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Asymmetric synthesis of propargylic alcohols catalyzed by (−)-MITH

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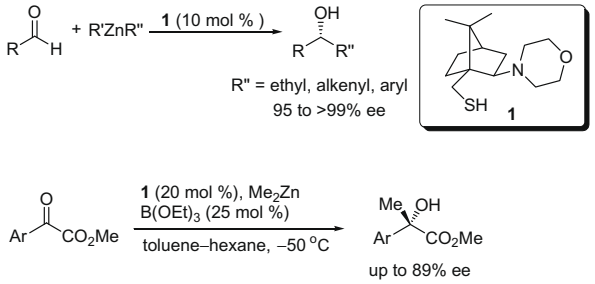
ABSTRACT

This investigation describes that in the presence of 2.5 mol % of (−)-2-*exo*-morpholinoisobornane-10-thiol (MITH) **1**, catalytic asymmetric alkynylation of aldehydes gives enantioenriched propargylic alcohols with good enantioselectivities.

1. Introduction

Chiral propargylic alcohols are versatile building blocks for the synthesis of optically active pharmaceutical ingredients and natural products.[1] Among the several efficient procedures that have been developed, such as Ti-mediated reactions,[2,3] there is a particular emphasis on the asymmetric nucleophilic addition of Zn-alkynylides to carbonyl compounds to prepare enantioenriched propargylic alcohols,[4–8] which offer the advantages of the low-toxicity of zinc metal and the wide functional group tolerance of organozinc reagents.[9] In literature reports[7,8] describing the asymmetric addition of Zn-alkynylides to aldehydes, preparing the corresponding propargylic alcohols in high ee usually requires high ligand loadings. Thus, it is desirable to develop an effective chiral mediator that promotes the enantioselective alkynylation of aldehydes at lower ligand loading.

As part of our endeavors to develop camphor-derived chiral ligands in catalytic asymmetric reactions,[10,11] (−)-2-*exo*-morpholinoisobornane-10-thiol (MITH) **1** has been demonstrated to be an effective promoter for the asymmetric addition of diethylzinc, arylzinc,[11a] and alkenylzinc[11b] species to aldehydes, affording the corresponding optically active alcohols with enantioselectivities ranging from 95% to >99% ee. Recently, ligand **1** was employed as a chiral promoter in the asymmetric addition of dimethylzinc to α-ketoesters, providing the corresponding hydroxyl esters bearing quaternary stereogenic centers with good yields and ee (Scheme 1).[11c] On the basis of these results, enantioselective addition of alkynylzinc reagents was investigated in order to expand the reaction scope. Herein, we report our recent developments in the catalytic asymmetric alkynylation of aldehydes.



Scheme 1. Asymmetric addition of organozincs to carbonyls catalyzed by ligand **1**.

2. Results and discussion

Initially, the preparation of zinc acetylide from phenylacetylene **2** and dimethylzinc was examined for our catalytic system. In the presence of ligand **1** (10 mol %), deprotonation of compound **2** at 70 °C in toluene, followed by the addition of benzaldehyde at −30 °C, gave alkynylation product **3** (Table 1, entry 1) predominantly,[7d] albeit, with a modest yield and low ee. Deprotonation at ambient temperature in either toluene or hexane led to unsatisfactory yields, and the methylated adduct was obtained as the major product (entries 2 and 3).[7b,c] Subsequently, using a mixed toluene–THF solvent system showed a better yield with higher ee, in which no methylation product was observed (entry 4).[6a,c]

The equivalents of zinc acetylide were subsequently optimized to achieve a better enantioselectivity with the toluene–THF mixed solvent system (Table 2). The reaction gave better ee when more than 4 equiv of organozincs were used (entries 1 and 2 vs entries 3–7). Although it was reported that a 1:1 mixture of alkynyl and dialkylzinc gave the propargylic alcohols in higher ee,[6a] adducts with comparable ee's were observed in our cases under different ratios of dimethylzinc to phenylacetylene (entries 3, 5, and 6). Alkylation product **4b** was obtained when dimethylzinc was substituted with diethylzinc (entry 7). Accordingly, 4 equiv of methylalkynylzinc for economical concern were applied for further optimization of solvents (entry 3).

