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Enantioselective alkynylations of aromatic and aliphatic aldehydes catalyzed by terpene derived chiral amino alcohols

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Dedicated in memory of Professors James Verghese and Herbert C. Brown

Abstract—Enantioselective alkynyl zinc additions to aromatic and aliphatic aldehydes have been studied using terpene derived chiral amino alcohol ligands. The limonene derived amino alcohol (1*R*,2*R*,5*S*)-2-methyl-5-(1-methylethenyl)-2-(1-pyrrolidinyl)cyclohexanol gave the most promising results. Chiral propargylic alcohols were obtained in good yields and moderate enantioselectivities (up to 60%).

1. Introduction

Enantioselective addition of organozinc reagents to aldehydes and ketones is a touchstone for the development of novel chiral β-amino alcohols as ligands.[1] Significant progress has been made particularly for the enantioselective alkynylzinc addition to aldehydes.[2] In 1990, Niwa and Soai's ephedrine-based ligand provided asymmetric inductions in the range of 7–34%.[2r] By 1994, Ishizaki and Honshino were able to obtain up to 90% ee for the addition of phenylacetylene to benzaldehyde using a tridentate amino alcohol.[2q] Recently, Carreira's use of $Zn(OTf)_2$ instead of Et_2Zn with ephedrine derivatives was more efficient and provided higher asymmetric inductions for a wider range of aldehyde and alkyne substrates.[2i,2m,2n] The use of terpenes as inexpensive, readily available starting materials to develop effective chiral β-amino alcohols as ligands has been a long standing focus in our laboratory. Over several years, we have synthesized several amino alcohols from naturally occurring terpenes, such as limonene, pinene, and carene.[3] Several of these amino alcohols were found to be efficient ligands for the asymmetric addition of diethyl zinc to aldehydes.[1c] Herein, we report the use of terpene-derived amino alcohols as chiral auxiliaries for the asymmetric alkynylation of aldehydes to form propargylic alcohols.

2. Results and discussion

Several representative β-amino alcohols derived from natural terpenes (Fig. 1) were screened as chiral directors in the addition of phenylacetylene to aldehydes. Recently we reported that the *cis*-diastereomer of (*R*)-(+)-limonene oxide can be separated in its diastereomerically pure form from the commercially available (1:1) diastereomeric mixture of limonene oxides.[4] Selective epoxide ring opening with secondary amines allows for the formation of a β-amino alcohol from the *trans*-epoxide. The unreacted *cis*-diastereomer can be recovered in up to 88% yield in greater than 98% purity (Scheme 1). The epoxide ring opening reaction can be carried out using a variety of nucleophilic amines. The observed regioselectivity of the opening has been explained by the conformational differences between the two epoxides.[4] The isopropenyl group prefers the equatorial orientation in both the *cis*- and *trans*-isomers due to the large *A* value. A nucleophilic amine would attack in an S_N2-type reaction at the less hindered C-2 carbon atom, while the *cis*-epoxide would first have to attain the energetically unfavorable 'boat-like' transition state and thus remain largely unreacted. Using this method, ligands **1**–**3** were prepared from piperidine, pyrrolidine, and isoquinoline, respectively.[1c] The free amine **5a**[5] was prepared in the same manner as **1**–**3** using ammonium hydroxide. The sulfonamide ligand **5** was then prepared by the *N*-tosylation of **5a**. Amino alcohol **6a**[5] can be prepared from the recovered pure *cis*-(*R*)-limonene oxide and an

