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Enantioselective alkynylation of aldehydes catalyzed by a camphor sulfonylated amino alcohols titanium(IV) catalyst system

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A new titanium(IV) complex has been developed for the effective enantioselective alkynylation of phenylacetylene addition to aldehydes. The titanium(IV) complex was readily prepared *in situ* from (*R*)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-(1*R*,2*S*)-*N*-(2-hydroxy-1,2-diphenyl-ethyl)-methanesulfonamide (1h) and tetraisopropyl titanate [Ti(*i*-OPr)$_4$]. A variety of aromatic aldehydes and α,β-unsaturated aldehydes were found to be suitable substrates in the presence of the camphor sulfonylated amino alcohol titanium(IV) complex [10 mol% 1h, 40 mol% Ti(*i*-OPr)$_4$]. The desired propargylic alcohols were afforded with high isolated yields (up to 90%) and moderate enantioselectivities (up to 65% ee) under mild conditions.

Keywords: aldehydes; amino alcohols; camphor; phenylacetylene; zinc

Introduction

Catalytic asymmetric carbon–carbon bond formation is a very important reaction in the field of organic chemistry.[1] Amongst these reactions, the enantioselective alkynylation of aldehydes has attracted much attention in asymmetric synthesis because of its simplicity and utility for the preparation of propargylic alcohols which are key building blocks used in the fine chemical and pharmaceutical industries.[2] Recently, numerous examples of using various chiral ligands such as (−)-*N*-methyl ephedrine,[3] BINOLs,[4] proline,[5] oxazolidine[6] and others[7] have been reported by different research groups. Despite the achievements made in this field of organometal (zinc) chemistry, the alkynylation of aldehydes has not yet reached the level of practicability that is required for a synthetically useful catalytic system. Thus, it is still necessary to develop new types of chiral ligands which are greatly needed to probe how the chiral catalysts work on the reaction and how to develop new types of chiral ligands. On the other hand, β-amino alcohols and camphor sulfonic acid and their derivatives have been used in many asymmetric reactions, and good to excellent results have been obtained.[8] Inspired by these works, we continued to search for a new highly efficient catalyst system using camphor sulfonic acid derivatives and amine or β-amino alcohols to achieve structural diversity. Therefore, a set of camphor sulfonic acid derivatives based on amine or β-amino alcohols were investigated (synthesis for the chiral ligands **1a–k**: see Experimental section for details). Herein, we wish to report a camphor sulfonylated amide or sulfonylated amino alcohols titanium complex that engenders a more effective catalyst for the asymmetric alkynylation of phenylacetylene addition to aldehydes (Fig. 1).

Results and Discussion

Chiral Catalyst System Screening

Chiral ligands **1a–k** were synthesized in good to excellent yields using (*R*)-camphor sulfonic acid and different amine or amine alcohol as start materials (Scheme 1).[9] Initially, we investigated the alkynylation of phenylacetylene addition to benzaldehyde in the presence of 10 mol% ligand **1** and 40 mol% tetraisopropyl titanate [Ti(*i*-OPr)$_4$] in dry dichloromethane (CH_2Cl_2) at 22 °C under nitrogen atmosphere. The results in Table **1** showed that the ligands **1a, 1b** and **1c**, which derive from (*R*)-camphor-10-sulfonic acid and hydrazine hydrate, gave 12, 17 and 14% ee with good yields (Table 1, entries 1–3). Ligand **1h,** which derives from (*R*)-camphor-10-sulfonic acid and (1*R*, 2*S*)-2-amino-1,2-diphenyl-ethanol, gave the highest ee with good yield (Table 1, entry 8); however, other camphor sulfonylated amino alcohols, which derive from (1*S*, 2*R*)-, (1*S*, 2*S*)- or (1*R*, 2*R*)-2-amino-1,2-diphenylethanol, gave lower ee with high yield (Table 1, entries 9–11), which might be attributed to the match pair or mismatch pair of the configuration between camphor-10-sulfonic acid and 2-amino-1,2-diphenyl-ethanol. Other camphor-sulfonylated amides, **1d–j**, which derive from benzylamine, 2-methoxyphenylamine, *tert*-butylamine or (*S*)-1-phenylethylamine, gave lower ee with good to excellent yield (Table 1, entries 4–7).