Over re-examination of the solvent effect was first focused on the role of tetrahydrofuran. After the zinc acetylide was prepared in toluene–THF (1.5:1), the solvents were removed and the

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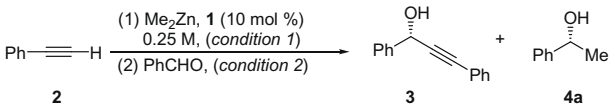
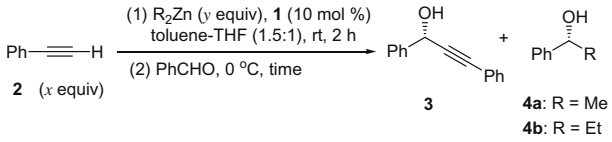
Table 1
The preparation of zinc phenylacetylide



Entry	Me_2Zn (equiv)	**2** (equiv)	Condition 1			Condition 2		**3**		**4a**
			Solvent	Temp (°C)	Time (h)	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)	yield[c] (%)
1[d]	6	7	Toluene	70	2.5	−30	24	66	39	<5
2	3	3	Hexane	rt	0.5	0	13	37	68	43
3	3	3	Toluene	rt	0.5	0	13	39	62	40
4	3	3	TOL–THF[e]	rt	2	0	28	80	81	ND[f]

[a] Isolated yield after column chromatography.
[b] Determination by chiral HPLC.
[c] Yield determined by crude ^{1}H NMR.
[d] The reaction was conducted in 0.125 M.
[e] TOL–THF = toluene/THF = 1.5:1 (v/v).
[f] Not detected by ^{1}H NMR.

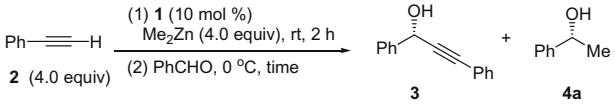
Table 2
Optimization of the reagent equivalents



Entry	R	*x*	*y*	Time (h)	**3**		**4**
					Yield[a] (%)	ee[b] (%)	yield[c] (%)
1	Me	1.5	1.5	36	93	70	ND
2	Me	2	2	36	98	69	ND
3	Me	4	4	28	85	82	ND
4	Me	8	8	36	94	81	ND
5	Me	4	8	21	91	80	ND
6	Me	4	2	48	85	81	ND
7	Et	4	4	22	80	79	19

[a] Isolated yield after column chromatography.
[b] Determined by chiral HPLC.
[c] Yield determined by crude ^{1}H NMR. ND: not detected by ^{1}H NMR.

Table 3
Optimization of the solvent system



Entry	Solvents[a]	Time (h)	**3**		**4a**
			Yield[b] (%)	ee[c] (%)	Yield[d] (%)
1	Toluene	21	82	8	ND
2[e]	HEX–THF (1.5:1)	38	90	79	ND
3	TOL–DCM (1.5:1)	24	61	64	17
4	TOL–DOX (1.5:1)	28	93	74	ND
5	TOL–DEE (1.5:1)	28	83	49	12
6	TOL–THF (1:2)	96	74	76	ND
7	TOL–THF (3:1)	24	94	83	ND
8	TOL–THF (9:1)	22	94	77	5

[a] Solvent abbreviations: TOL-toluene; THF-tetrahydrofuran; HEX-hexane; DCM-dichloromethane; DOX-dioxane; and DEE-diethyl ether.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC.
[d] Yield determined by crude ^{1}H NMR; ND: not detected by ^{1}H NMR.
[e] Me_2Zn (0.7 M in hexane) was used; the reaction was conducted in 0.10 M with respect to PhCHO.