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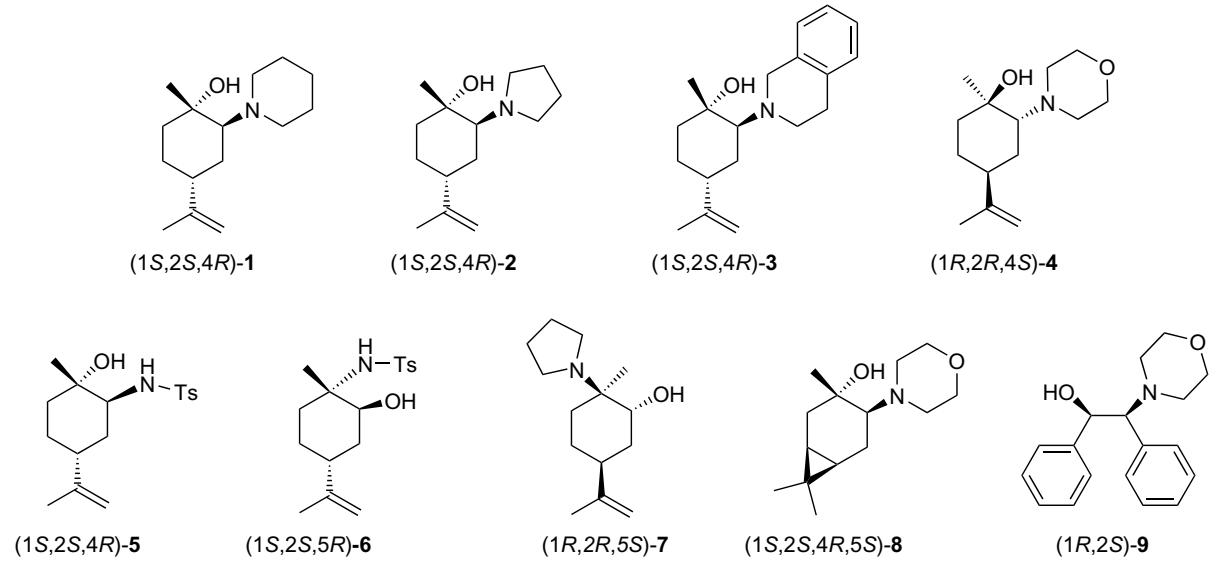
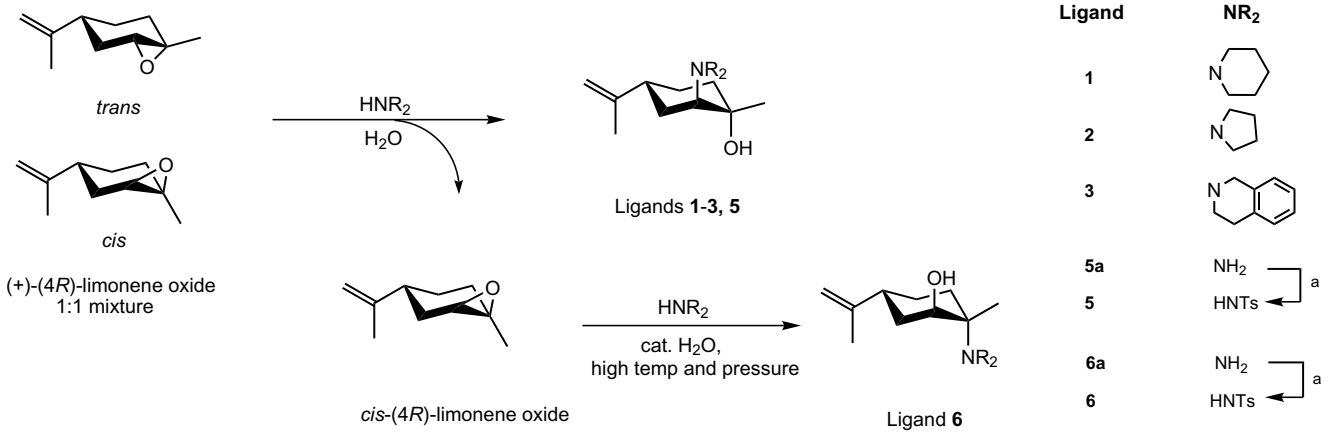


Figure 1. β-amino alcohols used in this study.

amine under high temperature and pressure (sealed tube) in the presence of a catalytic amount of water. Epoxide ring opening of the *cis*-diastereomer provides amino alcohols where the amine is attached to the more hindered C-1 carbon atom (Fig. 1). Subsequent *N*-tosylation of amino alcohol **6a** provides ligand **6**. The synthesis of ligands **4** and **7** takes place in the described procedure by starting with the 1:1 cis/trans mixture of (−)-(*S*)-limonene oxide. Ligand **4** was prepared by selective reaction of the *trans*-diastereomer with morpholine and a catalytic amount of water.[3a] The recovered *cis*-(*S*)-limonene oxide can then be used to prepare ligand **7** by reflux with pyrrolidine and a catalytic amount of water.

