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Lithium Binaphtholate-Catalyzed Enantioselective Enyne Addition to Ketones: Access to Enynylated Tertiary Alcohols

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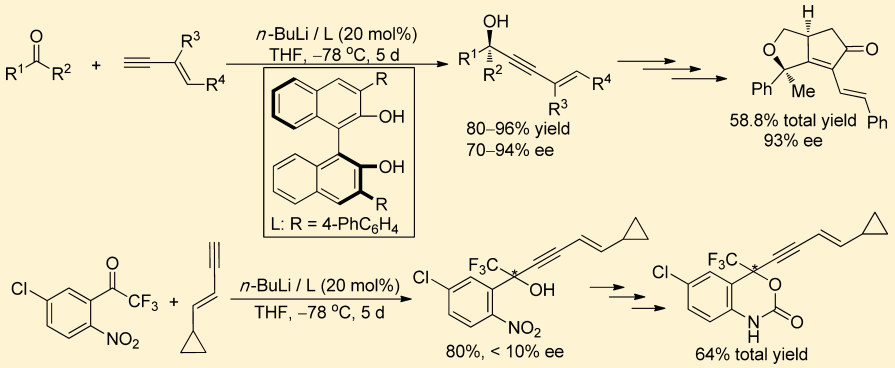
Supporting Information

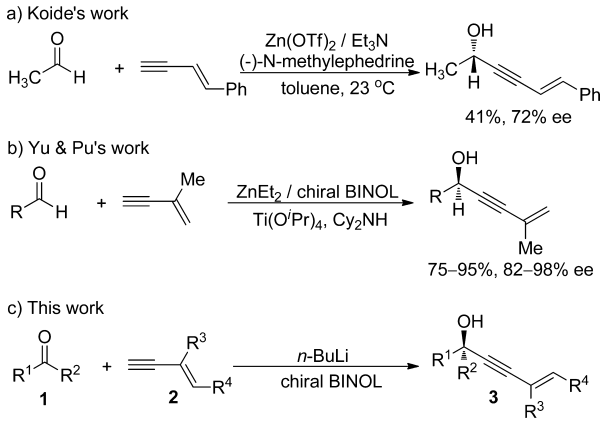


ABSTRACT: A new catalytic enantioselective enyne addition to ketones has been developed. In the presence of chiral lithium binaphtholate, the addition reaction proceeded smoothly to produce a series of enynylated tertiary alcohols in up to 96% yield and 94% enantiomeric excess. Convenient transformation of the adduct via Pauson–Khand cycloaddition reaction afforded the bicyclic product without detectable loss of enantioselectivity. Furthermore, catalytic asymmetric enyne addition to trifluoromethylketone was applied in the synthesis of the Efavirenz analogue.

INTRODUCTION

Optically active propargylic alcohols are important structural subunits that can be found in a wide range of natural products and biologically active compounds.[1] Catalytic enantioselective addition of alkynylating reagents to carbonyl compounds, which can construct a carbon skeleton with concomitant creation of a stereogenic center, represents one of the most direct and efficient methods for synthesis of optically active propargylic alcohols.[2] In this context, the catalytic enantioselective alkynylation of aldehydes and ketones has been extensively studied in the past decade, and many addition reactions have been successfully used in the efficient synthesis of natural products and bioactive compounds.[3] However, nearly all such studies have focused on the utility of alkynes and diynes, and little attention has been paid to exploring conjugated enynes as viable nucleophilic substrates in catalytic enantioselective addition to carbonyl compounds. Recently, Koide and co-workers[4a] provided an example of enantioselective enynylation of acetaldehyde by using a stoichiometric amount of chiral zinc complex (Scheme 1a), whereas Yu, Pu, and co-workers[4b] described titanium-catalyzed enantioselective addition of enynes to aldehydes (Scheme 1b). In contrast, the use of ketones as electrophilic acceptors for the catalytic enantioselective addition of enynes still remains a formidable challenge, and there has been no report in the literature to date of such a potentially useful transformation. Herein, we report our efforts in developing a new lithium binaphtholate-catalyzed enantioselective addition of conjugated enynes to ketones (Scheme 1c). This rapid approach would set the stereocenter of the tertiary alcohol and introduce the enyne moiety in a single chemical operation.

Scheme 1. Catalytic Enantioselective Addition of Conjugated Enynes to Carbonyl Compounds



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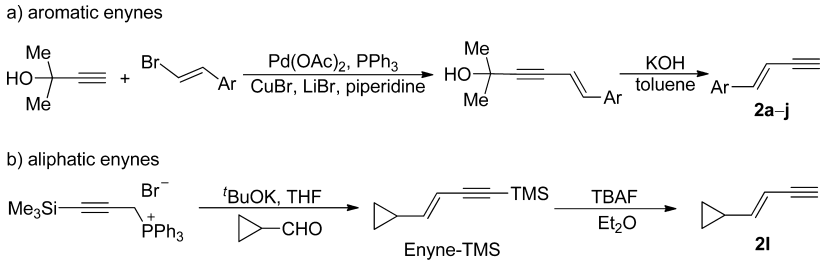
Scheme 2. Synthesis of Aromatic and Aliphatic Enynes



