Enantioselective Alkynylation of Aromatic Aldehydes Catalyzed by Readily Available Chiral Amino Alcohol-Based Ligands

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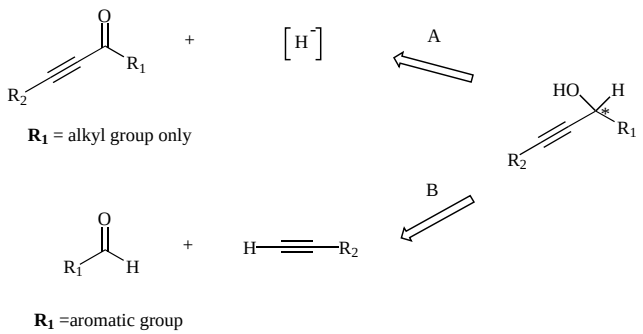
Abstract: The asymmetric alkynylation reaction catalyzed by amino alcohol derived ligands (1*R*,2*S*)-**3** or (1*S*,2*R*)-**4** with dimethylzinc provides a simple and practical method to make chiral propargylic alcohols, and it is complementary to the asymmetric reduction methods. In the presence of 10 mol% (1*R*,2S)-**3** or (1*S*,2*R*)-**4,** a variety of aromatic aldehydes were converted to the corresponding chiral propargylic alcohols with very good enantioselectivities and yields. This one-pot asymmetric reaction is carried out under mild reaction conditions. Neither strong base nor transmetallation is required. It is an efficient reaction, greatly accelerated by the added chiral ligand. Preliminary mechanistic and NMR studies have also been carried out.

Key words: catalytic, asymmetric alkynylation, amino alcohol, propargylic alcohols, dimethylzinc

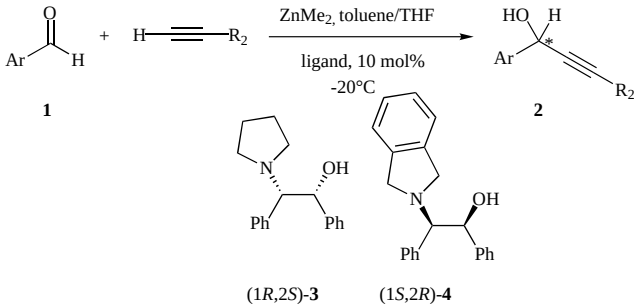
Chiral propargylic alcohols are useful building blocks for the enantioselective synthesis of complex molecules.[1] A powerful approach to these compounds involves the asymmetric reduction of α,β-ynones (approach A, Scheme 1) via either the catalytic asymmetric hydroboration[2] or transition metal catalyzed transfer hydrogenation.[3] While excellent yields and enantioselectivities are obtained for the alkyl substituted propargylic alcohols (R_1 = alkyl), there has been no report of reduction of the corresponding aromatic α,β-ynones (R_1 = Ar) by these methods. A complementary approach to these compounds involves the asymmetric addition of alkynes to aromatic aldehydes (approach B, Scheme 1).



Scheme 1

However, unlike the catalytic enantioselective addition of dialkyl-[4] and alkenylzinc[5] compounds to aldehydes where considerable progress has been made, the current methods for enantioselective alkynylation reactions are far from ideal.[6–8] Some suffer from the use of substoichiometric to stoichiometric amounts of ligands or catalysts, others from either moderate enantioselectivities or the formation of considerable amounts of byproducts (alkylated products).

Our research led us to the discovery of a practical and efficient enantioselective method for the alkynylation of aromatic aldehydes with both aromatic and aliphatic acetylene substrates catalyzed by readily available chiral ligands derived from commercially available amino alcohols. We have also devised the method to suppress the alkyl addition to the aldehydes.