Ligand **8** can be prepared in a straightforward manner[6] starting with the epoxidation of (+)-3-carene with MCPBA. This reaction occurs exclusively on the face opposite to the cyclopropyl ring to afford the epoxide,[7] which on reaction with morpholine provides ligand **8** as a white solid in good yield (66%).[6] Ligand **9** was easily synthesized from (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol and 2-bromoethyl ether with Et_3N in DMSO (25 °C),[8] and obtained in a good yield (70%) after recrystallization from hot toluene. We decided to include this ligand in our study of alkynylzinc additions to aldehydes for comparison with our terpene-based amino alcohols.

An initial study was done to determine the best reaction conditions using 10 mol % of ligand (1*S*,2*S*,4*R*)-**1** as catalyst in the addition reaction of phenylacetylene with benzaldehyde at 25 °C (Table 1). We used a mixture of toluene–THF (3:1) as a solvent, which has been reported previously as the optimal solvent system to suppress alkyl addition[2n] to aldehydes (Scheme 2). Increasing the amount of ligand to 20 mol % did not have any beneficial effect (Table 1, entries 1 and 2), therefore we decided to use 10 mol % of the ligand for our subsequent reactions. We observed a 5% increase in enantioselectivity when this reaction was carried out at 0 °C (Table 1, entries 1 and 3).



Scheme 1. Synthesis of ligands **1**–**3**, **5**, and **6** from (+)-(4*R*)-limonene oxide. Reagents and conditions: (a) TsCl, THF, 1M KOH, 0 °C to rt, 5 h.

Table 1. Determination of reaction conditions using ligand **1**[a]

Entry	Catalyst (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)	Ee[c] (%)
1	10	25	12	99	21 (*S*)
2	20	25	12	99	19 (*S*)
3	10	0	12	91	26 (*S*)
4	10	−78 to rt	12	99	27 (*S*)
5	10	−20	12	58	36 (*S*)
6	10	−20	24	73	40 (*S*)
7	5	−20	24	83	26 (*S*)

[a] Reactions were carried out following the general procedure in Section 4.
[b] % Conversion.
[c] Assigned by analogy with literature values[2o] using an HPLC analysis of crude reaction mixture on a Chiralcel OD column.

Table 2. Ligand study: alkynylation of benzaldehyde with phenylacetylene in the presence of ligands **1**–**9**

Entry	Ligand	Yield[a] (%)	Ee[b] (%)
1	**1**	73	40 (*S*)
2	**2**	86	14 (*S*)
3	**3**	69	31 (*S*)
4	**4**	81	34 (*R*)
5	**5**	71	36 (*R*)
6	**6**	80	35 (*R*)
7	**7**	99	47 (*S*)
8	**8**	51	24 (*S*)
9	**9**	98	55 (*S*)

[a] All reactions used a catalyst loading of 10 mol %.
[b] Absolute configuration assigned by comparison with known compound and known elution order from a Chiralcel OD column.

Some reports have shown that a significant increase in asymmetric induction can be achieved by using even lower temperatures.[2o] Using an acetone/dry ice bath for cooling and allowing the reaction mixture to warm (from −78 °C) to room temperature (25 °C) over 12 h gave an induction of 27% ee, very similar to the induction obtained at 0 °C (Table 1, entries 2 and 4). This caused us to speculate an optimal temperature for reaction conditions may exist somewhere between −78 and 0 °C. The range of −30 to −20 °C is often reported to be the optimal range for organozinc additions to aldehydes.[2k] Consequently, we studied this reaction at −20 °C using a constant temperature cryobath. Decreasing the temperature led to an increase in induction to 36% ee after 12 h, while the same reaction after 24 h showed a slightly improved induction of 40% ee. We decided to screen the remainder of the ligands under these conditions. The induction decreased to 26 mol % (Table 1, entry 7) when the catalyst loading was changed to 5 mol %.