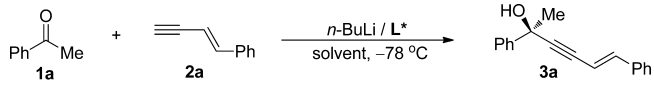
RESULTS AND DISCUSSION

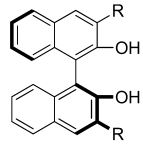
Preparation of Enynes. Aryl- and alkyl-substituted enynes were synthesized according to the procedures shown in Scheme 2. In the presence of $Pd(OAc)_2/PPh_3$, CuBr, and LiBr, the cross-coupling reaction of 2-aryl-1-bromoethenes with 2-methylbut-3-yn-2-ol proceeded smoothly to give the coupling intermediates, which were refluxed with KOH in toluene to afford the corresponding aryl-substituted enynes **2a–j** in 42–64% yields (Scheme 2a).[5] The aliphatic enyne **2l** was synthesized according to known methods in the literature.[6] The Wittig olefination of cyclopropanecarbaldehyde with trimethylsilyl-protected prop-2-yn-1-ylide gave the corresponding (*E*)-enynyltrimethylsilane (enyne-TMS) in 62% yield. Subsequent desilylation afforded (*E*)-but-1-en-3-yn-1-ylcyclopropane **2l** in essentially quantitative yield (Scheme 2b).

Optimization of Reaction Conditions. We recently developed both catalytic enantioselective alkynylation and diynylation of ketones in the presence of titanium and copper complexes by using zinc acetylides.[7] On the basis of these two precedents, we first examined the model reaction of acetophenone **1a** with enyne **2a** under otherwise identical reaction conditions. However, low reactivity and/or low enantioselectivity were observed. Inspired by the success with lithium acetylides in enantioselective alkynylations,[8] we subsequently investigated the use of lithium binaphtholate based on 3,3′-functionalization of (1,1′-binaphthalene)-2,2′-diol (BINOL). The results are listed in Table 1. In the presence of *n*-butyllithium, the simplest ligand BINOL (**L1**) catalyzed this enynlation reaction in tetrahydrofuran (THF) at −78 °C for 24 h to give adduct **3a** in 30% yield with 26% enantiomeric excess (ee) (entry 1). Next, a series of BINOL-type ligands containing various groups at the 3,3′-positions of the binaphthol backbone were tested for the model reaction (entries 2–12). The 4-biphenyl-substituted ligand **L10** proved to be optimal, delivering product **3a** in 80% yield with high enantioselectivity (86% ee), whereas all the other ligands resulted in a substantial decrease in the yield and/or enantioselectivity (entries 2–9, 11, and 12 versus entry 10). Subsequent screening of solvents revealed that this asymmetric addition is highly sensitive to the solvent used (entries 13–15), and THF was found to be the best solvent for this reaction. In addition, this reaction was carried out in higher yield and enantioselectivity with prolonged reaction time and/or by increasing the amount of ligand **L10** (entries 16–18). Finally, the addition reaction was run at 0 or 25 °C, and the desired adduct **3a** was also obtained in respectable yields and enantioselectivities (entries 19 and 20).

Scope of Enynylation Addition. Under these conditions, we examined the scope of lithium binaphtholate-catalyzed enantioselective addition of various enynes and ketones (Scheme 3). For a series of phenyl-substituted but-3-en-1-ynes, the position and electronic properties of the substituents on the phenyl ring have a limited effect on enantioselectivity of the addition. Regardless of whether there were electron-neutral, -donating, or -withdrawing groups on the phenyl ring, the addition reactions proceeded smoothly to give the desired adducts **3a–g** in good to high yields (80–96%) with high enantioselectivities (88–94% ee). 2-Naphthyl-, 1-naphthyl-, and 3-thiophenyl-substituted enynes were also good substrates, affording products **3h–j** in 81–90% yields with 90–92% ee. Three alkyl-substituted enynes were subjected to this addition reaction under the same conditions, and the desired products **3k–m** were obtained in 80–90% yields with good to high enantioselectivities.

Table 1. Effect of Ligand, Solvent, and Other Reaction Conditions on Addition Reaction[a]





L1: R = H
L2: R = Ph
L3: R = 1-Naphthyl
L4: R = 4-MeC_6H_4
L5: R = 4-$MeOC_6H_4$
L6: R = 3,5-$Me_2C_6H_3$
L7: R = 4-$TMSC_6H_4$
L8: R = 4-$NO_2C_6H_4$
L9: R = 4-BrC_6H_4
L10: R = 4-PhC_6H_4
L11: R = 3,5-$Ph_2C_6H_3$
L12: R = [3,5-$(CF_3)_2C_6H_3$]C_6H_4

entry	chiral ligand (mol %)	solvent	time, days	yield,[b] %	ee,[c] %
1	**L1** (10)	THF	1	30	26
2	**L2** (10)	THF	1	80	80
3	**L3** (10)	THF	1	42	67
4	**L4** (10)	THF	1	70	71
5	**L5** (10)	THF	1	62	85
6	**L6** (10)	THF	1	62	0
7	**L7** (10)	THF	1	60	10
8	**L8** (10)	THF	1	46	37
9	**L9** (10)	THF	1	50	3
10	**L10** (10)	THF	1	80	86
11	**L11** (10)	THF	1	40	25
12	**L12** (10)	THF	1	80	81
13	**L10** (10)	toluene	1	52	33
14	**L10** (10)	CH_2Cl_2	1	48	5
15	**L10** (10)	Et_2O	1	45	0
16	**L10** (10)	THF	2	90	86
17	**L10** (20)	THF	5	92	91
18	**L10** (40)	THF	5	93	91
19[d]	**L10** (20)	THF	0.5	86	86
20[e]	**L10** (20)	THF	0.5	88	85