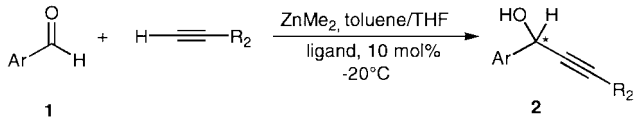


Scheme 2

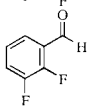
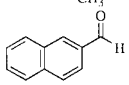
A typical procedure (Scheme 2) involves the addition of dimethylzinc (1.1–1.2 equiv) in toluene to a solution of the alkyne (1.2 equiv) in THF at –20 °C. The chiral ligand (0.1 equiv) is added as a solid under nitrogen atmosphere after 15 minutes, and after another 15 minutes, the arylaldehyde (1 equiv) is added. The reactions are generally complete in 18–25 hours at –20 °C to –30 °C. An array of aromatic aldehydes has been studied under these conditions, and the representative results are summarized in Table 1. As illustrated in Table 1, the corresponding chiral propargylic alcohols **2** were formed in very good yields and good enantioselectivities. Most of the substituted arylaldehydes underwent the addition reaction with higher levels of enantioselectivity compared with the parent benzaldehyde. Comparison of entries **1d** and **1i** suggests, that for sterically similar substrates, electronic properties have an effect on the enantioselectivity of the addition. The results from entries **1f**, **1g** demonstrate that this chemistry is applicable to both aromatic and aliphatic acetylenes. Stud-

ies have also been carried out with disubstituted aldehydes, such as 2,3-difluorobenzaldehyde (entry **1c**), which provided similar results with their corresponding mono-substituted aldehydes.

Table 1 Asymmetric Alkynylation of Aldehydes Catalyzed by (1*R*,2*S*)-**3** and (1*S*,2*R*)-**4** with Dimethylzinc[a]

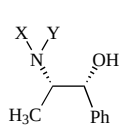


1 2

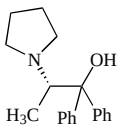
Entry	Aldehyde	R_2	Ligand	ee (%)[b]	Yield (%)[d]
1a		Ph	(1*R*,2*S*)-**3**	68(–)(*S*)[c]	70
1b		Ph	(1*S*,2*R*)-**4**	82(–)	90
1c		Ph	(1*S*,2*R*)-**4**	81(+)	94
1d		Ph	(1*R*,2*S*)-**3**	80(+)	77
1e		Ph	(1*R*,2*S*)-**3**	80(+)	77
1f		Ph	(1*R*,2*S*)-**3**	76(+)	81
1g		C_3H_7	(1*R*,2*S*)-**3**	85(+)	67
1h		Ph	(1*R*,2*S*)-**3**	82(+)	74
1i		Ph	(1*R*,2*S*)-**3**	62(+)	65
1j		Ph	(1*S*,2*R*)-**4**	75(–)	87

[a] Reactions were carried out at -20 ºC to –30 °C with 10 mol % ligand **3** or **4** following the general procedure.
[b] The enantioselectivities were determined by HPLC analysis of crude reaction mixture using chiral columns. The sign of rotation of the predominant enantiomer is indicated in parentheses.
[c] The absolute configuration is based on measurement of the optical rotation and comparison with the literature. See: 7b and Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem*. **1992**, *57*, 2379.
[d] Isolated yield of the corresponding propargylic alcohols.

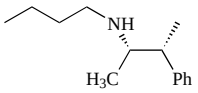
The efficiency of the catalytic asymmetric alkynylation reaction relies on the use of appropriate chiral ligands. A series of chiral ligands, which included multidentate,[9] tridentate and bidentate ligands,[10] was explored for the catalysis of the alkynylation of 2-chlorobenzaldehyde with phenylacetylene at 0 ºC. Among them only the amino alcohol derived bidentate ligands with tertiary substituted amino groups[6,11](e.g. **3–7**) provided promising results as shown in Table 2. It is interesting to note that ligands with a secondary amino group, such as ligand **8**, were ineffective for the asymmetric alkynylation reaction, presumably due to the strong chelation of the NH moiety with the zinc reagent. Encouraging results were obtained with (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine (ligand **6**). Further modification of ligand **6** led to the development of ligands **3**[12] and **4**, which catalyzed the alkynylation reaction with the best results in terms of both enantioselectivity and reactivity. Ligands **3** and **4** can easily be prepared by the *N*-alkylation of the commercially available chiral 2-amino-1,2-diphenylethanol with the corresponding dibromo reagents.



