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Highly enantioselective addition of linear alkyl alkynes to aromatic aldehydes

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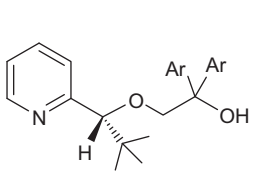
ABSTRACT

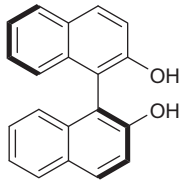
An asymmetric linear alkyl alkyne addition to aromatic aldehydes catalyzed by the Ti-(*R*)-BINOL system is reported with high enantioselectivity and yield. Our study expands upon the synthetic scope of propargylic alcohols, which could serve as potentially useful intermediates for the synthesis of various natural products.

1. Introduction

Chiral propargylic alcohols are key intermediates in the synthesis of complex organic compounds including natural products, pharmaceuticals, and materials.[1] One efficient method to obtain this class of compounds is a catalytic asymmetric alkyne addition to aldehydes, which could simultaneously form a new C–C bond and a chiral alcohol center in a single transformation. Over the last few years, great progress has been made in developing this catalytic enantioselective reaction.[2–9] For example, Hoshino et al. discovered that the pyridyl alcohol ligand **1** was effective for the asymmetric alkynylzinc addition to aldehydes.[2] However, the reaction of 1-octyne with benzaldehyde gave much lower yield and enantioselectivity, and the scope of the substrates was very limited. Recently, Pu et al. found that 1,1′-bi-2-naphthol (BINOL) in combination with $Ti(O^iPr)_4$ could catalyze the alkynylzinc addition to both aromatic and aliphatic aldehydes with high enantioselectivity.[4b,4c] More recently, this system was successfully applied to highly enantioselective reactions of alkynoates with aldehydes[4f] and of linear alkyl alkynes with linear aldehydes.[4h] However, the number of studies on the enantioselective additions of linear alkyl alkynes with aromatic aldehydes using a Ti-BINOL catalytic system is small. We are currently interested in the development of propargylic alcohols and their application in the synthesis of natural products; and we attempted to evaluate the efficiency of this catalytic system for the reaction of 1-octyne with benzaldehyde in our preliminary study.[4i] Herein, we report in detail the asymmetric addition of linear alkyl alkynes to aromatic aldehydes catalyzed by a Ti-BINOL system to generate useful aliphatic propargylic alcohols with high enantioselectivity and in high yields.



1 Ar = α-Naphthyl



(*S*)-BINOL

2. Results and discussion

Hoshino et al. have reported the use of pyridyl alcohol ligand **1** to catalyze the asymmetric addition of 1-octyne to benzaldehyde in low yield and moderate enantioselectivity (41% yield and 78% ee).[2] The reaction included two steps: 1) the treatment of 1-octyne with fresh diethylzinc at reflux; and 2) the addition of benzaldehyde in the presence of the catalyst. The first step probably generated the ethyl 1-octynyl zinc intermediate **2**, which then added to benzaldehyde to form the chiral propargyl alcohol **3**. According to above procedure, we, therefore, tested the use of (*R*)-BINOL and $Ti(O^iPr)_4$ as the catalyst for the asymmetric reaction of 1-octyne with benzaldehyde (Scheme 1). We found that the use of (*R*)-BINOL-$Ti(O^iPr)_4$ is favorable for the synthesis of chiral propargyl alcohol **3** in 72% yield and 83% ee (Table 1, entry 1), which is better than the results of the **1**-catalyzed reaction.