[a]Reactions were conducted with 1 equiv of **1a**, 2 equiv of **2a**, 2 equiv of *n*-BuLi (2.5 M in hexane), and the ligand in solvent at −78 °C. [b]Yield of isolated products. [c]The ee values were determined by HPLC analysis on a chiral stationary phase. [d]Reaction temperature was 0 °C. [e]Reaction temperature was 25 °C.

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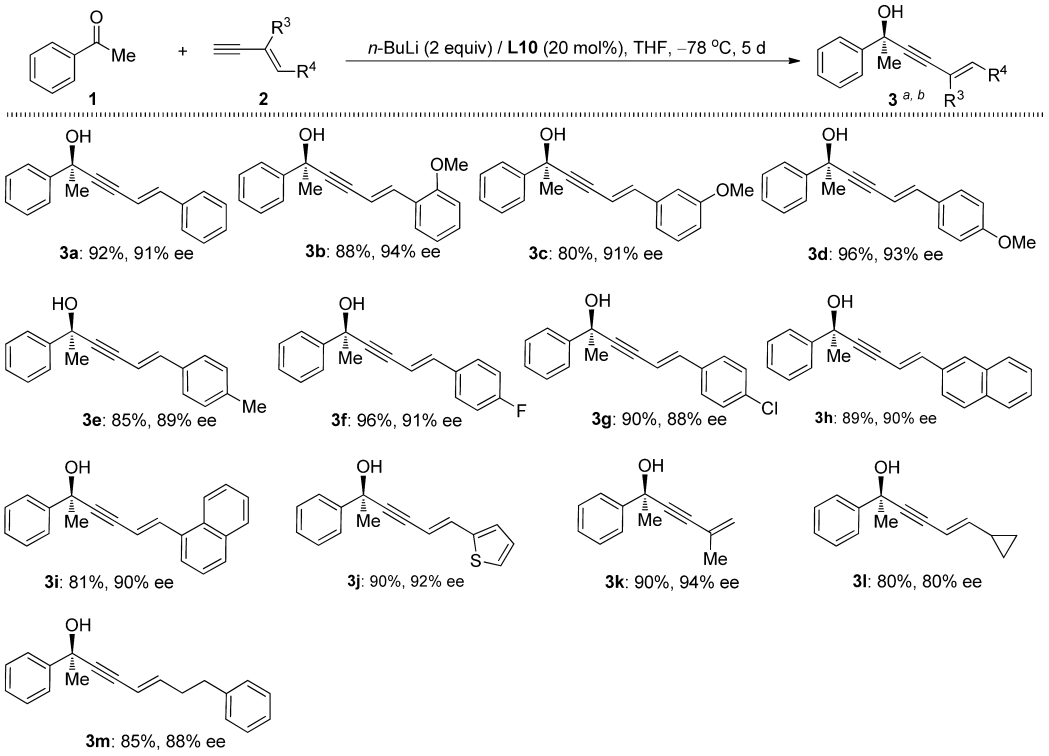
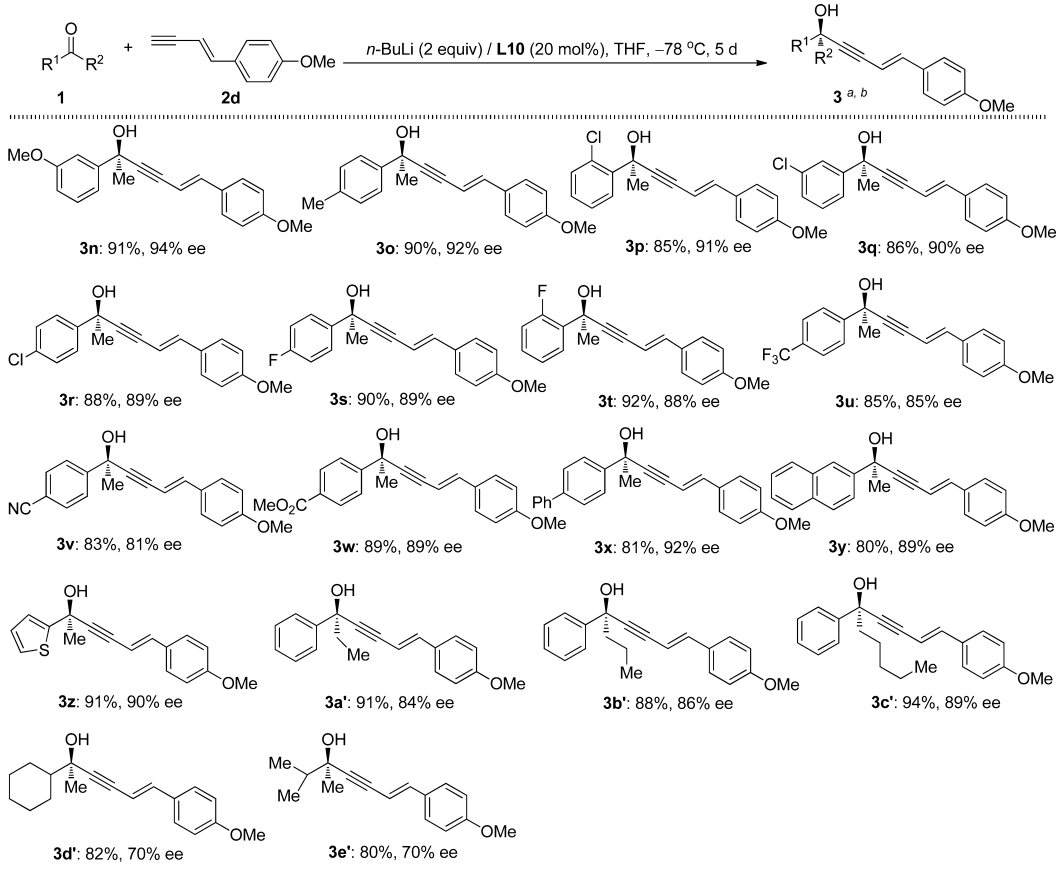
Scheme 3. Enantioselective 1,2-Addition of Various Enynes 2 to Acetophenone 1a[a,b]