5. X = Y = *n*Bu (1*R*,2*S*)
6. X, Y = -$(CH_2)_4$- (1*R*,2*S*)

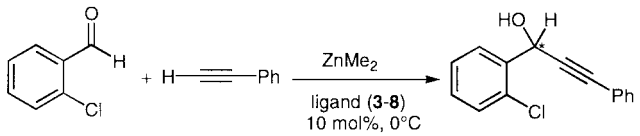


(*S*)-**7**



(1*R*,2*S*)-**8**

Table 2 Ligand Study: Alkynylation of 2-Chlorobenzaldehyde with Phenylacetylene in the Presence of Ligands **3**–**8**[a]



Ligand	**3**	**4**	**5**	**6**	**7**	**8**
Ee (%)[b]	71	72	57	67	21	2
Conv. (%)[c]	95	97	88	96	50	58

[a] Reactions were carried out at 0 ºC with 10 mol % ligands following the general procedure described in the experimental section.
[b] Determined by HPLC analysis of crude reaction mixture using Chiral Cell OD-H column (10% IPA/hexane).
[c] Determined by HPLC analysis of crude reaction mixture. In all cases, no products other than the propargylic alcohols were detected.

A major challenge in the catalytic alkynylations with dialkylzinc reagents is to suppress or eliminate the undesired transfer of the alkyl group, which was introduced by the zinc reagent, to aldehydes. As reported in the literature,[4] dialkylzincs are powerful regents for the transfer of the alkyl groups to aldehydes. Indeed, alkylation of the aldehydes has been reported as a major side reaction in the organozinc mediated enantioselective alkynylation reactions in the literature.[8b] In our system, when the asymmetric alkynylation reaction was carried out in toluene, the corresponding α-methylaryl alcohol was obtained as a byproduct in 5–12% yield. We were pleased to discover that the use of 2.75/1 toluene/THF[13] totally eliminated or

greatly suppressed the methyl addition. In our optimized conditions, the chiral propargylic acids were obtained as the only product in all entries except in entry **1f** where 2–3 % of the α-methylaryl alcohol was detected in the NMR of the crude reaction mixture.

A preliminary mechanistic study of the system was carried out. Examination of the alkynylation reaction using ligands of varying enantiomeric compositions provided evidence that the intermediates involved are not monomeric.[14] As demonstrated in the Figure, a nonlinear correlation between ligand ee and product ee was observed for the dimethylzinc mediated alkynylation of 2-fluorobenzaldehyde with phenylacetylene at –20 ºC catalyzed by 10 mol% of ligand (1*R*,2*S*)-**3**.

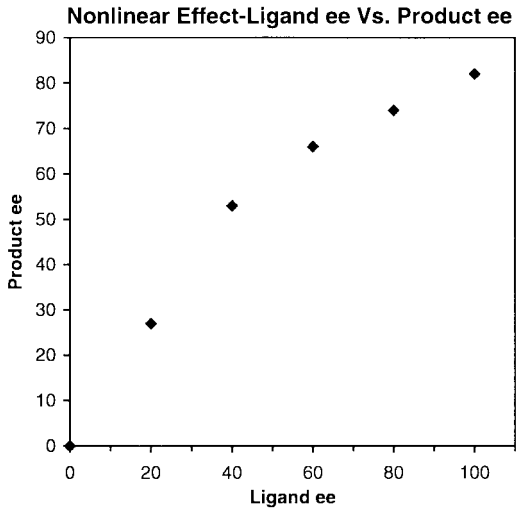


Figure Plot of ee of the propargylic alcohol as a function of ee of ligand **3** in the dimethylzinc mediated enantioselective alkynylation of 2-fluorobenzaldehyde with phenylacetylene in the presence of 10 mol% ligand **3** at –20 ºC. The enantioselectivities were determined by HPLC analysis of crude reaction mixtures using Chiralcell OD-H column (10% IPA in hexane).