The results obtained from ligands **1** to **9** are summarized in Table 2. Ligand **2**, which has a pyrrolidine ring at a secondary carbon atom, gave a low asymmetric induction of 14% ee for the (*S*)-enantiomer product (Table 2, entry 2). The regioisomer of this amino alcohol, with the pyrrolidine ring attached to the tertiary carbon, showed a promising induction of 47% ee of the (*S*)-enantiomer (Table 2, entry 7). The 1,2-diphenylethanol derived ligand **9** provided an induction of 55% ee under the experimental conditions. The carene based ligand **8** (Table 2, entry 8) showed a lower induction of 24% ee, probably due to the amino group attached to the secondary carbon atom.

Based on the Noyori transition state model for the amino alcohol catalyzed asymmetric diethyl zinc addition to aldehydes,[9] we propose a transition state model for our alkynyl zinc addition using limonene amino alcohol **7** (Fig. 2). The facial selectivity observed is controlled by the amine moiety and the C(1) methyl group. The initial reaction of diethyl zinc with the hydroxyl group resulted in a zinc ion that is coordinated to the amine lone pair to form a diequatorially oriented five-membered

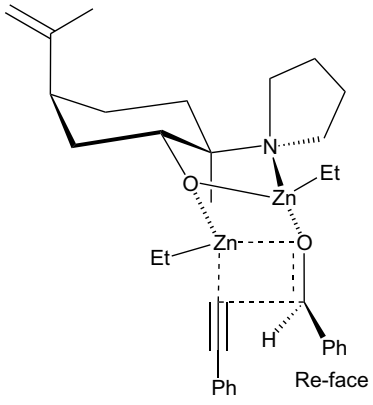
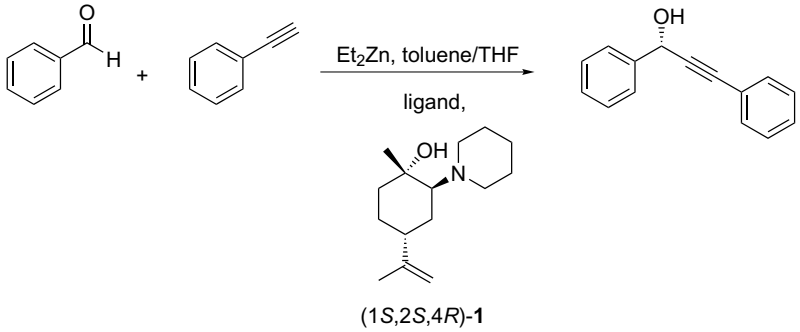
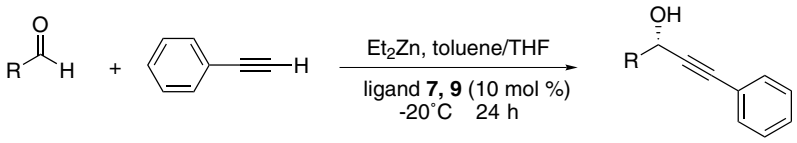


Figure 2. Facial selectivity of phenylacetylene addition to benzaldehyde with limonene amino alcohol **7**.

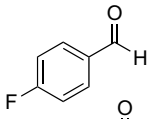
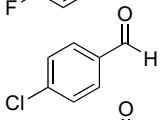
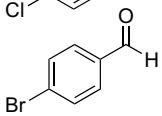
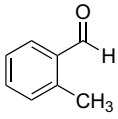
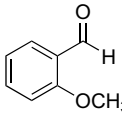
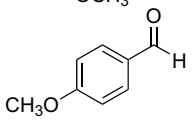
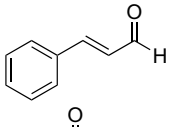
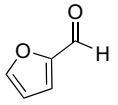
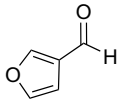
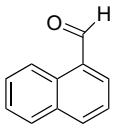
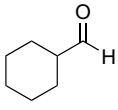


Scheme 2. Enantioselective alkynylation using (1*S*,2*S*,4*R*)-1-methyl-4-(1-methylethenyl)-2-(1-piperidinyl)cyclohexanol.