[a]Yield of isolated products. [b]The ee values were determined by HPLC analysis on a chiral stationary phase.

Scheme 4. Enantioselective 1,2-Addition of Enyne 2a to a Series of Ketones 1[a,b]



[a]Yield of isolated products. [b]The ee values were determined by HPLC analysis on a chiral stationary phase.

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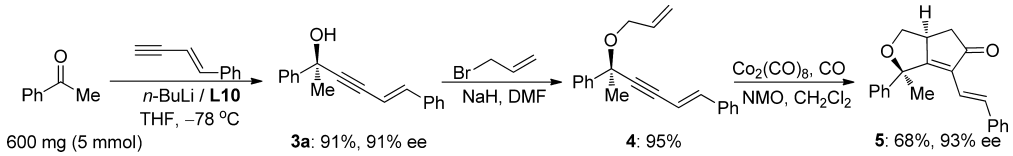
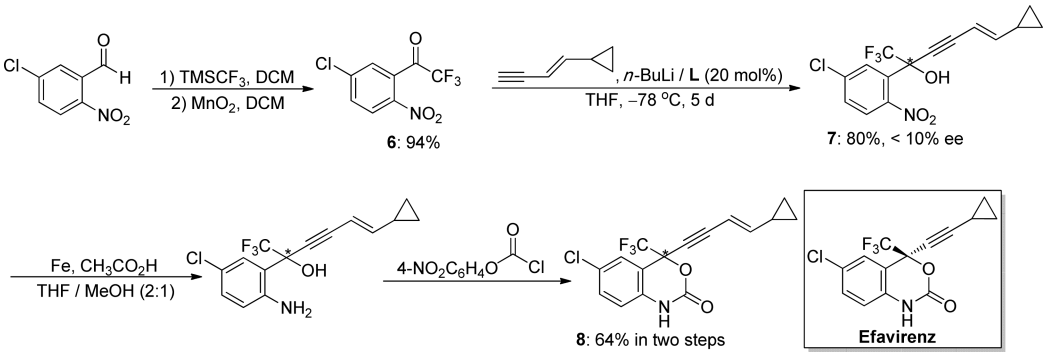
Scheme 5. Scaled-up Version of Addition Reaction and Further Synthetic Transformation of Adduct 3a



Scheme 6. Preparation of Analogue 8 of Anti-HIV Drug Efavirenz



Next, this protocol was extended to the use of various ketones (Scheme 4). The results showed that addition reactions took place to afford the adducts **3n**−**z** in yields of 80−92% with 81−94% ee for aromatic- and heteroaromatic-substituted methylketones. One of the enynylated tertiary alcohols (**3u**) was crystallized from CH_2Cl_2−petroleum ether, and its absolute configuration was determined to be *R* from the X-ray structural analysis.[9] Interestingly, two acetophenones bearing 4-cyano and ester groups on the phenyl ring participated in the addition reaction, affording the desired products **3v** and **3w** with exceptional chemoselectivity. To further define the scope of our methodology, the addition reactions of different alkyl-substituted phenylketones were also tested. The corresponding products **3a′**−**3c′** were also obtained in high yields and enantioselectivities. In addition, we investigated the addition reaction with alkyl-substituted ketones. These substrates were found to give good yields and ee values. For example, in the presence of ligand **L10**, 1-cyclohexylethanone and 3-methyl-butan-2-one provided the adducts **3d′** and **3e′** in good yields with 70% ee.