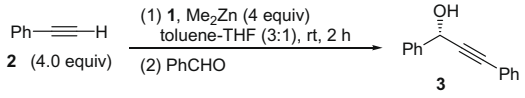
addition reaction was performed in toluene since the ether solvent was considered to promote the background reaction.[11b] However, we found that the absence of tetrahydrofuran in the system delivered quite low ee (Table 3, entry 1 vs Table 2, entry 3). Changing the reaction medium from toluene–THF to hexane-THF was not beneficial to the ee and yield (entry 2). Using other solvents in place of THF with toluene gave no better results (entries 3–5). Thus, co-solvent mixtures of toluene and THF with different ratios were tested; a ratio of 3:1 was found to be a better solvent system for the asymmetric addition of phenylethynyl zinc to benzaldehyde, and (*S*)-1,3-diphenylprop-2-yn-1-ol **3** was isolated in 94% yield and 83% ee (entry 7).

Conducting the reactions at low temperature enhanced the enantioselectivities (Table 4, entries 1-5) with the best result of 87% ee along with 75% yield (entry 4). A better enantioselectivity (90% ee) was obtained at −30 °C (entry 5), but the yield was low and a longer reaction time was necessary. However, as the ligand loading decreased to 2.5 mol %, a slightly deteriorated enantioinduction was observed. In general, 87–84% ee's were observed through 10–2.5 mol % of ligand **1** at −20 °C (entries 4 and 6–8).

After obtaining good enantioselectivity in the alkynylation of benzaldehyde with only 2.5 mol % of ligand **1**, our attention was then turned to the effects of additives (Table 5). Accordingly, additives such as isopropanol (entries 1–6) and alkyl borates (entries 7–10) were investigated to improve the asymmetric induction, because they have been reported to accelerate similar catalytic organozinc reactions.[11c,12] However, the addition of isopropanol as well as a variety of borates in catalytic to stoichiometric amounts showed no improvement in the ee of the adduct. Furthermore, the ratio of the mixed solvent system was examined again at −20 °C (entries 11–14), and it was found that a slightly lower percentage of THF in the co-solvent system could enhance the yield without a loss of ee (entry 12).

The scope of this catalytic system was investigated to include a variety of aldehydes (Table 6). In the cases of substituted benzaldehydes bearing diverse functional groups on the *para*-, *meta*-, and *ortho*-positions, asymmetric alkynylation gave the corresponding propargylic alcohols with 80–87% ee (entries 1–8). Addition to cinnamaldehyde provided a lower ee (61% ee) of the adduct (entry 9), while in the case of the α-substituted analogues, higher ee (71% ee) was observed (entry 10). Zinc alkynylides bearing substituents were also utilized, and the corresponding propargylic alcohols were obtained in 66–84% ee, although with unsatisfactory yields (15–55%) (entries 12–15).

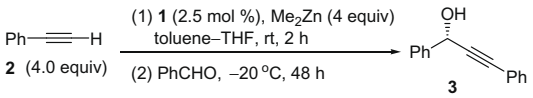
Table 4
Optimization of temperatures and ligand loadings



Entry	**1** (mol %)	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	10	rt	6	91	76
2	10	10	16	99	79
3	10	10	24	91	84
4	10	−20	24	75	87
5	10	−30	72	61	90
6	5	−20	42	73	86
7	2.5	−20	48	61	84
8	1	−20	72	73	51

[a] Isolated yield after column chromatography; methylation product was observed in <5% yield by crude ^{1}H NMR in all cases.
[b] Determined by chiral HPLC.

Table 5
Optimization based on 2.5 mol % of ligand **1**



Entry	Toluene–THF	Additives[a]	Yield[b] (%)	ee[c] (%)
1	3:1	2.5 mol % *i*-PrOH	61	65
2	3:1	5 mol % *i*-PrOH	58	62
3	3:1	10 mol % *i*-PrOH	63	76
4	3:1	25 mol % *i*-PrOH	62	74
5	3:1	50 mol % *i*-PrOH	66	72
6	3:1	100 mol % *i*-PrOH	55	67
7	3:1	10 mol % $B(OEt)_3$	67	82
8	3:1	10 mol % $B(Oi\text{-}Pr)_3$	52	87
9	3:1	10 mol % $B(Ot\text{-}Bu)_3$	55	87
10[d]	3:1	10 mol % $B(Ot\text{-}Bu)_3$	70	79
11	4:1	—	59	87
12	5:1	—	68	86
13	7:1	—	61	85
14	9:1	—	55	83

[a] Additives were added to the reaction mixture after step 1.
[b] Isolated yield after column chromatography; methylation product was observed in <5% yield under crude ^{1}H NMR in all cases.
[c] Determined by chiral HPLC.
[d] 8 equiv of alkyne were used.