Scheme 3. Alkynylation of aldehydes with phenylacetylene.

Table 3. Asymmetric alkynylation of aldehydes with phenylacetylene catalyzed by chiral ligands **7** and **9**

Entry	Aldehyde	Ligand **7**		Ligand **9**	
		Conv. (%)	Ee (%)	Conv. (%)	Ee (%)
1		72	37 (*S*)	79	60 (*S*)
2		67	33 (*S*)	51	60 (*S*)
3		71	33 (*S*)	73	61 (*S*)
4		70	47 (*S*)	67	55 (*S*)
5		70	37 (*S*)	70	69 (*S*)
6		47	36 (*S*)	73	60 (*S*)
7		80	52 (*S*)	70	49 (*S*)
8		85	34 (*S*)	90	30 (*S*)
9		86	41 (*S*)	95	45 (*S*)
10		68	44 (*S*)	73	55 (*S*)
11		72	18 (*S*)	70	20 (*S*)
12		70	10 (*S*)	69	10 (*S*)
13		79	60 (*S*)	80	50 (*S*)

heterocyclic ring. In this conformation, both the isopropenyl- and amino-groups hinder the coordination of the aldehyde to the catalyst in such a way that only the *re*-face is available for the addition of the alkynyl group. This results in propargylic alcohols having an (*S*)-configuration.

Since ligands **7** and **9** provided the most promising results, we used these ligands to check the trend of the asymmetric induction in the reaction of phenylacetylene with a series of aromatic and aliphatic aldehydes under our optimal conditions (Scheme 3, Table 3). The results revealed that the limonene based ligand **7** provided moderate enantioselectivities for various aromatic aldehydes, including benzaldehydes substituted at the *ortho*-, *para*-, and *meta*-positions (Table 3, entries 1–5). No significant change in enantiomeric excess was noted within the *para*-substituted halogenated benzaldehydes. A slightly higher asymmetric induction was noted for the methyl electron donating group at the *ortho*-position with 47% ee (entry 4) compared to the other substituted benzaldehydes. However, induction decreased by 10% for the *ortho*- and *para*-methoxybenzaldehydes. The α,β-unsaturated *trans*-cinnamaldehyde provided one of the better inductions with 52% ee and an 80% conversion. Isobutyraldehyde (entry 11) provided a low induction of 18% ee, and as the steric bulk at the α-position increased in trimethylacetaldehyde, the asymmetric induction was observed to decrease to 10% ee. These results do not show a clear correlation between asymmetric induction and the effects of electron withdrawing or electron donating groups.

In comparison, ligand **9** showed increased induction over ligand **7** between substrates from a 2% ee difference (entry 11) up to a 32% ee difference for *ortho*-methoxybenzaldehyde (entry 5). In several cases, ligand **7** provided better asymmetric induction over ligand **9** (entries 7, 8, and 13). The best asymmetric induction for the limonene derived amino alcohol **7** was 60% ee by using cyclohexanecarboxaldehyde as a substrate (entry 13).

3. Conclusion

The development of new or improved methods for the preparation of chiral propargylic alcohols is important due to their significance as useful building blocks and intermediates for the synthesis of unique and biologically active molecules. Our simple catalytic system is developed from inexpensive, naturally occurring terpene substrates. The homochiral limonene derived amino alcohol (1*R*,2*R*,5*S*)-2-methyl-5-(1-methylethenyl)-2-(1-

pyrrolidinyl)cyclohexanol **7** was found to promote the enantioselective alkynylation of aldehydes to provide chiral propargylic alcohols in good yields and moderate enantiomeric excesses. Our system is comparable to the existing amino alcohol ligand systems for alkynyl additions using a terminal alkyne and diethylzinc. Even though the maximum asymmetric induction obtained was 60%, these results are important in developing a terpene amino alcohol system of maximum efficiency for catalytic reactions. Currently we are working on developing more efficient amino alcohols for alkynylzinc additions to aldehydes.