Optimization of the Catalyst System

Having realized the most promising complex in the enantioselective alkynylaltion of benzaldehyde, the effect of several reaction parameters, such as catalyst loading and reaction solvent, were studied with the aim of optimizing the reaction conditions and developing a more efficient catalytic system.

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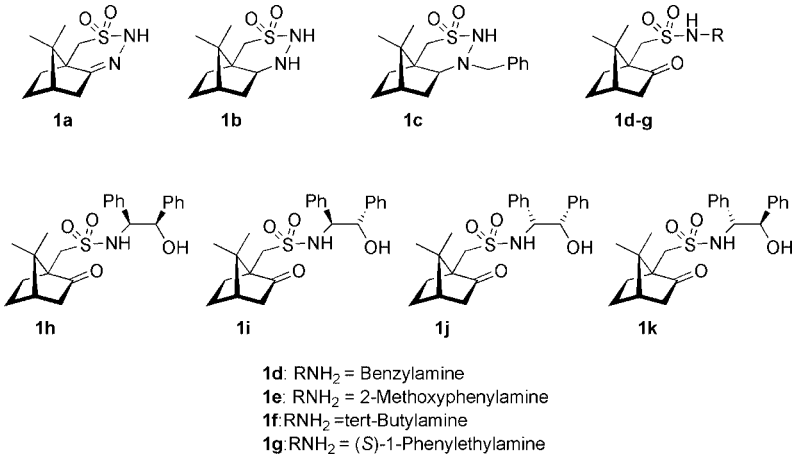
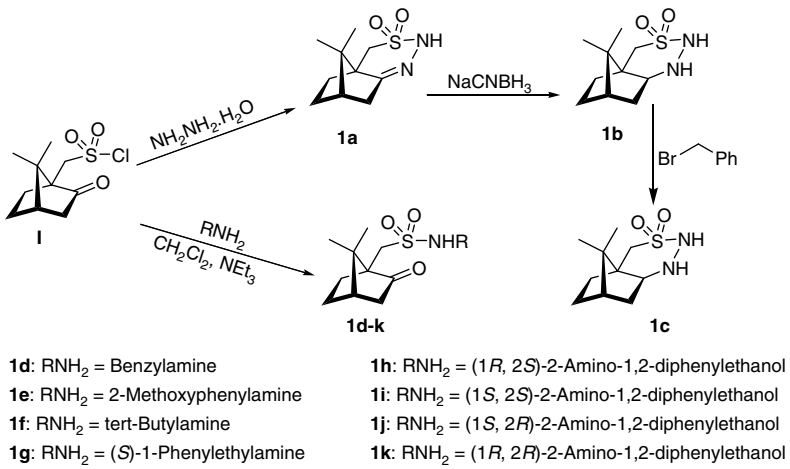


Figure 1. The structures of the ligands screened in the reaction.



Scheme 1. The synthesis of chiral ligands **1a**–**k**.

First, we investigated the effect of different reaction solvents (toluene, CH_2Cl_2, THF, Et_2O and hexane) using the best **1h**–Ti(IV) complex (Table 2, entries 1–5). It was found that THF and Et_2O gave very low ee and yield with longer reaction time than toluene (Table 2, entries 2 and 3). Hexane gave moderate ees with moderate yield (Table 2, entry 4). The highest ee of 56 with 90% yield was obtained in toluene (Table 2, entry 1).

The optimum loading of **1h** and Ti(*i*-OPr)$_4$ was investigated under the best conditions (Table 3). It was found that the best loading was 10 mol% **1h** and 40 mol% Ti(*i*-OPr)$_4$, respectively. With increased or decreased loading of Ti(*i*-OPr)$_4$, dissatisfactory results were afforded (Table 3, entries 2–4). The above results show the general feature of excess Ti(*i*-OPr)$_4$ required to achieve the best enantioselectivities and reactivities in asymmetric alkynylation of aldehydes. With increasing or decreasing the loading of **1h** from 10 to 20 or 5 mol% under same conditions, unfavourable ee was obtained (Table 3, entries 5–6 entry 1).