Various conditions were explored for the reaction of 1-octyne with benzaldehyde, and the results are summarized in Table 1. We first tested the use of solvents for the two steps (entries 2-5). Both good yield (81%) and high enantioselectivity (92%) were observed when using toluene in step 1 and tetrahydrofuran (THF) in step 2 (entry 2), respectively. The results revealed that toluene in step 1 may be more favorable for the formation of alkynylzinc **2**, while THF in step 2 may favor the chiral inducement of

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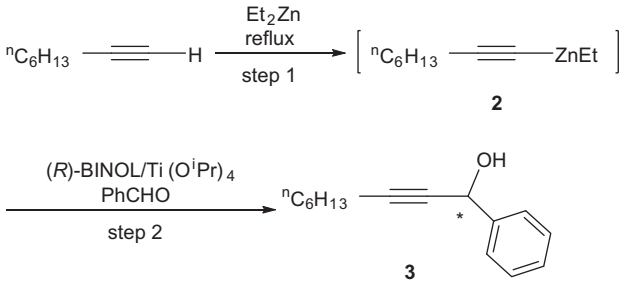


Scheme 1. Asymmetric alkynylzinc addition to benzaldehyde.

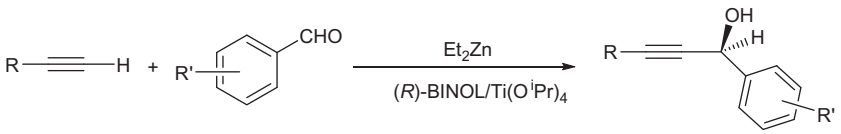
(*R*)-BINOL and $Ti(O^iPr)_4$. We then varied the temperature in step 2 for this reaction; a slightly increased ee value but a lower yield were observed at 0°C (entry 6), thus indicating that room temperature is suitable for the reaction. Increasing the amount of Et_2Zn, BINOL and $Ti(O^iPr)_4$ showed no great improvement in either the enantioselectivity or the yield (entries 7-9). Meanwhile, decreasing the amount of $Ti(O^iPr)_4$ gave distinctly decreased ees (entries 10 and 11). Thus, entry 2 was identified as the optimized condition for this reaction because of the good yield and excellent enantioselectivity. The configuration of the product was determined (*S*) by the literature.[4f] In comparison with our previous results, fresh diethylzinc. which could generate zinc intermediate **2**, led to significantly improved ees. Zinc precipitated from homogeneous solution might decrease the enantioselectivity, and even the opposite configuration of product was found in our preliminary study.[4i]

The optimized procedure was applied to the reaction of linear alkyl alkynes with a variety of aromatic aldehydes. The results summarized in Table 2 demonstrate that the reactions of 1-octyne and 1-hexyne with *ortho*-, *meta*-, or *para*-substituted benzaldehydes took place with excellent enantioselectivities. For the addition of 1-octyne, reactions with methylbenzaldehyde and methoxybenzaldehyde gave 86%-92% ees and 87-93% ees, respectively (entries 2-6). Reactions with *meta*- and *para*-substituted benzaldehydes gave slightly higher enantioselectivities than those involving *ortho*-substituted benzaldehydes. For example, the reaction of *m*-methoxybenzaldehyde gave an excellent enantioselectivity of 93% ee (entry 5). Halogen-containing benzaldehydes with fluoro-, chloro- and bromo-substituents on different positions also gave their relative products with excellent stereoselectivities (82-95% ee, entries 7-11). Likewise, *meta*- and *para*-halogenated benzaldehydes showed outstanding enantioselectivities. The reaction of *p*-bromobenzaldehyde gave the product with 95% ee (entry 9), while using *ortho*-chlorobenzaldehyde gave a slightly worse result (entry 10). This addition was also suitable for 1-hexyne, which could react smoothly with several of the above aromatic aldehydes to give propargylic alcohols with good enantioselectivity (74-92% ee, entries 12-15). For the two linear alkynes, 1-octyne with a longer chain gave better results than the other.