3. Conclusion

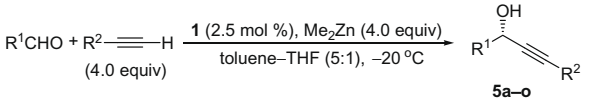
In conclusion, the asymmetric addition of zinc alkynylides to aldehydes to give optically active propargylic alcohols catalyzed by ligand **1** has been developed, affording the products in 49–87% ee. Notably, this catalytic system required only 2.5 mol % of the chiral ligand to afford propargylic alcohols derived from substituted benzaldehydes with >80% ee without additional additives. To the best of our knowledge, ligand **1** is the first chiral mediator bearing a β-amino thiol reported to catalyze the alkynylzinc addition reaction with aldehydes.

4. Experimental

4.1. General experimental procedure for the catalytic, asymmetric alkynylation with aldehydes

A flame-dried 10-mL flask containing (−)-MITH (6.4 mg, 0.025 mmol, 2.5 mol %) was filled with argon. Tetrahydrofuran (667 μL), dimethylzinc (3.3 mL, 4 mmol, 1.2 M in toluene), and phenylacetylene (439 μL, 4 mmol) were added sequentially in the flask. The mixture was stirred at ambient temperature for two hours before the system was cooled to −20 °C. The mixture was stirred at −20 °C for 10 min, followed by the addition of the aldehyde (1 mmol). The reaction mixture was worked up after 48 h by the addition of saturated aq NH_4Cl. The mixture was diluted with 1 M aq HCl (20 mL), and was extracted with dichloromethane (20 mL × 3). The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product, which was purified by column chromatography to give the corresponding propargylic alcohol. The ee value was determined by HPLC on a chiral stationary phase.

Table 6
Asymmetric alkynylation of various aldehydes catalyzed by 2.5 mol % of ligand **1**



Entry	R^1	R^2		Time (h)	Yield[a] (%)	ee[b] (%)
1	4-Tol	Ph	**5a**	72	70	86
2	3-Tol	Ph	**5b**	72	88	85
3	2-Tol	Ph	**5c**	72	79	86
4	4-Cl–Ph	Ph	**5d**	48	80	86
5	3-Cl–Ph	Ph	**5e**	48	82	86
6	2-Cl–Ph	Ph	**5f**	48	79	83
7	4-MeO–Ph	Ph	**5g**	72	27[c]	80
8	4-CF_3–Ph	Ph	**5h**	48	84	87
9	Cinnamyl	Ph	**5i**	48	41	61
10	α-Me-cinnamyl	Ph	**5j**	48	21[d]	71
11	$PhCH_2CH_2$	Ph	**5k**	48	69	49
12	Ph	4-CF_3–Ph	**5l**	48	46	84
13	Ph	4-MeO–Ph	**5m**	48	55	76
14	Ph	4-Cl–Ph	**5n**	48	15	66
15	Ph	*n*-Bu	**5o**	48	15	75

[a] Isolated yield after column chromatography, and methylation product was observed in <5% yield in crude ^{1}H NMR in all cases.
[b] Determination by chiral HPLC.
[c] The aldehyde was recovered in 68%.
[d] The aldehyde was recovered in 59%.

4.1.1. (1*S*)-1,3-Diphenyl-prop-2-yn-1-ol 3

A colorless oil. $[\alpha]_D^{27} = -2.4$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.60 (m, 2H), 7.48–7.45 (m, 2H), 7.42–7.29 (m, 2H), 5.68 (d, *J* = 6.0 Hz, 1H), 2.32 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6 (C), 131.6 (CH x2), 128.5 (CH ×2), 128.4 (CH), 128.2 (CH), 128.2 (CH ×2), 126.6 (CH ×2), 122.3 (C), 88.8 (C), 86.5 (C), 64.9 (CH); IR (neat) 3365, 3062, 3032, 2872, 2229, 1955, 1885, 1809, 1749, 1598, 1490, 1455, 1031, 757, 692 cm^{-1}; HRMS calcd for $C_{15}H_{12}O$ 208.0888, found 208.0882. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 10.7 min (7.0%), 19.6 min (93.0%), 86% ee.