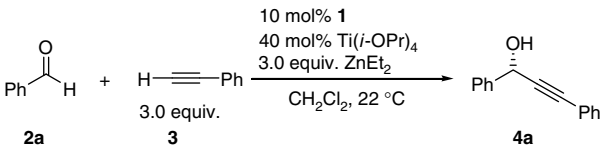
Substrate Generality

To study the generality of the complex **1h**–Ti(IV) for the enantioselective alkynylation to various aldehydes, a number of aromatic aldehydes having electron-donating and electron-withdrawing groups were examined under the optimized conditions reported in Table 4. In comparison to the results obtained with **2a**, the electron-donating group (Me or OMe) led to a slight increase in the ees of the products **3b** and **c** (Table 4, entries 2 and 3 vs entry 1). Electron-withdrawing groups (F, Cl or Br, Table 4, entries 4–6) showed moderate yields and similar ees with benzaldehyde. The reaction of β- and α-naphthaldehydes **2g** and **2h**, respectively, resulted in good yields and moderate ees (Table 4, entries 7 and 8). Furan-2-carbaldehyde gave lower yield and ee than benzaldehyde (Table 4, entry 9 vs entry 1). The reaction of α,β-unsaturated aldehyde (*trans*-cinnamaldehyde) only gave 42% ee after 48 h (Table 4, entry 10). In general, good yields and moderate enantioselectivities of the propargylic alcohols **4a**–**j** were obtained (Table 4).

Conclusion

In summary, we have developed a Ti(IV) catalyst system based on (*R*)-camphor sulfonic acid, (1*R*,2*S*)-2-amino-1,2-diphenylethanol and tetraisopropyl titanate [Ti(*i*-OPr)$_4$], which was readily prepared in one simple step from commercially available starting materials for the asymmetric alkynylation of phenylacetylene addition to aldehyde. The corresponding titanium(IV) complex, which was prepared using 10 mol% **1h** and 40 mol% Ti(*i*-OPr)$_4$ *in situ*, showed excellent catalytic activities and moderate enantioselectivities (up to 65% ee) in the asymmetric alkynylation of phenylacetylene

Table 1. Enantioselective alkynylation of phenylacetylene addition to benzaldehyde catalyzed by **1**–Ti(IV) complex



2a **3** **4a**

Entry[a]	Ligand	Time (h)	Yield (%)[b]	Ee(%)[c]
1	**1a**	24	91	12
2	**1b**	24	87	17
3	**1c**	24	90	14
4	**1d**	24	93	7
5	**1e**	24	98	3
6	**1f**	24	87	10
7	**1g**	24	76	15
8	**1h**	40	84	49
9	**1i**	40	85	10
10	**1j**	24	96	7
11	**1k**	24	91	37

[a] Concentration of benzaldehyde: 2.0 M in toluene; the loading of ligand **1**: 10 mol%, 40 mol% Ti(*i*-OPr)$_4$ in toluene; $ZnEt_2$: 3.0 equiv. in hexene; the reactions were performed for 24–40 h at 22 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC (Chiralcel OD-H); the configuration is *S* of the major enantiomer of the product.[4g]

Table 2. Enantioselective alkynylation of phenylacetylene addition to benzaldehyde in the presence of **1h**–Ti(IV) complex

Entry[a]	Solvent	Time(h)	Yield (%)[b]	Ee(%)[c]
1	CH_2Cl_2	40	84	49
2	THF	24	21	14
3	Et_2O	24	19	12
4	Hexene	10	83	37
5	Toluene	24	90	56

[a] Concentration of benzaldehyde: 2.0 M in $PhCH_3$; the loading of ligand **1i**: 10 mol%, 40 mol% Ti(*i*-OPr)$_4$ in $PhCH_3$; $ZnEt_2$: 3.0 equiv. in hexene; the reactions were performed at 22 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC (Chiralcel OD-H); the configuration is *S* of the major enantiomer of the product.[4g]

addition to various aldehydes under mild conditions. Further investigation on the applications of these ligands for other asymmetric reactions is ongoing.

