2), 2.75–2.70 (m, 2H, CH_2), 2.30–2.25 (m, 2H, CH_2), 1.85–1.80 (m, 6H, CH_2), 1.60–1.55 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.1, 138.4, 137.4, 137.2, 135.8, 131.8, 129.8, 128.1, 127.5, 127.4, 127.2, 126.6, 126.2, 126.1, 73.5, 71.9, 52.7, 29.6, 27.8, 22.9, 22.8; HR-MS (ESI): m/z = 500.2889, calcd. for $C_{36}H_{38}NO$ $[M+H]^+$: 500.2953; $[\alpha]_D^{20}$: +5.6 (*c* 1.0, CH_2Cl_2).

General Procedure for the Nucleophilic Addition of Alkynes to Aldehydes[17]

To a solution of phenylacetylene (52.7 μL, 0.48 mmol) in toluene (1 mL) was added a solution of dimethylzinc (2 M, 0.22 mL, 0.44 mmol) in toluene. The mixture was stirred at 0 °C for 30 min. A solution of (1R_a,2*S*,3*R*)-**2** (10 mg, 0.02 mmol) in toluene (1 mL) was added. After stirring the mixture for 30 min, the aldehyde (0.2 mmol) was added in one portion with a syringe. The mixture was stirred at 0 °C for 24 h, and the reaction was quenched with aqueous HCl solution (5%, 2 mL). The mixture was extracted with diethyl ether (3 × 2 mL). The organic layer was separated and concentrated at reduced pressure, and was purified using flash chromatography to afford the product. The enantiomeric excess of the product was determined by HPLC analysis.

(*S*)-1,3-Diphenylprop-2-yn-1-ol:[18] Yield: 87%; 72% *ee* determined by HPLC analysis; Daicel Chiralcel OD-H, λ = 254 nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(R)$ = 11.4 min, $t_r(S)$ = 22.0 min.

(*S*)-1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol:[18] Yield: 86%; 82% *ee* determined by HPLC analysis; Daicel Chiralcel OD, λ = 254 nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(R)$ = 7.8 min, $t_r(S)$ = 9.2 min.

(+)-1-(2-Fluorophenyl)-3-phenylprop-2-yn-1-ol:[17] Yield: 83%; 77% *ee* determined by HPLC analysis; Daicel Chiralcel OD, λ = 254 nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: t_r(minor) = 7.3 min, t_r(major) = 12.0 min.

(+)-1-(2-Nitrophenyl)-3-phenylprop-2-yn-1-ol:[17] Yield: 90%; 85% *ee* determined by HPLC analysis; Daicel Chiralcel OD, λ = 254 nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: t_r(major) = 16.7 min, t_r(minor) = 20.6 min.

(+)-1-(2-Nitrophenyl)hex-2-yn-1-ol:[17] Yield: 88%; 83% *ee* determined by HPLC analysis; Daicel Chiralcel OJ, λ = 254 nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: t_r(minor) = 10.1 min, t_r(major) = 12.0 min.

(*S*)-1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-ol:[19] Yield: 87%; 76% *ee* determined by HPLC analysis, Daicel Chiralcel OD, λ = 254 nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(R)$ = 16.5 min, $t_r(S)$ = 20.9 min.

(*S*)-1-(2-Methylphenyl)-3-phenylprop-2-yn-1-ol:[19] Yield: 85%; 84% *ee* determined by HPLC analysis; Daicel Chiralcel OD-H, λ = 254 nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(R)$ = 8.7 min, $t_r(S)$ = 21.5 min.

(*S*)-1-Cyclohexyl-3-phenylprop-2-yn-1-ol:[18] Yield: 81%; 34% *ee* determined by HPLC analysis; Daicel Chiralcel OD-H, λ = 270 nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(R)$ = 5.8 min, $t_r(S)$ = 12.0 min.