Table 1
Attempted reactions of 1-octyne with benzaldehyde

Entry	1-octyne/Et_2Zn (mmol)	BINOL (mmol)	$(TiO^iPr)_4$ (mmol)	Solvent Step 1	Solvent Step 2	Temp (°C)	Yield (%)	ee (%)
1	4/4	0.4	1.0	THF	THF	rt	72	83
2	**4/4**	**0.4**	**1.0**	**Toluene**	**THF**	**rt**	**81**	**92**
3	4/4	0.4	1.0	Toluene	Toluene	rt	61	84
4	4/4	0.4	1.0	Toluene	CH_2Cl_2	rt	73	88
5	4/4	0.4	1.0	Toluene	Ether	rt	65	85
6	4/4	0.4	1.0	Toluene	THF	0	64	95
7	4/6	0.4	1.0	Toluene	THF	rt	79	93
8	4/8	0.4	1.0	Toluene	THF	rt	76	94
9	4/4	0.6	1.5	Toluene	THF	rt	82	93
10	4/4	0.4	0.7	Toluene	THF	rt	76	48
11	4/4	0.4	0.4	Toluene	THF	rt	73	47

Table 2
Results for the asymmetric addition of linear alkyl alkynes to aromatic aldehydes



Entry	R	R′	Isolated yield (%)	ee (%)
1	n-C_6H_{13}	H	81	94
2	n-C_6H_{13}	*o*-Me	76	86
3	n-C_6H_{13}	*m*-Me	72	92
4	n-C_6H_{13}	*p*-Me	72	92
5	n-C_6H_{13}	*m*-MeO	82	93
6	n-C_6H_{13}	*p*-MeO	83	87
7	n-C_6H_{13}	*m*-F	92	94
8	n-C_6H_{13}	*m*-Cl	86	94
9	n-C_6H_{13}	*m*-Br	89	95
10	n-C_6H_{13}	*o*-Cl	76	82
11	n-C_6H_{13}	*p*-F	84	92
12	n-C_4H_9	H	68	74/(*S*)[a]
13	n-C_4H_9	*p*-Me	84	90
14	n-C_4H_9	*m*-MeO	75	92
15	n-C_4H_9	*m*-F	73	86

[a] The absolute configuration was based on the measurement of the specific rotation in comparison with the literature values.[8d,9]

3. Conclusion

We have successfully demonstrated that the effective (*R*)-BINOL ligand in combination with $Ti(O^iPr)_4$ can catalyze the highly enantioselective reaction of aliphatic terminal alkynes with aromatic aldehydes including those with various substituents on different positions. This method could expand the scope of terminal alkynes in asymmetric alkynylzinc additions to aldehydes, and the resulting propargylic alcohols could serve as precursors for the synthesis of natural products and pharmaceutical compounds.

4. Experimental

4.1. General methods

All reactions were carried out in a round bottomed flask and under nitrogen. All solvents were dried according to the standard methods prior to use. 4-Fluorobenzaldehyde, diethylzinc were purchased from Aldrich Chemical; 2-chlorobenzaldehyde, 3-chlorobenzaldehyde, 3-bromobenzaldehyde, titanium isopropoxide, 1-octyne, 1-hexyne, *n*-butyl lithium were purchased from ACROS Co. and used directly. Isopropanol and n-hexane for HPLC were purchased from Fisher Co. Other reagents were purchased from China and purified according to standard procedures.

The ^{1}H NMR spectra and ^{13}C NMR spectra were obtained using the Bruker-400 MHz spectrometer and the Bruker-100 MHz spectrometer, respectively. Mass Spectra were obtained using the Agilent 6890-5973N Mass Spectroscopy facility. HPLC analyses were carried out with the Waters1525 by using the Diacel Chiralcel OD column and eluting with 10% isopropanol in hexane at 1.0mL/min unless otherwise indicated, and were detected at 254 nm by the Waters 2487 (5% isopropanol in hexane at 1.0 mL/min for 1-phenyl-non-2-yn-1-ol and 1-(3-fluorophenyl)-hept-2-yn-1-ol. The specific rotation was determined with a Polarimeter Autopol IV automatic polarimeter (Rudolph, America).