4.1.2. (1*S*)-3-Phenyl-1-*p*-tolyl-prop-2-yn-1-ol 5a

A white solid (mp 58–62 °C). $[\alpha]_D^{27} = -5.2$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.43 (m, 4H), 7.32–7.27 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.64 (d, *J* = 6.0 Hz, 1H), 2.36 (s, 3H), 2.21 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (C), 137.7 (C), 131.6 (CH ×2), 129.1 (CH ×2), 128.3 (CH), 128.1 (CH ×2), 126.6 (CH ×2), 122.4 (C), 89.0 (C), 86.3 (C), 64.6 (CH), 21.0 (CH_3); IR (neat) 3369, 3053, 3024, 2921, 2864, 2228, 1949, 1904, 1803, 1597, 1489, 1178, 1031, 962, 757, 691 cm^{-1}; HRMS calcd for $C_{16}H_{14}O$ 222.1045, found 222.1049. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 8.5 min (7.0%), 17.4 min (93.0%), 86% ee.

4.1.3. (1*S*)-3-Phenyl-1-*m*-tolyl-prop-2-yn-1-ol 5b

A colorless, viscous oil. $[\alpha]_D^{27} = -5.8$ (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.44 (m, 2H), 7.41–7.39 (m, 3H), 7.33–7.24 (m, 4H), 7.16–7.14 (m, 2H), 5.64 (d, *J* = 6.2 Hz, 1H), 2.38 (s, 3H), 2.24 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5 (C), 138.1 (C), 131.6 (CH ×2), 128.9 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH ×2), 127.3 (CH), 123.7 (CH), 122.4 (C), 89.0 (C), 86.2 (C), 64.7 (CH), 21.2 (CH_3); IR (neat) 3368, 3054, 3023, 2920, 2865, 2230, 1951, 1883, 1801, 1607, 1598, 1490, 1032, 757, 691 cm^{-1}; HRMS calcd for $C_{16}H_{14}O$ 222.1045, found 222.1049. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 9.7 min (7.6%), 23.3 min (92.4%), 85% ee.

4.1.4. (1*S*)-3-Phenyl-1-*o*-tolyl-prop-2-yn-1-ol 5c

A colorless, viscous oil. $[\alpha]_D^{27} = +12.2$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.74–7.70 (m, 1H), 7.47–7.42 (m, 2H), 7.32–7.26 (m, 3H), 7.26–7.18 (m, 3H), 5.83 (d, *J* = 5.6 Hz, 1H), 2.49 (s, 3H), 2.18 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3 (C), 135.8 (C), 131.6 (CH ×2), 130.6 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH ×2), 126.5 (CH), 126.1 (CH), 122.4 (C), 88.6 (C), 86.2 (C), 62.7 (CH), 18.9 (CH_3); IR (neat) 3367, 3062, 3023, 2955, 2923, 2862, 2229, 1953, 1886, 1809, 1598, 1489, 1177, 1034, 961, 756, 691 cm^{-1}; HRMS calcd for $C_{16}H_{14}O$ 222.1045, found 222.1053. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 8.3 min (7.0%), 17.8 min (93.0%), 86% ee.

4.1.5. (1*S*)-1-(4-Chloro-phenyl)-3-phenyl-prop-2-yn-1-ol 5d

A white solid (mp 46–48 °C). $[\alpha]_D^{27} = -7.9$ (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.56–7.53 (m, 2H), 7.46–7.44 (m, 2H), 7.37–7.28 (m, 5H), 5.66 (d, *J* = 6.0 Hz, 1H), 2.30 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0 (C), 134.0 (C), 131.6 (CH ×2), 128.6 (CH), 128.6 (CH ×2), 128.2 (CH ×2), 128.0 (CH ×2), 122.0 (C), 88.3 (C), 86.7 (C), 64.1 (CH); IR (neat) 3341, 3055, 2873, 2226, 1949, 1903, 1597, 1488, 1090, 1015, 963, 756, 691 cm^{-1}; HRMS calcd for $C_{15}H_{11}ClO$ 242.0498, found 242.0505. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 8.7 min (6.8%), 27.6 min (93.2%), 86% ee.