An NMR study of the reaction revealed some further mechanistic insights. When dimethylzinc was added to the solution of phenylacetylene in the absence of ligand, ^{1}H and ^{13}C NMR spectra of the mixture exhibited only the independent signals of each compound. In particular, the chemical shift of the triple bond in phenylacetylene still remained at its original positions (79.1 and 84.4 ppm) in the ^{13}C NMR spectra. Thus, no interaction between dimethylzinc and phenylacetylene was observed at this point. As the ligand (1*R*,2*S*)-**3** was added to the mixture, the formation of new species were observed in both ^{1}H and ^{13}C NMR. A lowfield shift of the triple bond resonances from 79.1 and 84.4 ppm to 107.8 and 114.1 ppm respectively in the ^{13}C NMR spectrum indicated the zinc-acetylide formation. The NMR study suggests that as the electronic and steric properties around zinc were changed with the addition of the ligand, substitution of the methyl group with an acetylene group became possible. Therefore, it is reasonable to postulate that there is no formation of the methyl (alkynyl) zinc species before the addition of the ligand. In the presence of the ligand, a complex involving zinc, the alkynyl group and the ligand is formed; this complex is responsible for the transfer of the alkynyl group to the aldehyde. Thus it is not surprising to find that the catalytic asymmetric alkynylation reaction described above is accelerated to a significant extent by the added ligand. In the presence of 10 mol% ligand (1*R*,2*S*)-**3**, the dimethylzinc mediated addition of phenylacetylene to 2-chlorobenzenealdehyde was completed in 3 hours at 0ºC. By comparison, in the absence of the chiral ligand, the reaction proceeded to 30% conversion in 17 hours at 0ºC to room temperature. Ligand acceleration is an important phenomenon, and has been identified in several other asymmetric catalytic reactions.[15]

The asymmetric alkynylation reaction catalyzed by amino alcohol derived ligand (1*R*,2*S*)-**3** or (1*S*,2*R*)-**4** outlined above provides a simple and practical method to make chiral propargylic alcohols, and it is complementary to the asymmetric reduction methods. This one-pot asymmetric reaction is carried out under mild reaction conditions. Neither strong base nor transmetallation is required. It is also an efficient reaction, greatly accelerated by the added catalytic amount of chiral ligand. Our NMR studies illustrate, for the first time, the ligand's role in the formation of chiral zinc-acetylide species. Applications of the catalyst system to other enantioselective reactions are in progress.

Reagents are used as received unless otherwise stated. 3Å molecular sieves were used to dry solvents for the alkynylation reaction. Unless otherwise noted, all manipulations were carried out under an inert atmosphere of N_2. The glassware was oven dried prior to use for the alkynylation reactions. Flash column chromatography was performed using silica gel (EM Science, Silica gel 60, 230–400 mesh ASTM). Dimethylzinc was obtained from Aldrich as a 2M solution in toluene, and was used as it was. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm; coupling constants are reported in Hz. ^{1}H and ^{13}C NMR were recorded on Bruker 300 AM. IR spectra were recorded on a Nicolet 510P FT-IR Spectrometer. Elemental analyses were obtained from Quantitative Technologies Inc, Whitehouse, NJ.

(–)-1,3-Diphenylprop-2-yn-1-ol (2a)[7a]

The typical procedure for **2c** was followed. The compound was purified by flash chromatography (silica gel) by elution with 8% EtOAc/hexane. The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Chiralcel OD-H column (20% IPA/hexane).