Further Synthetic Transformation of Enynylation Adduct. To evaluate this catalytic system on a large scale, 5 mmol of acetophenone **1a** was used to perform the enynylation reaction, and adduct **3a** was obtained in 91% yield and 91% ee (Scheme 5). Treatment of **3a** with sodium hydride and allyl bromide in *N*,*N*-dimethylformamide (DMF) led to formation of optically active dienyne **4** in 95% yield. Then we tested the Pauson−Khand cycloaddition reaction of dienyne **4** by using a $Co_2(CO)_8$ catalyst and CO at atmospheric pressure. Bicyclic adduct **5** was obtained in 68% yield without detectable loss of enantioselectivity. Simple recrystallization provided the single stereoisomer **5** with excellent optical purity. Furthermore, X-ray structure analysis revealed the syn relationship between the methyl group and the newly formed bridgehead hydrogen.[9]

Efavirenz Analogue Synthesis. Subsequently, a short synthesis of the Efavirenz[10] analogue was also conducted (Scheme 6). Trifluoromethylketone **6** was synthesized in two steps in high yield.[10c] The enantioselective catalytic addition of (*E*)-but-1-en-3-yn-1-ylcyclopropane to trifluoromethylketone **6** provided the desired adduct **7** in 80% yield, albeit with 10% ee. Apparently, the electron-withdrawing substituents at the phenyl ring and the trifluoromethyl group could influence the stereoselectivity of this reaction. Reduction of **7** in the presence of iron powder and acetic acid in THF/MeOH gave the corresponding amine, which was then converted in good overall yield to 1*H*-benzo[*d*][1,3]oxazin-2(4*H*)-one **8**, an analogue of the anti-HIV drug Efavirenz. Further investigation will be necessary to improve the enantioselectivity of this reaction and to assess the biological activity of this intriguing compound.

■ CONCLUSION

In summary, we have successfully developed the first catalytic enantioselective 1,2-addition of enynes to ketones. In the presence of chiral lithium binaphtholate, the addition reaction proceeded smoothly to give a broad variety of tertiary propargylic alcohols in 80−96% yields with 70−94% ee. Synthetic transformation of the adduct via Pauson−Khand cycloaddition reaction afforded the bicyclic product without detectable loss of enantioselectivity. Furthermore, catalytic asymmetric enyne addition to trifluoromethylketone was applied in synthesis of the Efavirenz analogue. Further extension of this enynylation addition to other substrates and investigation of the biological activity of the relative derivatives are ongoing in our laboratory, and the results will be reported in due course.

■ EXPERIMENTAL SECTION

General Information. Solvents were distilled following standard procedures before use. Analytical thin-layer chromatography (TLC) was performed on 0.20 mm silica gel plates. Silica gel (200−300 mesh) was used for flash chromatography. ^1H, ^{13}C, and ^{19}F NMR were recorded at 400 or 600 MHz (^1H NMR), 100 or 150 MHz (^{13}C NMR), and 376 or 565 MHz (^{19}F NMR). Chemical shifts were reported in parts per million (ppm) downfield from internal Me_4Si and external CCl_3F, respectively. High-resolution mass spectra (HRMS) were recorded by using the following ion sources: time-of-flight (TOF) QII or Fourier transform mass spectrometer with electrospray ionization (FTMS-ESI) or with matrix-assisted laser desorption ionization (FTMS-MALDI).

Materials. Tetrahydrofuran (THF), diethyl ether, and toluene were distilled from sodium/benzophenone prior to use; CH_2Cl_2 (dichloromethane, DCM) were distilled from CaH_2. All purchased reagents

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were used without further purification. Aliphatic enyne **2m**[6] and 3,3′-disubstituted (*S*)-BINOLs **L2**−**L12**[11] are known compounds and could be prepared according to inatiliterature methods.

General Procedure for Preparation of Aryl-Substituted Enynes 2a−2j.[5a] Under a nitrogen atmosphere, 2-aryl-1-bromoethene (27.3 mmol), $Pd(OAc)_2$ (18.2 mg, 0.082 mmol), CuBr (52.1 mg, 0.36 mmol), and PPh_3 (143.2 mg, 0.55 mmol) were mixed and stirred for a few minutes at ambient temperature. Piperidine (80 mL, distilled from CaH_2) and 2-methyl-3-butyn-1-ol (2.73 g, 32.8 mmol) were added to this mixture, and it was stirred at 50 °C for 30 min. Then LiBr (166.0 mg, 1.9 mmol) was added and the mixture was further stirred for 1.5 h. The reaction was quenched with water, and the mixture was extracted with ether (30 mL × 3). The organic layer was combined, washed twice with 2 N HCl solution, and dried over Na_2SO_4. The solvent was distilled under vacuum, and the residue was purified by flash column chromatography to give the corresponding enynol for the next step.

To a solution of enynol (10.7 mmol) in toluene (200 mL) was added powdered potassium hydroxide (1.2 g, 21.4 mmol). The mixture was refluxed for 1 h under an argon atomsphere. After completion of the reaction (monitored by TLC), the reaction mixture was filtered and solvent was removed under reduced pressure. The residue was purified by column chromatography to give the corresponding aryl-substituted enynes **2a**−**2j**.