General Procedure for the Catalytic Addition of Arylzinc to Benzaldehyde[14h]

A toluene solution (1.5 mL) of phenylboronic acid (1.2 mmol, 146.3 mg) was mixed with a diethylzinc solution (1.1 M in toluene, 3.6 mmol, 3.27 mL) in a sealed vessel under nitrogen atmosphere. After stirring the reaction mixture at 60 °C for 12 h, the vessel was cooled to 0 °C and a toluene solution of (1R_a,2*S*,3*R*)-**2** (0.05 mmol) was added with continued stirring for 15 min. 4-Chlorobenzaldehyde (0.50 mmol, 70.3 mg) was subsequently added and the mix-

ture was allowed to stir at 0 °C overnight. The reaction was then quenched with aqueous HCl solution (5%, ~6 mL). The reaction mixture was extracted with ethyl acetate (3× 5 mL) and was dried with Na_2SO_4. The crude product diarylmethanol was purified by column chromatography (silica gel, 10% EtOAc-hexane), giving the product with 95% yield and 96% *ee*. The enantiomeric excess was determined by HPLC analysis with a 25 cm × 4.6 mm Chiralcel OB-H column (Daicel Chemical Industries Ltd.).

(*R*)-(4-Chlorophenyl)phenylmethanol:[20] Yield: 95%; 96% *ee* determined by HPLC analysis; Daicel Chiralcel OB-H, $\lambda = 270$ nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(R) = 13.5$ min, $t_r(S) = 21.2$ min.

(*R*)-(2-Chlorophenyl)phenylmethanol:[20] Yield: 92%; 95% *ee* determined by HPLC analysis; Daicel Chiralcel OD-H, $\lambda = 254$ nm, hexane:*i*-PrOH = 95:5, 1.0 mL min^{-1}, retention time: $t_r(R) = 11.2$ min, $t_r(S) = 14.8$ min.

(*R*)-(3-Chlorophenyl)phenylmethanol:[21] Yield: 93%; 95% *ee* determined by HPLC analysis; Daicel Chiralcel OB-H, $\lambda = 254$ nm, hexane:*i*-PrOH = 95:5, 1.0 mL min^{-1}, retention time: $t_r(R) = 24.8$ min, $t_r(S) = 42.4$ min.

(*R*)-(4-Biphenyl)phenylmethanol:[20] Yield: 93%; 92% *ee* determined by HPLC analysis; Daicel Chiralcel OB-H, $\lambda = 254$ nm, hexane:*i*-PrOH = 95:5, 1.0 mL min^{-1}, retention time: $t_r(R) = 40.2$ min, $t_r(S) = 61.0$ min.

(*R*)-(2-Methoxyphenyl)phenylmethanol:[20] Yield: 89%; 86% *ee* determined by HPLC analysis; Daicel Chiralcel OD-H, $\lambda = 254$ nm, hexane:*i*-PrOH = 97 : 3, 1.0 mL min^{-1}, retention time: $t_r(S) = 38.9$ min, $t_r(R) = 43.9$ min.

(*R*)-(2-Tolyl)phenylmethanol:[20] Yield: 92%; 95% *ee* determined by HPLC analysis; Daicel Chiralcel OD-H, $\lambda = 254$ nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(S) = 15.4$ min, $t_r(R) = 17.5$ min.

(*R*)-(4-Bromophenyl)phenylmethanol:[13] Yield: 95%; 91% *ee* determined by HPLC analysis; Daicel Chiralcel OB-H, $\lambda = 254$ nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(R) = 22.0$ min, $t_r(S) = 31.3$ min.

(*R*)-(1-Naphthyl)phenylmethanol:[13] Yield: 95%; 93% *ee* determined by HPLC analysis; Daicel Chiralcel OD-H, $\lambda = 254$ nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(S) = 13.8$ min, $t_r(R) = 28.4$ min.

(*S*)-(4-Tolyl)phenylmethanol:[20] Yield: 92%; 95% *ee* determined by HPLC analysis; Daicel Chiralcel OD-H, $\lambda = 254$ nm, hexane:*i*-PrOH = 98:2, 1.0 mL min^{-1}, retention time: $t_r(S) = 25.8$ min, $t_r(R) = 30.5$ min.

(*R*)-(2-Bromophenyl)phenylmethanol:[13] Yield: 90%; 91% *ee* determined by HPLC analysis; Daicel Chiralcel OD-H, $\lambda = 254$ nm, hexane:*i*-PrOH = 90:10, 1.0 mL min^{-1}, retention time: $t_r(R) = 8.0$ min, $t_r(S) = 10.3$ min.

Acknowledgements

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