IR (nujol gel): ν = 3365, 3062, 3031, 2198, 1597, 1453, 1031, 756 cm^{-1};

^{1}NMR ($CDCl_3$, 300 MHz): δ = 7.66 (m, 2 H, ArH), 7.52–7.48 (m, 2 H, ArH), 7.46–7.32 (m, 6 H, ArH), 5.71 (d, *J* = 6.1 Hz, 1 H), 2.50 (d, *J* = 6.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.7, 131.8, 128.7, 128.6, 128.5, 128.4, 126.8, 122.5, 88.8, 86.7, 65.2.

Anal Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81; O, 7.68. Found: C, 86.83; H, 5.82; O, 8.08.

(–)-1-(2-Fluorophenyl)-3-phenylprop-2-yn-1-ol (2b)[16]
The typical procedure for **2c** was followed. The compound was purified by flash chromatography (silica gel) by gradient elution with 4% EtOAc/hexane (250 mL) and then 8% EtOAc/hexane (500 mL). The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Chiralcel OD-H column (10% IPA/hexane).

IR (nujol gel): ν = 3336, 2923, 2853, 2230, 1588, 1377, 1224, 754, 690 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.75 (td, J_1 = 7.5 Hz, J_2 = 1.7 Hz, 1 H, ArH), 7.50–7.47 (m, 2 H, ArH), 7.36–7.32 (m, 4 H, ArH), 7.23–7.18 (m, 1 H, ArH), 7.14–7.07 (m, 1 H, ArH), 5.98 (s, 1 H), 2.38 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 160.3 (d, J_{CF} = 248.5), 131.8, 131.1 (d, J_{CF} = 8.3), 128.8, 128.5 (d, J_{CF} = 3.3), 128.4, 127.9 (d, J_{CF} = 13), 124.5 (d, J_{CF} = 3.4), 122.3, 115.8 (d, J_{CF} = 21.6), 87.6, 86.6, 59.6 (d, J_{CF} =4.7).

Anal. Calcd for $C_{15}H_{11}FO$: C, 79.63; H, 4.90; F, 8.40. Found: C, 79.67; H, 4.85; F, 8.19

Asymmetric Alkynylation Reactions. (+)-1-(2,3-Difluorophenyl)-3-phenylprop-2-yn-1-ol (2c); Typical Procedure
Phenylacetylene (285.6 µL, 2.6 mmol) was added via a gas tight syringe to a 15 mL two-neck round bottom flask containing 0.4 mL sieve-dried THF at r.t. under N_2. The stirred mixture was then cooled to –20 ºC for 5 minutes, followed by the addition of dimethylzinc in toluene 2M (1.2 mL, 2.4 mmol). The resulting solution was stirred at –20 ºC for 15 min, and ligand (1*S*,2*R*)-**4** (63.08 mg, 0.2 mmol) was added as a solid under N_2. The homogenous solution was stirred at –20 ºC for 15 min, and then 2,3-difluorobenzaldehyde (**1c**) (284.2 mg, 2.0 mmol) was added via a syringe. The resulting mixture was stirred at –20 ºC as reaction progress was monitored by HPLC. When the reaction was complete (98% conversion, 18 h), it was quenched by the addition of MeOH (1 mL) at –20 ºC, and as it warmed to 0 ºC, sat. NH_4Cl (2 mL) was added. EtOAc (50 mL) and sat. NH_4Cl (10 mL) were then added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 10/1 hexane/EtOAc) to afford 460.8 mg (94% yield, 81% ee) pure product. The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Chiralcel OD-H column (5–10% IPA/hexane).