4. Experimental

All reactions were carried out in oven-dried glassware under an inert atmosphere of argon. Reagents were used as received from the Aldrich Chemical company. Phenylacetylene was obtained from Acros chemicals. Tetrahydrofuran was distilled over sodium under nitrogen. All the solvents were stored over 4 Å molecular sieves. The NMR spectra were recorded on a Bruker system (250 MHz for ^{1}H, 62.5 MHz for ^{13}C). Optical rotations were recorded on a Jasco DIP-371 polarimeter. Enantiomeric excess of the crude reaction mixture was determined by HPLC analysis carried out with the Beckman System Gold HPLC system by using a Daicel Chiralcel OD column. Elution took place with 10% *i*-PrOH in hexanes at 1.0 mL/min unless otherwise indicated, and detection was at 254 nm. Crude products were compared to a prepared racemic mixture of appropriate propargylic alcohol and were also compared with literature references.

4.1. Procedure for the preparation of amino alcohols

4.1.1. (1*S*,2*S*,4*R*)-2-Amino-1-methyl-4-(1-methylethenyl)cyclohexanol 4-toluenesulfonamide 5. A 250 mL three necked flask equipped with a magnetic stirring bar, a thermometer, a nitrogen bubbler, and a rubber septum was charged with 2.00 g (11.8 mmol) of (1*S*,2*S*,4*R*)-2-amino-1-methyl-4-(1-methylethenyl)cyclohexanol **5a** and 40 mL of tetrahydrofuran. The resulting solution was cooled with an ice bath and 2.48 g (13 mmol) of 4-toluenesulfonyl chloride was added. To the cooled reaction mixture, 17 mL (17 mmol) of 1 M potassium hydroxide was added. The ice bath was removed and the reaction mixture allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with 100 mL of deionized water. The diluted reaction mixture was transferred to a separatory funnel and extracted with three 100 mL portions of diethyl ether. The combined ether extracts were dried over anhydrous magnesium sulfate. After filtration, the ether was removed by rotoevaporation to give 3.60 g of colorless oil. The oil was mixed with 40 mL of *n*-heptane. The mixture was warmed on a steam bath, and ethyl acetate slowly added until a solution formed. The solution was cooled, with stirring, to room temperature and a small additional amount of ethyl acetate was added and the mixture was allowed to stir overnight. The solution was diluted with a small amount of *n*-heptane and cooled on an ice bath. A slurry of white solid was formed. The solid was isolated by filtration, washed with *n*-heptane, air dried, and vacuum dried to give 1.90 g of (1*S*,2*S*,4*R*)-2-amino-1-methyl-4(1-methylethenyl)cyclohexanol 4-toluenesulfonamide as a white solid. Mp 116.5–117 °C. $[\alpha]_D^{28} = +36.4$ (*c* 2.0, methanol); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.18$ (s, 3H), 1.21–1.52 (m, 5H), 1.56 (s, 3H), 1.61–1.82 (m, 1H), 1.94 (m, 1H), 2.43 (s, 3H), 3.23 (m, 1H), 4.54 (s, 1H), 4.68 (s, 1H), 7.30 (d, $J = 8$ Hz, 2H), 7.77 (d, $J = 8$ Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 21.2$, 21.6, 25.4, 26.0, 26.1, 31.8, 34.5, 38.1, 57.6, 71.1, 109.8, 127.2, 129.8, 130.0, 137.5.