4.1.6. (1*S*)-1-(3-Chloro-phenyl)-3-phenyl-prop-2-yn-1-ol 5e

A colorless, viscous oil. $[\alpha]_D^{27} = -14.2$ (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.61–7.60 (m, 1H), 7.49–7.45 (m, 3H), 7.33–7.31 (m, 5H), 5.66 (d, *J* = 6.0 Hz, 1H), 2.37–2.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4 (C), 134.2 (C), 131.6 (CH ×2), 129.7 (CH), 128.6 (CH), 128.2 (CH), 128.2 (CH ×2), 126.7 (CH), 124.7 (CH), 121.9 (C), 88.0 (C), 86.8 (C), 64.0 (CH); IR (neat) 3361, 3062, 3021, 2876, 2230, 1945, 1880, 1808, 1759, 1690, 1597, 1489, 1188, 969, 756 cm^{-1}; HRMS calcd for $C_{15}H_{11}ClO$ 242.0498, found 242.0505. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 8.9 min (7.2%), 29.3 min (92.8%), 86% ee.

4.1.7. (1*S*)-1-(2-Chloro-phenyl)-3-phenyl-prop-2-yn-1-ol 5f

A colorless, viscous oil. $[\alpha]_D^{27} = +46.2$ (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.83–7.81 (m, 1H), 7.48–7.43 (m, 2H), 7.40–7.38 (m, 1H), 7.35–7.25 (m, 5H), 6.03 (d, *J* = 5.6 Hz, 1H), 2.54 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8 (C), 132.6 (C), 131.7 (CH ×2), 129.6 (CH), 129.5 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH ×2), 127.1 (CH), 122.2 (C), 87.6 (C), 86.4 (C), 62.2 (CH); IR (neat) 3371, 3064, 2928, 2854, 2230, 1953, 1923, 1811, 1597, 1574, 1490, 1442, 1032, 756, 691 cm^{-1}; HRMS calcd for $C_{15}H_{11}ClO$ 242.0498, found 242.0499. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 0.5 mL/min, UV 254 nm; t_R = 8.2 min (8.5%), 9.7 min (91.5%), 83% ee.

4.1.8. (1*S*)-1-(4-Methoxy-phenyl)-3-phenyl-prop-2-yn-1-ol 5g

A colorless, viscous oil. $[\alpha]_D^{27} = -4.2$ (*c* 1.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.55–7.51 (m, 2H), 7.47–7.44 (m, 2H), 7.31–7.28 (m, 3H), 6.93–6.89 (m, 2H), 5.63 (d, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 2.21 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (C), 132.9 (C), 131.6 (CH x2), 128.3 (CH), 128.1 (CH ×2), 128.0 (CH ×2), 122.4 (C), 113.8 (CH ×2), 89.1 (C), 86.2 (C), 64.3 (CH), 55.1 (CH_3); IR (neat) 3412, 3001, 2956, 2934, 2836, 2228, 1610, 1511, 1251, 1173, 1033, 834, 757, 692 cm^{-1}; HRMS calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0998. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 11.9 min (10.1%), 26.4 min (89.9%), 80% ee.

4.1.9. (1*S*)-3-Phenyl-1-(4-trifluoromethyl-phenyl)-prop-2-yn-1-ol 5h

A colorless, viscous oil. $[\alpha]_D^{27} = -6.9$ (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.74–7.72 (m, 1H), 7.66–7.64 (m, 1H), 7.47–7.44 (m, 2H), 7.34–7.29 (m, 3H), 5.74 (d, *J* = 5.8 Hz, 1H), 2.39 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3 (C), 131.7 (CH ×2), 130.3 (q, *J* = 32 Hz, C), 128.8 (CH), 128.3 (CH ×2), 126.9 (CH ×2), 125.4 (q, *J* = 3.7 Hz, CH ×2), 124.0 (q, *J* = 270 Hz, C), 121.9 (C), 88.0 (C), 87.1 (C), 64.2 (CH); IR (neat) 3346, 3063, 2881, 2230, 1916, 1804, 1620, 1490, 1326, 1167, 1127, 1018, 850, 757, 691 cm^{-1}; HRMS calcd for $C_{16}H_{11}F_3O$ 276.0762, found 276.0756. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 7.9 min (6.7%), 36.7 min (93.3%), 87% ee.