IR (nujol gel): ν = 3270, 2923, 2853, 2270, 1376, 1272, 755 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.53–7.46 (m, 3 H, ArH), 7.45–7.29 (m, 3 H, ArH), 7.22–7.10 (m, 2 H, ArH), 5.98 (s, 1 H), 2.30 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.5 (dd, J_{1CF} = 261.2 Hz, J_{2CF} = 12.7 Hz), 148.4 (dd, J_{1CF} = 250.5 Hz, J_{2CF} = 12.7 Hz), 131.8, 130.3 (d, J_{CF} = 10.1 Hz), 128.9, 128.4, 124.4 (dd, J_{1CF} = 6.5 Hz, J_{2CF} = 4.9 Hz), 123.1 (t, J_{CF} = 2.8 Hz), 122.1, 117.4 (d, J_{CF} = 17.1), 87.0 (d, J_{CF} = 20.9 Hz), 59.2 (dd, J_{1CF} = 5.1 Hz, J_{2CF} = 3.0 Hz).

Anal Calcd for $C_{15}H_{10}F_2O$: C, 73.76; H, 4.13; F, 15.56. Found: C, 73.77; H, 4.04; F, 15.46.

(+)-1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol (2d)
The typical procedure for **2c** was followed. The compound was purified by flash chromatography (silica gel) by elution with 9% EtOAc/hexane. The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Chiralcel OD-H column (10% IPA/hexane).

IR (nujol gel): ν = 3180, 2923, 2854, 2270, 1488, 1376, 1023, 746 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.85 (d, J = 7.3 Hz, 1 H, ArH), 7.48 (m, 2 H, ArH), 7.43–7.27 (m, 6 H, ArH), 6.06 (s, 1 H), 2.70 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.9, 132.9, 131.8, 129.8, 129.7, 128.7, 128.5, 128.4, 127.3, 122.3, 87.6, 86.7, 62.5.

Anal Calcd for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57; O, 6.59; Cl, 14.61. Found: C, 73.96; H, 4.74; O, 6.96; Cl, 14.63.

(+)-1-(2-Bromophenyl)-3-phenylprop-2-yn-1-ol (2e)[17]
The typical procedure for **2c** was followed. The compound was purified by flash chromatography (silica gel) by elution with 10% EtOAc/hexane. The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Chiralcel OD-H column (5% IPA/hexane).

IR (nujol gel): ν = 3190, 2924, 2854, 1488, 1377, 1050, 1021, 753 cm^{-1}.

^1HNMR ($CDCl_3$, 300 MHz): δ = 7.86 (dd, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1 H, ArH), 7.60 (dd, J_1 = 7.9 Hz, J_2 = 1.0 Hz, 1 H, ArH), 7.50–7.47 (m, 2 H, ArH), 7.42–7.32 (m, 4 H, ArH), 7.26–7.19 (m, 1 H, ArH), 6.03 (d, 1 H, J = 5.2 Hz), 2.67 (d, 1 H, J = 5.2 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.6, 133.1, 131.9, 130.0, 128.7, 128.4, 128.0, 122.9, 122.4, 87.9, 86.8, 64.7.

Anal. Calcd for $C_{15}H_{11}BrO$: C, 62.74; H, 3.86; O, 5.57; Br, 27.83. Found: C, 62.67; H, 4.05; O, 5.79; Br, 28.18.

(+)-1-(2-Nitrophenyl)-3-phenylprop-2-yn-1-ol (2f)
The typical procedure for **2c** was followed. The compound was purified by flash chromatography (silica gel) by elution with 8% EtOAc/hexane. The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Chiralcel OD-H column (10% IPA/hexane).

IR (nujol gel): ν = 3180, 2923, 2854, 2220, 1522, 1376, 1033, 753 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 8.03–7.98 (m, 2 H, ArH), 7.69 (td, J_1 = 7.61 Hz, J_2 = 1.31 Hz, 1 H, ArH), 7.53 (td, J_1 = 7.85 Hz, J_2 = 1.42 Hz, 1 H, ArH), 7.48–7.41 (m, 2 H, ArH), 7.37–7.28 (m, 3 H, ArH), 6.21 (s, 1 H), 3.28 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.1, 135.5, 133.9, 131.9, 129.6, 129.4, 128.9, 128.4, 125.1, 121.9, 86.9, 86.6, 61.9.

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.80; H, 4.52; N, 5.37.