*(E)-1-(But-1-en-3-ynyl)benzene (**2a**).* Liquid; 864.0 mg, 63% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, J = 7.3 Hz, 2H), 7.33−7.27 (m, 3H), 7.03 (d, J = 16.3 Hz, 1H), 6.12 (dd, J = 16.3, 1.8 Hz, 1H), 3.05 (d, J = 1.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2, 136.0, 129.0, 128.8, 126.5, 107.2; HRMS (ESI) found m/z 129.0703 [M + H]$^+$, calcd for $C_{10}H_8$ + H 129.0704; IR (KBr) ν 3298, 3055, 2935, 1601, 1509, 1446, 1223, 987, 706, 695, 622, 520 cm^{-1}.

*(E)-1-(But-1-en-3-ynyl)-2-methoxybenzene (**2b**).* Liquid; 846.4 mg, 50% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (dd, J = 14.3, 5.6 Hz, 2H), 7.30 (t, J = 7.8 Hz, 1H), 6.97 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.28 (dd, J = 16.5, 2.3 Hz, 1H), 3.86 (s, 3H), 3.10 (d, J = 2.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.1, 138.6, 130.0, 127.0, 124.9, 120.7, 111.1, 107.6, 83.8, 78.8, 55.45; HRMS (ESI) found m/z 159.0812 [M + H]$^+$, calcd for $C_{11}H_{10}O$ + H 159.0810; IR (KBr) ν 3312, 3066, 3011, 2975, 2865, 1605, 1501, 1482, 1261, 1130, 1058, 982, 752, 626, 505 cm^{-1}.

*(E)-1-(But-1-en-3-ynyl)-3-methoxybenzene (**2c**).* Liquid; 711.0 mg, 42% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54−7.04 (m, 3H), 6.98−6.73 (m, 2H), 6.65 (s, 1H), 5.98 (d, J = 15.6 Hz, 1H), 3.71 (s, 3H), 3.00 (d, J = 34.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 141.8, 136.5, 133.9, 116.4, 114.6, 111.7, 110.1, 82.6, 80.5, 55.7; HRMS (ESI) found m/z 159.0812 [M + H]$^+$, calcd for $C_{11}H_{10}O$ + H 159.0810; IR (KBr) ν 3308, 3030, 2980, 1619, 1483, 1298, 1251, 1187, 1054, 981, 804, 625, 498 cm^{-1}

*(E)-1-(But-1-en-3-ynyl)-4-methoxybenzene (**2d**).* White solid; mp 46−47 °C; 1083.4 mg, 64% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 16.3 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 5.99 (dd, J = 16.3, 2.3 Hz, 1H), 3.82 (s, 3H), 3.01 (d, J = 2.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.5, 142.9, 128.9, 127.9, 114.4, 104.7, 83.5, 78.6, 55.51; HRMS (ESI) found m/z 159.0810 [M + H]$^+$, calcd for $C_{11}H_{10}O$ + H 159.0810; IR (KBr) ν 3278, 2988, 2955, 1602, 1512, 1274, 1258, 1176, 1029, 964, 851, 814, 687, 534 cm^{-1}.

*(E)-1-(But-1-en-3-ynyl)-4-methylbenzene (**2e**).* Liquid; 882.5 mg, 58% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 16.3 Hz, 1H), 6.11 (dd, J = 16.3, 2.2 Hz, 1H), 3.06 (d, J = 2.2 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.3, 139.2, 133.3, 129.6, 126.4, 106.0, 79.0, 21.5; HRMS (ESI) found m/z 143.0860 [M + H]$^+$, calcd for $C_{11}H_{10}$ + H 143.0861; IR (KBr) ν 3283, 3028, 2920, 1607, 1512, 1449, 1412, 1211, 1181, 959, 800, 522 cm^{-1}.

*(E)-1-(But-1-en-3-ynyl)-4-fluorobenzene (**2f**).* White solid; mp 29−30 °C; 875.8 mg, 56% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38−7.33 (m, 2H), 7.02 (dd, J = 20.9, 12.4 Hz, 3H), 6.05 (d, J = 16.3 Hz, 1H), 3.06 (d, J = 1.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2 (d, J = 247.7 Hz), 142.0, 132.2, 128.2 (d, J = 8.1 Hz), 116.0 (d, J = 10.1 Hz), 107.0 (d, J = 2.4 Hz), 82.9, 79.4; ^{19}F NMR (565 MHz, $CDCl_3$) δ −112.01∼−112.06 (m, 1F); HRMS (ESI) found m/z 147.0605 [M + H]$^+$, calcd for $C_{10}H_7F$ + H 147.0610; IR (KBr) ν 3271, 2962, 1585, 1499, 1402, 1034, 937, 824, 656, 560 cm^{-1}.

*(E)-1-(But-1-en-3-ynyl)-4-chlorobenzene (**2g**).* White solid; mp 39−40 °C; 1096.2 mg, 63% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (s, 4H), 6.98 (d, J = 16.3 Hz, 1H), 6.10 (dd, J = 16.3, 2.3 Hz, 1H), 3.07 (d, J = 2.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.9, 134.8, 134.5, 129.1, 127.7, 107.9, 82.7, 80.0; HRMS (ESI) found m/z 163.0313 [M + H]$^+$, calcd for $C_{10}H_7Cl$ + H 163.0315; IR (KBr) ν 3272, 2918, 1591, 1496, 1403, 1089, 1010, 954, 804, 614, 515 cm^{-1}.