4.2. General procedure for the preparation of the racemic propargylic alcohols

The racemic products of benzaldehyde and 3-methoxybenzaldehyde with 1-octyne were prepared for HPLC analysis in accordance with the following procedure. Under nitrogen, distilled THF (6 mL) and a 1-octyne (4.0 mmol, 600 μL) were added to a 25 mL flask, which was cooled to –78°C with dry ice / acetone bath after which 1.6 M ^{n}BuLi in hexanes (4.0 mmol) was added. After stirring for 3 h, the aldehyde (2.0 mmol) was then added and the reaction mixture was stirred for 10 h. The reaction was then quenched with ice, extracted with methylene chloride, dried over magnesium sulfate and concentrated under reduced pressure. After the residue was passed through a short silica gel column and the solvent was removed by rotoevaporation, the pure racemic propargylic alcohol product was isolated. Other racemic products were prepared by racemic BINOL according to the procedure for the asymmetric addition.

4.3. General procedure for the asymmetric addition

In a 25 mL flask, a toluene solution (2 mL) of 1-octyne or 1-hexyne (4.0 mmol, 600 μL) and diethylzinc (4.0mmol, 1.5M in toluene) was heated at reflux under nitrogen for 2 h. After returning to room temperature, (*R*)-BINOL (0.40 mmol, 120 mg), THF (16 mL), $Ti(O^iPr)_4$ (1.0 mmol, 300 μL) were added sequentially and stirred for 1 h, after which aromatic aldehyde (1.0 mmol) was added. After 5 h, the reaction was quenched with saturated ammonium chloride. The resulting mixture was extracted with methylene chloride, dried over magnesium sulfate and concentrated under vacuum. After the residue was passed through a short silica gel column and the solvent was removed by reduced pressure distillation, the product was isolated.

4.3.1. 1-Phenyl-non-2-yn-1-ol

81% yield. 94% ee determined by HPLC analysis. Retention time: t_{major} = 5.3 min and t_{minor} = 7.0 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53-7.29 (m, 5H), 5.41 (s, 1H), 2.55 (br, 1H), 2.27-2.22 (t, *J* = 8.2 Hz, 2H), 1.54-1.25 (m, 8H), 0.90-0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 141.4, 128.5, 128.5, 128.1, 126.7, 126.7, 87.6, 80.1, 64.8, 31.3, 29.5, 28.6, 22.6, 18.9, 14.1. GC-MS calcd. for $[C_{15}H_{20}O]^+$: 216.32, found: 216. $[\alpha]_D^{20} = -100.4$ (*c* 0.91, $CHCl_3$).

4.3.2. 1-(2-Methylphenyl)-non-2-yn-1-ol

76% yield. 86% ee determined by HPLC analysis. Retention time: t_{major} = 5.3 min, and t_{minor} = 5.7 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66-7.64 (d, *J* = 8.2 Hz, 1H), 7.24-7.19 (m, 2H), 7.17-7.15 (d, *J* = 8.8 Hz, 1H), 5.58 (s, 1H), 2.43 (s, 3H), 2.27-2.23 (t, *J* = 8.2 Hz, 2H), 2.12 (br, 1H), 1.54-1.25 (m, 8H), 0.90-0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.0, 135.9, 130.7, 128.2, 126.4, 126.2, 87.5, 79.7, 62.6, 31.3, 29.7, 28.6, 22.6, 18.9, 18.9, 14.1. GC-MS calcd. for $[C_{16}H_{22}O]^+$: 230.34, found: 230. $[\alpha]_D^{20} = -29.4$ (*c* 0.50, $CHCl_3$).