4.1.10. (3*S*)-1,5-Diphenyl-pent-1-en-4-yn-3-ol 5i

Colorless crystals (mp 64–65 °C). $[\alpha]_D^{27} = -7.3$ (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.50–7.24 (m, 10H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.42–6.36 (m, 1H), 5.29 (d, *J* = 6.0 Hz, 1H), 2.47 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9 (C), 131.6 (CH), 131.6 (CH ×2), 128.3 (CH ×2), 128.3 (CH), 128.1 (CH ×2), 127.9 (CH), 127.8 (CH), 126.6 (CH ×2), 122.2 (C), 88.1 (C), 86.1 (C), 63.0 (CH); IR (neat) 3349, 3058, 3028, 2914, 2850, 2225, 1952, 1597, 1489, 1443, 1006, 964, 755, 690 cm^{-1}; HRMS calcd for $C_{17}H_{14}O$ 234.1045, found 234.1045. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.5 mL/min, UV 254 nm; t_R = 9.6 min (19.7%), 30.9 min (80.3%), 61% ee.

4.1.11. (3*S*)-2-Methyl-1,5-diphenyl-pent-1-en-4-yn-3-ol 5j

A colorless, viscous oil. $[\alpha]_D^{27} = +31.6$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.44 (m, 2H), 7.36–7.30 (m, 6H), 7.25–7.21 (m, 2H), 6.75 (s, 1H), 5.14 (d, *J* = 5.6 Hz, 1H), 2.09 (d, *J* = 5.6 Hz, 1H), 2.06 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0 (C), 136.7 (C), 131.6 (CH x2), 128.9 (CH x2), 128.4 (CH), 128.2 (CH ×2), 128.0 (CH ×2), 127.1 (CH), 126.7 (CH), 122.4 (C), 88.1 (C), 86.1 (C), 68.6 (CH), 14.1 (CH_3); IR (neat) 3415, 3057, 3025, 2917, 2853, 2200, 1616, 1600, 1489, 1443, 1278, 1062, 756, 691 cm^{-1}; HRMS calcd for $C_{18}H_{16}O$ 248.1201, found 248.1194. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 9.0 min (14.4%), 38.6 min (85.6%), 71% ee.

4.1.12. (3*S*)-1,5-Diphenyl-pent-1-yn-3-ol 5k

A colorless, viscous oil. $[\alpha]_D^{27} = +28.4$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.41 (m, 2H), 7.31–7.19 (m, 8H), 4.61–4.56 (m, 1H), 2.85 (t, *J* = 8.0 Hz, 2H), 2.14–2.03 (m,2H), 1.88 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2 (C), 131.6 (CH ×2), 128.4 (CH ×2), 128.3 (CH ×2), 128.2 (CH), 128.1 (CH ×2), 125.8 (CH), 122.5 (C), 89.9 (C), 85.0 (C), 62.0 (CH), 39.1 (CH_2), 31.4 (CH_2); IR (neat) 3357, 3027, 2925, 2861, 2230, 1948, 1869, 1600, 1490, 1455, 1338, 1042, 756, 691 cm^{-1}; HRMS calcd for $C_{17}H_{16}O$ 236.1201, found 236.1200. Chiral HPLC analysis:

Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 11.4 min (25.5%), 22.7 min (74.5%), 49% ee.