*(E)-2-(But-1-en-3-ynyl)naphthalene (**2h**).* White solid; mp 77−78 °C; 1068.0 mg, 56% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72−7.66 (m, 3H), 7.62 (s, 1H), 7.45 (dd, J = 8.6, 1.5 Hz, 1H), 7.41−7.37 (m, 2H), 7.12 (d, J = 16.3 Hz, 1H), 6.18 (dd, J = 16.3, 2.1 Hz, 1H), 3.07 (d, J = 2.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.3, 133.7, 133.5, 133.4, 128.6, 128.4, 127.8, 127.3, 126.6, 122.8, 107.4, 83.3, 79.8; HRMS (ESI) found m/z 179.0863 [M + H]$^+$, calcd for $C_{14}H_{10}$ + H 179.0861; IR (KBr) ν 3287, 3053, 2922, 1688, 1597, 1505, 1360, 1264, 1170, 956, 858, 813, 747, 645 cm^{-1}.

*(E)-1-(But-1-en-3-ynyl)naphthalene (**2i**).* White solid; mp 54−55 °C; 1144.3 mg, 60% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 16.0 Hz, 3H), 7.64 (d, J = 7.2 Hz, 1H), 7.53 (dd, J = 13.0, 7.5 Hz, 2H), 7.46 (t, J = 7.7 Hz, 1H), 6.21 (dd, J = 16.1, 2.2 Hz, 1H), 3.12 (d, J = 1.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.5, 133.8, 133.5, 131.0, 129.5, 128.8, 126.7, 126.2, 125.7, 123.8, 123.6, 109.9, 83.3, 79.2; HRMS (ESI) found m/z 179.0861 [M + H]$^+$, calcd for $C_{14}H_{10}$ + H 179.0861; IR (KBr) ν 3287, 3050, 1594, 1510, 1430, 1375, 1252, 1189, 951, 773, 628 cm^{-1}.

*(E)-2-(But-1-en-3-ynyl)thiophene (**2j**).* Liquid; 818.5 mg, 57% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (d, J = 5.0 Hz, 1H), 7.15 (d, J = 16.1 Hz, 1H), 7.05 (d, J = 3.4 Hz, 1H), 7.00 (dd, J = 4.9, 3.7 Hz, 1H), 5.96 (dd, J = 16.0, 1.8 Hz, 1H), 3.09 (d, J = 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.0, 136.0, 127.9, 127.6, 125.9, 106.3, 82.8, 79.8; HRMS (ESI) found m/z 135.0263 [M + Na]$^+$, calcd for C_8H_6S + H 135.0268; IR (KBr) ν 3301, 3038, 2971, 1627, 1532, 1469, 1226, 991, 812, 723, 629, 523 cm^{-1}.

General Procedure for Enantioselective Addition of Enynes to Ketones. A solution of (*E*)-but-1-en-3-yn-1-ylbenzene (**2a**) (51.2 mg, 0.4 mmol) and ligand **L10** (23.6 mg, 0.04 mmol) in THF (1 mL) was stirred at −78 °C for 20 min under Ar_2. *n*-BuLi (2.5 M in hexane, 0.16 mL, 0.4 mmol) was slowly dropped into the above solution via syringe and the homogeneous solution was stirred for 20 min, and then acetophenone (23.5 μL, 0.2 mmol) was added. The mixture was allowed to stir at −78 °C for 5 days. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted by ether (5 mL × 3). The organic layer was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified via flash column chromatography (silica gel) with 5% ethyl acetate in petroleum ether as eluent to give the addition product **3a**. The enantiomeric excess was determined by HPLC analysis on a Chiralcel column. Other adducts **3b**−**k**, **3m**−**z**, and **3a′**−**e′** were obtained through similar procedures.

*(R,E)-2,6-Diphenylhex-5-en-3-yn-2-ol (**3a**).* Liquid; 45.6 mg, 92% yield; 91% ee; $[\alpha]_D^{20}$ = +21.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, J = 7.5 Hz, 2H), 7.40 (dd, J = 7.2, 4.8 Hz, 4H), 7.36−7.29 (m, 4H), 7.01 (d, J = 16.3 Hz, 1H), 6.25 (d, J = 16.3 Hz, 1H), 2.50 (s, 1H), 1.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.8, 142.0, 136.3, 128.9, 128.5, 127.9, 126.5, 125.1, 107.6, 94.8, 84.3, 70.6, 33.4; HRMS (ESI) found m/z 271.1100 [M + Na]$^+$, calcd for $C_{18}H_{16}O$ + Na 271.1099; IR (KBr) ν 3481, 3031, 2992, 2933, 2836, 1600, 1510, 1489, 1250, 1170, 1021, 956, 823, 760, 701, 530 cm^{-1}; HPLC (Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (major) = 6.3 min, t_R (minor) = 7.0 min.