4.3.3. 1-(3-Methylphenyl)-non-2-yn-1-ol

72% yield. 92% ee determined by HPLC analysis. Retention time: t_{major} = 4.8 min, and t_{minor} = 6.1 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.33 (d, *J* = 11.2 Hz, 2H), 7.28-7.24 (s, 1H), 7.14-7.12 (d, *J* = 7.6 Hz, 1H), 5.41 (s, 1H), 2.37 (s, 3H), 2.17 (br, 1H), 2.29-2.25 (t, *J* = 8.0 Hz, 2H), 1.58-1.27 (m, 8H), 0.91-0.86 (t, *J* = 9.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 141.3, 138.2, 129.0, 128.5, 127.3, 123.7, 87.6, 80.1, 64.9, 31.4, 29.7, 28.6, 22.6, 21.4, 18.7, 14.1. GC-MS calcd. for $[C_{16}H_{22}O]^+$: 230.34, found: 230. $[\alpha]_D^{20} = -14.9$ (*c* 0.50, $CHCl_3$).

4.3.4. 1-(4-Methylphenyl)-non-2-yn-1-ol

72% yield. 92% ee determined by HPLC analysis. Retention time: t_{major} = 4.9 min, and t_{minor} = 5.5 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44-7.42 (d, *J* = 8.0 Hz, 2H), 7.19-7.17 (d, *J* = 8.0 Hz, 2H), 5.42 (s, 1H), 2.36 (s, 3H), 2.29-2.25 (t, *J* = 8.2 Hz, 2H), 2.17 (br, 1H), 1.66-1.22 (m, 8H), 0.91-0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.6, 137.9, 129.7, 129.2, 126.6, 126.6, 87.5, 80.2, 64.7, 31.3, 29.7, 28.6, 22.5, 21.1, 18.8, 14.0. GC-MS calcd. for $[C_{16}H_{22}O]^+$: 230.34, found: 230. $[\alpha]_D^{20} = -23.0$ (*c* 0.50, $CHCl_3$).

4.3.5. 1-(3-Methoxyphenyl)-non-2-yn-1-ol

82% yield. 93% ee determined by HPLC analysis. Retention time: t_{major} = 6.1 min, and t_{minor} = 8.2 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29-7.25 (t, *J* = 8.0 Hz, 1H), 7.12-7.11 (m, 2H), 6.86-6.83 (d, *J* = 12.0 Hz, 1H), 5.41 (s, 1H), 3.81 (s, 3H), 2.40 (br, 1H), 2.28-2.24 (t, *J* = 8.2 Hz, 2H), 1.55-1.26 (m, 8H), 0.90-0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.8, 142.9, 129.5, 118.9, 113.9, 112.0, 87.7, 79.9, 64.7, 55.2, 31.3, 28.6, 28.6, 22.5, 18.8, 14.0. GC-MS calcd. for $[C_{16}H_{22}O_2]^+$: 246.34, found: 246. $[\alpha]_D^{20} = -56.1$ (*c* 0.50, $CHCl_3$).

4.3.6. 1-(4-Methoxyphenyl)-non-2-yn-1-ol

83% yield. 87% ee determined by HPLC analysis. Retention time: t_{major} = 5.9 min, and t_{minor} = 6.6 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44-7.40 (d, *J* = 14.4 Hz, 2H), 6.87-6.83 (d, *J* = 14.4 Hz, 2H), 5.35 (s, 1H), 3.75 (s, 3H), 2.84 (br, 1H), 2.27-2.21 (t, *J* = 8.2 Hz, 2H), 1.55-1.29 (m, 8H), 0.90-0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.4, 133.8, 128.3, 127.7, 114.1, 113.5, 87.3, 80.3, 64.2, 55.2, 31.7, 29.6, 28.6, 22.6, 18.8, 14.1. GC-MS calcd. for $[C_{16}H_{22}O_2]^+$: 246.34, found: 246. $[\alpha]_D^{20} = -59.7$ (*c* 0.50, $CHCl_3$).