4.1.2. (1*S*,2*S*,5*R*)-2-Amino-2-methyl-5-(1-methylethenyl)cyclohexanol 4-toluenesulfonamide 6. A 25 mL flask was charged with (1*S*,2*S*,5*R*)-2-amino-2-methyl-5-(1-methylethenyl)cyclohexanol **6a** (3 mmol, 0.507 g), triethylamine (4.5 mmol, 0.63 mL), and dichloromethane (10 mL), cooled to 0 °C, followed by the dropwise addition of 4-toluenesulfonyl chloride (3.75 mmol, 0.70 mL in 3 mL dichloromethane). The solution was allowed to warm to room temperature and then concentrated by rotoevaporation. The concentrate was then dissolved in the minimum amount dichloromethane, and filtered. Ethyl acetate was then added and the solution filtered. The filtrate was concentrated and purified on silica gel (4:1 hexanes–ethyl acetate) leaving 0.639 g (66% yield) of **6** as a white solid. Mp = 119 °C. $[\alpha]_D^{25} = +11.9$ (*c* 4.0, chloroform). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.18$ (s, 3H), 1.24–1.62 (m, 5H), 1.67 (s, 3H), 1.72–1.87 (m, 1H), 2.17–2.33 (m, 1H), 2.42 (s, 3H), 3.97 (t, $J = 2.5$ Hz, 1H), 4.65 (s, 1H), 4.73 (s, 1H), 7.29 (d, $J = 8.25$, 2H), 7.77 (d, $J = 8.25$ Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 21.1$, 21.4, 22.4, 25.4, 32.7, 32.9, 37.0, 59.1, 71.3, 109.3, 126.8, 129.5, 140.4, 143.0, 148.3.

4.1.3. (1*R*,2*R*,5*S*)-2-Methyl-5-(1-methylethenyl)-2-(1-pyrrolidino)cyclohexanol 7. A 100 mL single-necked flask equipped with a magnetic stirring bar and a reflux condenser fitted with a nitrogen bubbler was charged with *cis*-(*S*)-(−)-limonene oxide (7.20 g, 0.05 mol), pyrrolidine (50 mL), and deionized water (2 mL). The mixture was heated to reflux and held there for 18 h. The condenser was replaced with a short-path distillation head (equipped with a Vigreux column) and the excess pyrrolidine distilled off at atmospheric pressure. The residue was transferred to a separatory funnel and mixed with diethyl ether (50 mL) and deionized water (50 mL). The aqueous layer was made strongly acidic with 12 M hydrochloric acid and the layers separated. The aqueous layer was extracted with diethyl ether (2×50 mL). The aqueous layer was made strongly basic with 50% sodium hydroxide and extracted with diethyl ether (3×50 mL). The combined organic layers were washed with deionized water (50 mL), dried over anhydrous magnesium sulfate, and evaporated leaving a pale orange oil that rapidly crystallized. The solid was recrystallized from *n*-heptane to give 3.74 g (0.018 mol) of the title compound as white needles. Mp 75.5–76.5 °C; $[\alpha]_D^{23} = -29.8$ (*c* 4.0, methanol); ^{1}H NMR (250 MHz,

DMSO): δ = 0.87 (s, 3H), 1.39–1.78 (m, 11H), 2.05 (m, 2H), 2.24 (m, 1H), 2.44–2.51 (m, 4H), 3.65 (s, 1H), 4.63 (s, 2H); ^{13}C NMR (62.5 MHz, DMSO): δ = 13.3, 21.3, 24.0, 25.8, 31.6, 33.3, 37.3, 44.2, 56.9, 70.3, 108.4, 150.9.

4.2. Typical procedure for the preparation of racemic propargylic alcohols

All the racemic propargylic alcohols used for the HPLC analyses were prepared according to the following procedure unless otherwise indicated. Under argon, *n*-BuLi in hexanes (1.6 M, 0.95 mmol, 0.6 mL) was added into a solution of the alkyne (1.0 mmol) in tetrahydrofuran (3 mL) in a 25 mL round bottomed flask over an ice bath. After the mixture was stirred for 3 h, an aldehyde (0.9 mmol) was added and stirring continued for 8 h. The reaction was quenched with ice and extracted with methylene chloride. The extract was dried over magnesium sulfate. After rotoevaporation, the residue was passed through a short silica gel plug to afford the desired product.