4.1.13. (1*S*)-1-Phenyl-3-(4-trifluoromethyl-phenyl)-prop-2-yn-1-ol 5l

Colorless crystals (mp 50–54 °C). $[\alpha]_D^{27} = +1.3$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.60–7.52 (m, 5H), 7.43–7.33 (m, 4H), 5.71 (br, 1H), 2.45 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2 (C), 131.9 (CH ×2), 130.3 (q, *J* = 33 Hz, C), 128.7 (CH ×2), 128.6 (CH), 126.7 (CH ×2), 126.2 (C), 125.2 (q, *J* = 3.7 Hz, CH ×2), 123.7 (q, *J* = 271 Hz, C), 91.2 (C), 85.1 (C), 64.9 (CH); IR (neat) 3337, 3066, 3034, 2923, 2237, 1615, 1324, 1168, 1127, 1068, 1018, 842, 698 cm^{-1}; HRMS calcd for $C_{16}H_{11}F_3O$ 276.0762, found 276.0752. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 6.9 min (91.9%), 8.3 min (8.1%), 84% ee.

4.1.14. (1*S*)-3-(4-Methoxy-phenyl)-1-phenyl-prop-2-yn-1-ol 5m

A colorless, viscous oil. $[\alpha]_D^{26} = +1.9$ (c 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.61–7.59 (m, 2H), 7.41–7.31 (m, 5H), 6.84–6.82 (m, 2H), 5.66 (d, *J* = 6.0 Hz, 1H), 3.79 (s, 3H), 2.27 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (C), 140.7 (C), 132.9 (CH ×2), 128.2 (CH ×2), 127.9 (CH), 126.5 (CH ×2), 114.3 (C), 113.6 (CH ×2), 87.5 (C), 86.1 (C), 64.5 (CH), 54.9 (CH_3); IR (neat) 3401, 3033, 2936, 2838, 2226, 2048, 1890, 1606, 1510, 1249, 1032, 832, 701 cm^{-1}; HRMS calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0995. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 14.0 min (12.1%), 26.6 min (87.9%), 76% ee.

4.1.15. (1*S*)-3-(4-Chloro-phenyl)-1-phenyl-prop-2-yn-1-ol 5n

A colorless, viscous oil. $[\alpha]_D^{26} = +2.6$ (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.59–7.58 (m, 2H), 7.42–7.27 (m, 7H), .67 (d, *J* = 6.0 Hz, 1H), 2.31 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3 (C), 134.3 (C), 132.8 (CH ×2), 128.43 (CH ×2), 128.38 (CH ×2), 128.2 (CH), 126.5 (CH ×2), 120.7 (C), 89.8 (C), 85.2 (C), 64.6 (CH); IR (neat) 3360, 3065, 2875, 2230, 1956, 1901, 1593, 1488, 1190, 1092, 1015, 963, 828 698 cm^{-1}; HRMS calcd for $C_{15}H_{11}ClO$ 242.0498, found 242.0500. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 0.5 mL/min, UV 254 nm; t_R = 17.3 min (82.8%), 19.0 min (17.2%), 66% ee.

4.1.16. (1*S*)-1-Phenyl-hept-2-yn-1-ol 5o

A colorless oil. $[\alpha]_D^{25} = -18.1$ (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.52 (m, 2H), 7.38–7.28 (m, 3H), 5.43 (d, *J* = 5.6 Hz, 1H), 2.26 (td, *J* = 7.2, 2.0 Hz, 2H), 2.13 (d, *J* = 5.6 Hz, 1H), 1.55–1.36 (m, 4H), 0.898 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2 (C), 128.3 (CH ×2), 127.9 (CH), 126.5 (CH ×2), 87.3 (C), 79.9 (C), 64.5 (CH), 30.5 (CH_2), 21.8 (CH_2), 18.3 (CH_2), 13.4 (CH_3); IR (neat) 3397, 3031, 2958, 2933, 2873, 2227, 1950, 1884, 1809, 1603, 1494, 1455, 1135, 1002, 698 cm^{-1}; HRMS calcd for $C_{13}H_{16}O$ 188.1201, found 188.1192. Chiral HPLC analysis: Chiralcel OD-H, 2-propanol/hexane (10:90), 1.0 mL/min, UV 254 nm; t_R = 11.0 min (87.5%), 13.8 min (12.5%), 75% ee.

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