Experimental Section

General Remarks

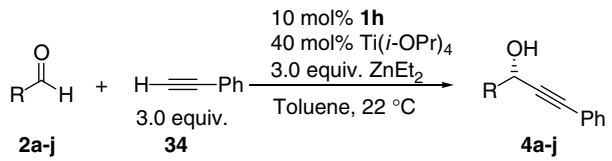
^{1}H NMR spectra were recorded on commercial instruments (300 MHz). Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*, Hz), integration and assignment. ^{13}C NMR spectra were collected on commercial instruments (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). Enantiomeric ratios of the products were determined using chiral HPLC (OD-H or OD column) techniques. Optical rotations were measured on a commercial polarimeter and reported as follows: $[a]^T_D$ (*c* = g/100 ml, solvent). HRMS was recorded with ESI source (in CH_3OH). Elemental analyses were performed using commercial instruments. Analytical thin layer chromatography (TLC) was carried out on commercial plates coated with 0.25 mm of silica gel. Preparative flash silica chromatography was performed using silica gel 200–400 mesh. All reactions were carried out under

Table 3. Optimization the ratio of **1h** to Ti(*i*-OPr)$_4$ in the alkynylation of phenylacetylene addition to benzaldehyde

Entry[a]	**1h** (mol%)	Ti(*i*-Opr)$_4$ (mol%)	Yield (%)[b]	Ee(%)[c]
1	10	40	90	56
2	10	50	94	46
2	10	30	90	10
3	10	20	99	7
4	10	0	19	4
5	20	40	91	38
6	5	20	70	31

[a] Concentration of benzaldehyde: 2.0 M in $PhCH_3$; $ZnEt_2$: 3.0 equiv. in hexene; the reactions were performed at 22 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC (Chiralcel OD-H); the configuration is *S* of the major enantiomer of the product.[4g]

Table 4. Enantioselective alkynylation of phenylacetylene addition to different aldehydes in the presence of **1h**–Ti(IV) complex



2a-j **34** **4a-j**

Entry[a]	Aldehyde	Time(h)	Yield (%)[b]	Ee(%)[c]
1	Benzaldehyde (**2a**)	24	90	56
2	*p*-MeOC_6H_4 (**2b**)	48	73	61
3	*p*-MeC_6H_4 (**2c**)	40	87	63
4	*p*-FC_6H_4 (**2d**)	40	77	56
5	*p*-ClC_6H_4 (**2e**)	40	71	54
6	*p*-BrC_6H_4 (**2f**)	40	74	52
7	Naphthalene-2-carbaldehyde (**2g**)	24	88	65
8	Naphthalene-1-carbaldehyde (**2h**)	24	83	51
9	Furan-2-carbaldehyde (**2i**)	48	79	45
10	(*E*)-Cinnamaldehyde (**2j**)	48	57	42

[a] Concentration of benzaldehyde: 2.0 M in toluene; the loading of ligand **1h**: 10 mol%, 40 mol% Ti(*i*-OPr)$_4$ in toluene; $ZnEt_2$: 3.0 equiv. in hexene; the reactions were performed at 22 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC (Chiralcel OD or OD-H); the configuration is *S* of the major enantiomer of the product.[4g,h]

an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring unless otherwise indicated.

Materials

(*R*)-(+)-10-Camphorsulfonyl chloride **I**,[9b] chiral ligands **1a**–**c**,[9b] **1d**,[9c,e] **1f**,[9d] **1g**[9e] and **1h**–**k**[9a] were synthesized according to the literature procedures. These known compounds were characterized by comparing the ^{1}H, ^{13}C NMR spectra with those published in the literature. All liquid aldehydes were used after distilled; phenylacetylene, diethylzinc, Ti(*i*-OPr)$_4$ and other chemical reagents are commercially available, and were used directly without further purification. Anhydrous solvents such as THF, CH_2Cl_2, toluene, hexene and Et_2O were treated by standard methods.

Synthesis for Chiral Ligands 1a–c

*(R)-Cyclic camphor sulfonyl hydrazone (**1a**)*

To a solution of (*R*)-(+)-10-camphorsulfonyl chloride **I** (1.25 g, 5.0 mmol) in 20 ml of methanol were added hydrazine monohydrate (0.5 ml, 10 mmol) and acetic acid (0.15 ml, 2.5 mmol). The mixture was stirred under reflux condition for 4 h. Then the reaction mixture was cooled down. The mixture was dissolved in small amount of water and extracted with ethyl acetate for three times (3 × 20 ml). The pH value of the aqueous phase was adjusted to 9–10 by K_2CO_3 and extracted with ethyl acetate (3 × 20 ml). The combined extracting organic layer was washed with brine and dried with anhydrous Na_2SO_4, followed by filtration and concentration to obtain white solid of cyclic camphor sulfonyl hydrazone **1a** in 89% yield. $[a]^{25}_D = +12.5$ ($c = 1.0$, CH_2Cl_2) {Lit.[9b] $[a]^{20}_D = -13.1$ ($c = 1.03$, $CHCl_3$) for *S*-enantiomer}.