(+)-1-(2-Nitrophenyl)hex-2-yn-1-ol (2g)
The typical procedure for **2c** was followed. The compound was purified by flash chromatography (silica gel) by elution with 10% EtOAc/hexane. The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Chiralpak AS column (5% IPA/hexane).

IR (nujol gel): ν = 3385, 2964, 2934, 2872, 2220, 1608, 1350, 1034, 725 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.96 (t, J = 1.93 Hz, 1 H, ArH), 7.93 (dd, J_1 = 2.39 Hz, J_2 = 1.5 Hz, 1 H, ArH), 7.66 (td, J_1 = 7.59 Hz, J_2 = 1.15 Hz, 1 H, ArH), 7.49 (td, J_1 = 7.69 Hz, J_2 = 1.44 Hz, 1 H, ArH), 5.97 (t, J_1 = 1.97 Hz, 1 H), 2.22 (td, J_1 = 7.13 Hz, J_2 = 2.06 Hz, 2 H), 2.17 (s, 1H), 1.60–1.49 (m, 2H), 0.97 (t, J = 7.33 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.2, 136.0, 133.7, 129.4, 129.1, 124.9, 88.0, 78.0, 61.5, 21.9, 20.7, 13.5.

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39; O, 21.89. Found: C, 65.83; H, 5.99; N, 6.43; O, 21.53.

(+)-1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (2h)
The typical procedure for **2c** was followed. The compound was purified by flash chromatography (silica gel) by gradient elution with 5% EtOAc/hexane (350 mL) and 11% EtOAc/hexane (600 mL). The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Chiralcel OD column (10% IPA/hexane).

IR (nujol gel): ν = 3397, 2924, 2854, 2240, 1489, 1247, 1028, 763 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.66 (dd, J_1 = 7.52 Hz, J_2 = 1.72 Hz, 1 H, ArH), 7.52–7.46 (m, 2 H, ArH), 7.37–7.29 (m, 4 H, ArH), 7.02 (td, J_1 = 7.43 Hz, J_2 = 0.94 Hz, 1 H, ArH), 6.96–6.93 (m, 1 H, ArH), 5.94 (d, *J* = 5.65 Hz, 1 H), 3.93 (s, 3 H), 3.10 (d, *J* = 5.90 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.9, 131.8, 129.8, 128.9, 128.5, 128.3, 128.1, 122.8, 120.1, 111.0, 88.6, 86.1, 61.6, 55.7.

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92; O, 13.43. Found: C, 80.35; H, 5.87; O, 13.34.

(+)-1-(2-Methylphenyl)-3-phenylprop-2-yn-1-ol (2i)
The typical procedure for **2c** was followed. The compound was purified by flash chromatography (silica gel) by elution with 10% EtOAc/hexane. The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Chiralcel OD-H column (10% IPA/hexane).

IR (nujol gel): ν = 3246, 2923, 2853, 2220, 1376, 753 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.74 (m, 1 H, ArH), 7.48 (m, 2 H, ArH), 7.45–7.20 (m, 6 H, ArH), 5.85 (s, 1 H), 2.51 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.4, 136.1, 131.8, 130.9, 128.6, 128.5, 128.4, 126.7, 126.3, 122.6, 88.6, 86.5, 62.9, 19.1.

Anal Calcd for $C_{16}H_{14}O$: C, 86.45, H, 6.35; O, 7.20. Found: C, 86.32; H, 6.31; O, 7.21.

(–)-1-(2-naphthyl)-3-phenylprop-2-yn-1-ol (2j)
The typical procedure for **2c** was followed. The compound was purified by flash chromatography (silica gel) by elution with 10% EtOAc/hexane. The enantiomeric excess was determined by HPLC analysis of reaction mixtures on a Whelk-O column (4% IPA/hexane).