4.3.7. 1-(3-Fluorophenyl)-non-2-yn-1-ol

92% yield. 94% ee determined by HPLC analysis. Retention time: t_{major} = 5.2 min, and t_{minor} = 5.8 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.25 (m, 3H), 7.01-6.97 (t, *J* = 8.0 Hz, 1H), 5.43 (s, 1H), 2.40 (br, 1H), 2.28-2.24 (t, *J* = 8.0 Hz, 2H), 1.57-1.23 (m, 8H), 0.89-0.86 (t, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.6, 143.8, 129.8, 122.1, 114.8, 113.5, 87.8, 79.6, 63.8, 31.2, 28.5, 28.1, 22.4, 18.7, 13.9. GC-MS calcd. for $[C_{15}H_{19}FO]^+$: 234.32, found: 234. $[\alpha]_D^{20} = -54.4$ (*c* 0.88, $CHCl_3$).

4.3.8. 1-(3-Chlorophenyl)-non-2-yn-1-ol

86% yield. 94% ee determined by HPLC analysis. Retention time: t_{major} = 5.2 min, and t_{minor} = 5.7 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (s, 1H), 7.39-7.38 (d, *J* = 4.0 Hz, 1H), 7.31-7.26 (m, 2H), 5.41 (s, 1H), 2.41 (br, 1H), 2.28-2.24 (t, *J* = 8.0 Hz, 2H), 1.48-1.22 (m, 8H), 0.93- 0.89 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.2, 134.4, 129.8, 128.2, 126.8, 124.8, 88.3, 79.4, 64.1, 31.3, 28.6, 28.5, 22.6, 18.8, 14.1. GC-MS calcd. for $[C_{15}H_{19}OCl]^+$: 250.77, found: 250. $[\alpha]_D^{20} = -73.6$ (*c* 1.00, $CHCl_3$).

4.3.9. 1-(3-Bromophenyl)-non-2-yn-1-ol

89% yield. 95% ee determined by HPLC analysis. Retention time: t_{major} = 5.4 min, and t_{minor} = 5.8 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.70 (s, 1H), 7.45-7.43 (m, 2H), 7.26-7.21 (m, 1H), 5.41 (s, 1H), 2.29-2.25 (t, *J* = 8.0 Hz, 2H), 2.19 (br, 1H), 1.50-1.25 (m, 8H), 0.91-0.87 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.4, 131.2, 130.1, 129.8, 125.3, 122.5, 88.4, 79.4, 64.1, 31.1, 28.6, 28. 6, 22.7, 18.8, 14.1. GC-MS calcd. for $[C_{15}H_{19}OBr]^+$: 295.22, found: 295. $[\alpha]_D^{20} = -44.3$ (*c* 0.45, $CHCl_3$).

4.3.10. 1-(2-Chlorophenyl)-non-2-yn-1-ol

76% yield. 82% ee determined by HPLC analysis. Retention time: t_{major} = 6.1 min, and t_{minor} = 6.8 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.76-7.75 (d, *J* = 6.8 Hz, 1H), 7.36-7.22 (m, 3H), 5.80 (s, 1H), 2.53 (s, 1H), 2.27-2.23 (m, 2H), 1.42-1.26 (m, 8H), 0.90-0.83 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.6, 132.7, 129.6, 129.1, 128.3, 127.1, 87.8, 78.9, 62.3, 31.6, 31.3, 28.5, 22.6, 18.8, 14.1. GC-MS calcd. for $[C_{15}H_{19}OCl]^+$: 250.77, found: 250. $[\alpha]_D^{20} = +25.5$ (*c* 0.95, $CHCl_3$).

4.3.11. 1-(4-Fluorophenyl)-non-2-yn-1-ol

84% yield. 94% ee determined by HPLC analysis. Retention time: t_{major} = 5.3 min, and t_{minor} = 5.8 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53-7.50 (d, *J* = 14.0 Hz, 2H), 7.26 (s, 1H), 7.05 (s, 1H), 5.43 (s, 1H), 2.29-2.26 (m, 2H), 2.20 (br, 1H), 1.56-1.28 (m, 8H), 0.91-0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.8, 137.1, 128.5, 128.4, 115.4, 115.2, 88.0, 79.7, 64.1, 31.3, 28.5, 28.5, 22.5, 18.8, 14.0. GC-MS calcd. for $[C_{15}H_{19}OF]^+$: 234.32, found: 234. $[\alpha]_D^{20} = -18.0$ (*c* 0.52, $CHCl_3$).