*(R)-Cyclic camphor sulfonyl hydrazine (**1b**)*

To a solution of cyclic camphor sulfonyl hydrazone (**1a**) (460 mg, 2 mmol) in 5 ml of methanol was added 3.0 ml of acetic acid, followed by adding $NaCNBH_3$ dropwise. Then the reaction mixture was stirred at 25 °C for 12 h. The excess $NaCNBH_3$ was quenched by 1 M aqueous HCl solution. The pH value of the aqueous phase was adjusted to 9–10 by K_2CO_3 and extracted with ethyl acetate (3 × 20 ml). The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4, followed by further purification via column chromatography to give white solid of cyclic camphor sulfonyl hydrazine **1b** in 95% yield. $[a]^{25}_D = +88.6$ ($c = 1.0$, CH_2Cl_2) {Lit.[9b] $[a]^{20}_D = -89.0$ ($c = 1.04$, $CHCl_3$) for *S*-enantiomer}.

*(R)-N^{β}-Benzyl cyclic camphor sulfonyl hydrazine (**1c**)*

To a solution of cyclic camphor sulfonyl hydrazine **1b** (460 mg, 2 mmol) in 15 ml of dichloromethane were added K_2CO_3 (414 mg, 3 mmol) and tetrabutylammonium bromide (32 mg, 0.1 mmol), followed by benzyl bromide (0.36 ml, 3 mmol). The reaction was stirred at 22 °C for 2 days. Waters was added and the resulting mixture was extracted by ethyl acetate (3 × 20 ml). The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4 followed by further purification via column chromatography to give white solid of **1c** in 68% yield. $[a]^{25}_D = +148.7$ ($c = 1.0$, CH_2Cl_2) {Lit.[9b] $[a]^{20}_D = -150.6$ ($c = 1.005$, $CHCl_3$) for *S*-enantiomer}.

General Experimental Procedure For synthesis of 1d–l

To a solution (*R*)-(+)-10-camphorsulfonyl chloride (1.50 g, 5.5 mmol) in 20 ml dried CH_2Cl_2 were added NEt_3 (0.9 ml, 6 mmol) and the corresponding amine or amino alcohol (5.0 mmol) at 0 °C. Then the mixture was stirred at 25 °C for 5–10 h (using TLC to check the reaction procedure). The mixture was washed with 1 M aqueous HCl solution (3 × 10 ml), saturated $NaHCO_3$ aqueous (adjust the pH value to 6–7) and brine after the reaction finished. The organic phrase was dried over anhydrous Na_2SO_4, followed by further purification via column chromatography to give the corresponding products **1d**– **l**.

*(R)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-N-benzyl-methanesulfonamide (**1d**)*

Yield: 89%. $[a]^{25}_D = -6.91$ ($c = 1.0$, CH_2Cl_2). {Lit.[9c,e] $[a]^{20}_D = +6.68$ ($c = 1.0$, $CHCl_3$) for (*S*)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-*N*-benzyl-methanesulfonamide}.

*(R)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-N-(2-methoxy-phenyl)-methanesulfonamide (**1e**)*

Yield: 92%. M.p. 90–92 °C, $[a]^{25}_D = -27.56$ ($c = 1.0$, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.95$ (s, 3H, OCH_3), 1.06 (s, 6H, $2CH_3$), 1.59–1.65 (m, 2H, CH_2 of camphor), 1.79–1.90 (m, 2H, CH_2 of camphor), 2.43–2.51 (m, 1H, CH of camphor), 3.78 (s, 2H, CH_2-SO_2), 3.79–4.43 (dd, $J_1 = 6.3$ Hz, $J_2 = 12.3$ Hz, 2H, CH_2 of camphor), 5.10 (br, 1H, NH), 6.79–6.87 (m, 2H, Ar –H), 7.18–7.24 (m, 2H, Ar –H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 16.4$, 16.8 ($2CH_3$), 29.1, 30.2, 30.6, 39.2, 53.9, 54.9 (C-camphor), 55.3 (OCH_3), 56.1 (C-camphor), 91.0, 91.6, 110.4, 120.6, 125.3, 129.2, 129.9, 157.6 (C–Ar), 210.0 (C═O) ppm. HRMS: (ESI, CH_3OH) calcd for $C_{17}H_{23}NO_4S(M^+)$: requires 337.1348, found 337.1331. Anal. calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.15%; found: C, 60.42; H, 6.76; N, 4.08%.