IR (nujol gel): ν = 3267, 2924, 2854, 2220, 1597, 1376, 1169, 754 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 8.06 (s, 1 H, ArH), 7.90–7.86 (m, 3 H, ArH), 7.75 (dd, J_1 = 8.64 Hz, J_2 = 1.18 Hz, 1 H, ArH), 7.55–7.52 (m, 4 H, ArH), 7.37–7.34 (m, 3 H, ArH), 5.88 (d, *J* =1.63 Hz, 1H), 2.94 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.1, 133.4, 133.3, 131.9,128.7, 128.7, 128.4, 128.3, 127.8, 126.4, 125.6, 124.8, 122.5, 88.9, 86.9, 65.3.

Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46; O, 6.19. Found: C, 87.94; H, 5.09; O, 6.25.

(1*R*,2*S*)- 1,2-diphenyl-2-pyrrolidin-1-ylethanol (3)[12]
Sodium carbonate (8.48 g, 80 mmol) was added as a solid to a stirred solution of 1,4-dibromobutane (2.87 mL, 24 mmol) in CH_3CN (80 mL) in a 3-neck round bottom flask. After the addition, the mixture was stirred at r.t. for 5 min, and then (1*R*,2*S*)-2-amino-1,2-diphenylethanol (4.27 g, 20 mmol) was added. The resulting mixture was stirred vigorously and heated to reflux for 12 h, after which time it was cooled down to r.t. and H_2O (100 mL) was added. The layers were separated, and the aqueous layer was extracted with TBME (3 x 250 mL). The combined organic layers were washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by crystallization from hexane to give 4.5 g (85% yield) of pure (1*R*,2*S*)-**3** as a white solid.

IR (nujol gel): ν = 3450, 2922, 2853, 1376, 1335, 1193, 773 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.15–7.07 (m, 5 H, ArH), 6.99–6.92 (m, 5 H, ArH), 5.26 (d, *J* = 3.58 Hz,, 1 H), 3.72 (s, 1 H), 3.31 (d, *J* = 3.47 Hz, 1 H), 2.77–2.72 (m, 2 H), 2.64–2.57 (m, 2H), 1.87–1.83 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.7, 137.5, 129.3, 127.5, 127.3, 127.1, 126.8, 126.2, 76.9, 74.1, 53.0, 23.6.

Anal Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24; O, 5.98. Found: C, 80.79; H, 8.07; N, 5.07; O, 5.84.

(1*S*,2*R*)-2-(1,3-dihydroisoindol-2-yl)-1,2-diphenylethanol (4)[18]
Sodium carbonate (7.4 g, 70 mmol) was added as a solid to a stirred solution of α,α'-dibromo-*o*-xylene (3.96 g, 15 mmol) in CH_3CN (30 mL) in a 3-neck round bottom flask. After the addition, the mixture was stirred at r.t. for 5 min, and then (1*S*,2*R*)-2-amino-1,2-diphenylethanol (2.13 g, 10 mmol) was added. The resulting mixture was stirred vigorously and heated to reflux for 12 h, after which time it was cooled down to r.t. and H_2O (30 mL) was added. The layers were separated, and the aqueous layer was extracted with TBME (3 x 150 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (silica gel, 10:1 hexane: EtOAc). It was then dissolved in hexane, and filtered to get rid of the insoluble reddish solid. The filtrate was then concentrated to provide the pure product (70% yield) as a light colored solid.

IR (nujol gel): ν = 3200, 2923, 2853, 2283, 1376, 750 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.26–7.18 (m, 5 H, ArH), 7.16–7.13 (m, 5 H, ArH), 7.06–6.95 (m, 4 H, ArH), 5.34 (d, *J* = 3.35 Hz, 1 H), 4.10 (dd, J_1 = 23.24 Hz, J_2 = 11.74 Hz, 4 H), 3.76 (d, *J* = 3.34 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.3, 139.2, 136.5, 129.5, 127.6, 127.5, 127.1, 127.0, 126.2, 122.4, 76.6, 76.6, 74.0, 58.3.

Anal Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.59; H, 6.66; N, 4.33.

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