4.3. Typical procedure for the catalytic asymmetric alkynylation reactions

Phenylacetylene (2.4 mmol) was added into a 25 mL two-necked round bottomed flask containing 0.75 mL dry THF at rt under Ar. The stirred mixture was then cooled to −20 °C for 5 min, followed by the addition of a 1.1 M solution of diethylzinc in toluene (2.2 mmol). The resulting solution was stirred at −20 °C for 15 min, and the ligand (0.2 mmol, 10 mol %) was added. The homogenous solution was stirred at −20 °C for 15 min, and the aldehyde (2.0 mmol) added via syringe. The resulting mixture was stirred at −20 °C for 24 h. When the reaction was complete, it was quenched by the addition of MeOH (2 mL) at −20 °C, and as it warmed to 0 °C, satd NH_4Cl (4 mL) was added. EtOAc (50 mL) and satd NH_4Cl (10 mL) were then added and the layers separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine and dried with anhydrous magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 9/1 Hex/EtOAc) to afford the pure product. The enantiomeric excess was determined by HPLC analysis of the reaction mixture on a Daicel Chiralcel OD column.

4.3.1. (*S*)-1,3-Diphenylprop-2-yn-1-ol.[2o] 99% Conv., 47% ee determined by HPLC analysis. Retention time: t_{minor} = 9.7 min and t_{major} = 18.3 min.

4.3.2. (*S*)-1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-ol.[2e] 72% Conv., 37% ee determined by HPLC analysis (5% *i*-PrOH in hexanes). Retention time: t_{minor} = 13.7 min and t_{major} = 48.7 min.

4.3.3. (*S*)-1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol.[2e] 67% Conv., 33% ee determined by HPLC analysis. Retention time: t_{minor} = 9.4 min and t_{major} = 27.2 min.

4.3.4. (*S*)-1-(4-Bromophenyl)-3-phenylprop-2-yn-1-ol.[2e] 71% Conv., 33% ee determined by HPLC analysis. Retention time: t_{minor} = 8.9 min and t_{major} = 27.7 min.

4.3.5. (*S*)-1-(2-Methylphenyl)-3-phenylprop-2-yn-1-ol.[2j] 70% Conv., 47% ee determined by HPLC analysis. Retention time: t_{minor} = 9.5 min and t_{major} = 21.2 min.

4.3.6. (*S*)-1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-ol.[2e] 70% Conv., 37% ee determined by HPLC analysis. Retention time: t_{minor} = 14.0 min and t_{major} = 17.5 min.

4.3.7. (*S*)-1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-ol.[2e] 47% Conv., 36% ee determined by HPLC analysis. Retention time: t_{minor} = 12.5 min and t_{major} = 28.2 min.

4.3.8. (*S*)-(*E*)-1,5-Diphenylpent-1-en-4-yn-3-ol.[2p] 80% Conv., 52% ee determined by HPLC analysis. Retention time: t_{minor} = 16.0 min and t_{major} = 45.6 min.

4.3.9. (*S*)-1-(Furan-2-yl)-3-phenylprop-2-yn-1-ol.[2r] 85% Conv., 34% ee determined by HPLC analysis. Retention time: t_{minor} = 9.2 min and t_{major} = 16.5 min.

4.3.10. (*S*)-1-(Furan-3-yl)-3-phenylprop-2-yn-1-ol.[2r] 86% Conv., 41% ee determined by HPLC analysis. Retention time: t_{minor} = 8.7 min and t_{major} = 21.4 min.

4.3.11. (*S*)-1-(1-Naphthyl)-3-phenylprop-2-yn-1-ol.[2j] 68% Conv., 44% ee determined by HPLC analysis. Retention time: t_{minor} = 17.7 min and t_{major} = 31.4 min.

4.3.12. (*S*)-4-Methyl-1-phenylpent-1-yn-3-ol.[2m] 72% Conv., 18% ee determined by HPLC analysis. Retention time: t_{minor} = 11.1 min and t_{major} = 27.8 min.

4.3.13. (*S*)-4,4-Dimethyl-1-phenylpent-1-yn-3-ol.[2m] 70% Conv., 10% ee determined by HPLC analysis. Retention time: t_{minor} = 5.8 min and t_{major} = 7.6 min.

4.3.14. (*S*)-1-Cyclohexyl-3-phenylprop-2-yn-1-ol.[2q] 79% Conv., 60% ee determined by HPLC analysis. Retention time: t_{minor} = 5.7 min and t_{major} = 11.7 min.

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