*(R)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-N-*tert*-butyl-methanesulfonamide (**1f**)*

Yield: 95%. $[a]^{25}_D = -6.95$ ($c = 1.0$, CH_2Cl_2).

*(R)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-N-(S)-(1-phenyl-ethyl)-methanesulfonamide (**1g**)*

Yield: 65%%. $[a]^{25}_D = -17.3$ ($c = 1.5$, CH_2Cl_2). {Lit.[9e] $[a]^{20}_D = -16.7$ ($c = 1.0$, CH_2Cl_2)}.

*C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-N-(2-hydroxy-1, 2-diphenyl-ethyl)-methanesulfonamide (**1h**–**k**)*

Yields: 77-84% for **1h**–**k**. $[a]^{25}_D = -6.0$ (**1h**),–67.2 (**1i**), –3.4(**1j**), +46.6 (**1k**) ($c = 1.0$, CH_2Cl_2). {Lit.[9a] $[a]^{25}_D = +5.8$ ($c = 1.0$, CH_2Cl_2) for (*S*)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-*N*-(1*S*,2*R*)-(2-hydroxy-1,2-diphenyl-ethyl)-methanesulfonamide}.

General experimental procedure for the alkynylation of phenylacetylene addition to aldehyde

To a solution of ligand **1h** (10.68 mg, 0.25 mmol) and Ti(*i*-OPr)$_4$ (25 µl in toluene, 0.025 mmol) in dry toluene (0.5 ml) at room temperature, a solution of Et_2Zn (1.0 M in hexene, 0.75 ml) was added. After the mixture was stirred at the room temperature for 2.5 h, phenylacetylene (82.4 µl, 0.75 mmol) was added and

then stirring continued for 1.0 h. The corresponding aldehyde (0.25 mmol) was added to the solution after 10 min at 0 °C, then the resultant mixture was allowed to warm up to room temperature (22 °C) and stirred for the indicated time (24–48 h). After the reaction was completed, it was cooled to 0 °C and quenched by 1.0 M aqueous HCl (2.0 ml). The mixture was extracted with ethyl acetate (EtOAc) (3 × 20 ml). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel H, EtOAc : hexene = 1 : 10, v/v) to give the corresponding pure product. These compounds (**4a–j**) were characterized by comparing their ^1H, ^{13}C NMR spectra with those published in the literature.[3–5] The ee were determined by HPLC analysis (Chiralcel OD-H column), and the absolute configuration of major adducts was assigned by comparison with literature data.[4g–h]

*(S)-1,3-diphenyl-prop-2-yn-l-ol (**4a**)*

Yield 90% and ee 56% determined by HPLC analysis (Chiralcel OD-H column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times, t_1 (major) = 17.5 min, t_2 (minor) = 11.8 min; $[a]^{25}_D = -2.4$ (c = 0.5, CH_2Cl_2). {Lit.[4g] $[a]^{27}_D = +9.3$ (c = 0.6, $CHCl_3$) for *R* enantiomer in 96% ee}.

*(S)-1-(4-methoxyphenyl)-3-phenyl-prop-2-yn-1-ol (**4b**)*

Yield 73% and ee 61% determined by HPLC analysis (Chiralcel OD-H column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times t_1 (major) = 26.4 min, t_2 (min) = 15.1 min; $[a]^{25}_D = -4.3$ (c = 0.5, CH_2Cl_2). {Lit.[4h] $[a]^{22}_D = +7.8$ (c = 1.0, $CHCl_3$) for *R* enantiomer in 93% ee}.