4.3.12. 1-Phenyl-hept-2-yn-1-ol

68% yield. 74% ee determined by HPLC analysis. Retention time: t_{major} = 5.6 min, and t_{minor} = 7.4 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54-7.26 (m, 5H), 5.46 (s, 1H), 2.17 (br, 1H), 2.30-2.26 (t, *J* = 8.0 Hz, 2H), 1.55-1.25 (m, 4H), 0.94-0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 141.2, 131.3, 128.5, 128.2, 126.6, 126.6, 79.8, 77.0, 64.8, 30.6, 22.0, 18.5, 13.6. GC-MS calcd. for $[C_{13}H_{16}O]^+$: 188.27, found: 188. $[\alpha]_D^{20} = -54.1$ (*c* 0.79, $CHCl_3$).[8d,9]

4.3.13. 1-(4-Methylphenyl)-hept-2-yn-1-ol

84% yield. 90% ee determined by HPLC analysis. Retention time: t_{major} = 5.1 min, and t_{minor} = 5.6 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44-7.42 (d, *J* = 8.0 Hz, 2H), 7.19-7.17 (d, *J* = 8.0 Hz, 2H), 5.41 (s, 1H), 2.35 (s, 3H), 2.29-2.25 (t, *J* = 8.0 Hz, 2H), 2.06 (br, 1H), 1.58-1.38 (m, 4H), 0.93-0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.2, 137.8, 129.0, 129.0, 126.4, 126.4, 87.2, 79.8, 64.5, 30.5, 21.8, 21.0, 18.3, 13.4. GC-MS calcd. for $[C_{14}H_{18}O]^+$: 202.30, found: 202. $[\alpha]_D^{20} = -67.4$ (*c* 1.05, $CHCl_3$).

4.3.14. 1-(3-Methoxyphenyl)-hept-2-yn-1-ol

75% yield. 92% ee determined by HPLC analysis. Retention time: t_{major} = 6.5 min, and t_{minor} = 8.7 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31-7.26 (t, *J* = 9.8 Hz, 1H), 7.13-7.11 (m, 2H), 6.87-6.85 (d, *J* = 10.8 Hz, 1H), 5.42 (s, 1H), 3.82 (s, 3H), 2.29-2.25 (t, *J* = 8.0 Hz, 2H), 2.17 (br, 1H), 1.56-1.25 (m, 4H), 0.93-0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.5, 142.6, 129.4, 118.7, 113.8, 111.7, 87.5, 79.6, 64.6, 55.1, 30.4, 21.8, 18.3, 13.4. GC-MS calcd. for $[C_{14}H_{18}O_2]^+$: 218.29, found: 218. $[\alpha]_D^{20} = -63.2$ (*c* 1.02, $CHCl_3$).

4.3.15. 1-(3-Fluorophenyl)-hept-2-yn-1-ol

73% yield. 86% ee determined by HPLC analysis. Retention time: t_{major} = 7.8 min, and t_{minor} = 8.3 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37-7.26 (m, 3H), 7.03-6.99 (m, 1H), 5.44 (s, 1H), 2.30-2.26 (t, *J* = 7.8 Hz, 2H), 2.01 (br, 1H), 1.57-1.25 (m, 4H), 0.94-0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.1, 149.5, 129.8, 122.0, 114.8, 113.4, 87.9, 79.2, 64.0, 30.4, 21.8, 18.3, 13.4. GC-MS calcd. for $[C_{13}H_{15}FO]^+$: 206.25, found: 206. $[\alpha]_D^{20} = -49.0$ (*c* 0.97, $CHCl_3$).

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