*(S)-1-(4-methylphenyl)-3-phenyl-prop-2-yn-1-ol (**4c**)*

Yield 87% and ee 63% determined by HPLC analysis (Chiralcel OD-H column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times t_1 (major) = 17.6 min, t_2 (minor) = 9.4 min; $[a]^{25}_D = -1.7$ (c = 0.5, CH_2Cl_2). {Lit.[4g] $[a]^{25}_D = +2.99$ (c = 0.93, $CHCl_3$) for *R* enantiomer in 92.5% ee}.

*(S)-1-(4-fluorophenyl)-3-phenyl-prop-2-yn-1-ol (**4d**)*

Yield 77% and ee 56% determined by HPLC analysis (Chiralcel OD-H column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times t_1 (major) = 20.2 min, t_2 (minor) = 8.8 min; $[a]^{25}_D = -3.4$ (c = 0.5, CH_2Cl_2). {Lit.[4g] $[a]^{27}_D = +6.1$ (c = 1.22, $CHCl_3$) for *R* enantiomer in 96% ee}.

*(S)-1-(4-chlorophenyl)-3-phenyl-prop-2-yn-1-ol (**4e**)*

Yield 71% and ee 54% determined by HPLC analysis (Chiralcel OD-H column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times, t_1 (major) = 21.3 min, t_2 (minor) = 9.8 min; $[a]^{25}_D = -4.4$ (c = 0.5, CH_2Cl_2). {Lit.[4g] $[a]^{27}_D = +9.0$ (c = 1.22, $CHCl_3$) for *R* enantiomer in 92% ee}.

*(S)-1-(4-bromophenyl)-3-phenyl-prop-2-yn-1-ol (**4f**)*

Yield 74% and ee 52% determined by HPLC analysis (Chiralcel OD-H column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times, t_1 (major) = 24.8 min, t_2 (minor) = 9.3 min; $[a]^{25}_D = -4.1$ (c = 0.5, CH_2Cl_2). {Lit.[4h] $[a]^{25}_D = +8.4$ (c = 1.22, $CHCl_3$) for *R* enantiomer in 93.1% ee}.

*(S)-1-(2-naphthyl)-3-phenyl-prop-2-yn-1-ol (**4g**)*

Yield 88% and ee 65% determined by HPLC analysis (Chiralcel OD-H column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times, t_1 (major) = 40.5 min, t_2 (minor) = 13.5 min; $[a]^{25}_D = -7.5$ (c = 0.5, CH_2Cl_2). {Lit.[4g] $[a]^{27}_D = +13.7$ (c = 1.22, $CHCl_3$) for *R* enantiomer in 98% ee}.

*(S)-1-(1-naphthyl)-3-phenyl-prop-2-yn-1-ol (**4h**)*

Yield 83% and ee 51% determined by HPLC analysis (Chiralcel OD-H column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times, t_1 (major) = 29.5 min and t_2 (minor) = 12.4 min. $[a]^{25}_D = 12.0$ (c = 0.5, CH_2Cl_2). {Lit.[4h] $[a]^{25}_D = -27.8$ (c = 1.25, $CHCl_3$) for *R* enantiomer in 94.6% ee}.

*(S)-1-(2-Furyl)-3-phenyl-prop-2-yn-1-ol (**4i**)*

Yield 79% and ee 45% determined by HPLC analysis (Chiralcel OD-H column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times, t_1 (major) = 18.6 min, t_2 (minor) = 9.5 min; $[a]^{25}_D = -1.9$ (c = 0.5, CH_2Cl_2). {Lit.[4h] $[a]^{22}_D = +4.4$ (c = 0.81, $CHCl_3$) for *R* enantiomer in 87.5% ee}.

*(S)-(E)-1,5-diphenyl-pent-1-en-4-yn-3-ol (**4j**)*

Yield 61% and ee 46% determined by HPLC analysis (Chiralcel OD column, 10% *i*PrOH in hexane at 1.0 ml min^{-1}, 254 nm); retention times, t_1 (major) = 72.5 min, t_2 (minor) = 24.2 min; $[a]^{25}_D = -2.1$ (c = 0.5, CH_2Cl_2). {Lit.[4h] $[a]^{25}_D = +6.2$ (c = 0.85, $CHCl_3$) for *R* enantiomer in 91.7% ee}.

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