*(R,E)-6-(2-Methoxyphenyl)-2-phenylhex-5-en-3-yn-2-ol (**3b**).* Liquid; 48.9 mg, 88% yield; 94% ee; $[\alpha]_D^{20}$ = +17.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J = 7.8 Hz, 2H), 7.37 (dd, J = 14.8, 7.4 Hz, 3H), 7.30 (dd, J = 15.1, 6.6 Hz, 2H), 7.26−7.22 (m, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.31 (d, J = 16.4 Hz, 1H), 3.83 (s, 3H), 2.55 (s, 1H), 1.82 (s, 3H); ^{13}C

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NMR (150 MHz, $CDCl_3$) δ 157.1, 145.9, 137.4, 129.9, 128.5, 127.8, 127.1, 125.3, 125.2, 120.9, 111.2, 108.2, 94.2, 85.0, 70.6, 55.6, 33.4; HRMS (ESI) found m/z 301.1199 $[M + Na]^+$, calcd for $C_{19}H_{18}O_2$ + Na 301.1205; IR (KBr) ν 3396, 3057, 2983, 2837, 1597, 1488, 1463, 1247, 1163, 1027, 959, 924, 752, 700, 598, 579 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (major) = 7.4 min, t_R (minor) = 8.2 min.

(R,E)-6-(3-Methoxyphenyl)-2-phenylhex-5-en-3-yn-2-ol (**3c**). Liquid; 44.5 mg, 80% yield; 91% ee; $[\alpha]_D^{20}$ = +10.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.1 Hz, 2H), 7.35 (d, *J* = 7.0 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.06−6.97 (m, 2H), 6.95 (s, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.26 (d, *J* = 16.2 Hz, 1H), 3.84 (s, 3H), 2.59 (s, 1H), 1.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.0, 145.8, 141.9, 137.7, 129.9, 128.5, 127.9, 125.1, 119.2, 114.5, 111.8, 108.0, 94.9, 84.2, 70.6, 55.4, 33.4; HRMS (ESI) found m/z 301.1197 $[M + Na]^+$, calcd for $C_{19}H_{18}O_2$ + Na 301.1205; IR (KBr) ν 3414, 3028, 2928, 2851, 2836, 1578, 1490, 1450, 1289, 1242, 1155, 1042, 953, 765, 700, 510 cm^{-1}; HPLC (Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 92.5/7.5, 1.0 mL/min, 254 nm) t_R (major) = 15.9 min, t_R (minor) = 43.5 min.

(R,E)-6-(4-Methoxyphenyl)-2-phenylhex-5-en-3-yn-2-ol (**3d**). Liquid; 53.3 mg, 96% yield; 93% ee; $[\alpha]_D^{20}$ = +24.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.34 (dd, *J* = 11.1, 8.1 Hz, 3H), 6.98 (d, *J* = 16.3 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.12 (d, *J* = 16.3 Hz, 1H), 3.84 (s, 3H), 2.58 (s, 1H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 146.0, 141.6, 129.2, 128.5, 127.8, 125.2, 114.4, 105.2, 94.1, 84.6, 70.6, 55.5, 33.4; HRMS (ESI) found m/z 301.1201 $[M + Na]^+$, calcd for $C_{19}H_{18}O_2$ + Na 301.1205; IR (KBr) ν 3420, 3031, 2983, 2932, 2837, 1604, 1511, 1448, 1250, 1175, 1097, 1030, 956, 926, 813, 764, 700, 533 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 15.0 min, t_R (major) = 20.4 min.

(R,E)-2-Phenyl-6-(p-tolyl)hex-5-en-3-yn-2-ol (**3e**). Liquid; 44.6 mg, 85% yield; 89% ee; $[\alpha]_D^{20}$ = +16.5 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 16.3 Hz, 1H), 6.21 (d, *J* = 16.3 Hz, 1H), 2.65 (s, 1H), 2.38 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.9, 142.0, 139.0, 133.5, 129.6, 128.5, 127.8, 126.40, 125.1, 106.5, 94.4, 84.5, 70.6, 33.4, 21.5; HRMS (ESI) found m/z 285.1252 $[M + Na]^+$, calcd for $C_{19}H_{18}O$ + Na 285.1256; IR (KBr) ν 3299, 3026, 2961, 2929, 2871, 1601, 1513, 1448, 1261, 1182, 1074, 1027, 940, 800, 700, 521 cm^{-1}; HPLC (Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (major) = 6.2 min, t_R (minor) = 6.7 min.

(R,E)-6-(4-Fluorophenyl)-2-phenylhex-5-en-3-yn-2-ol (**3f**). Liquid; 51.1 mg, 96% yield; 91% ee; $[\alpha]_D^{20}$ = +6.7 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.41−7.30 (m, 5H), 7.03 (t, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 16.3 Hz, 1H), 6.15 (d, *J* = 16.3 Hz, 1H), 2.55 (s, 1H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (q, *J* = 247.4 Hz), 145.8, 140.7, 132.5, 128.5, 128.1(q, *J* = 8.1 Hz), 127.9, 125.1, 115.9 (q, *J* = 21.7 Hz), 107.4, 94.8, 84.0, 70.6, 33.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ −112.27; HRMS (ESI) found m/z 289.1002 $[M + Na]^+$, calcd for $C_{18}H_{15}FO$ + Na 289.1005; IR (KBr) ν 3419, 3037, 2983, 2931, 2839, 1600, 1508, 1234, 1158, 1096, 1070, 1028, 814, 764, 700, 526 cm^{-1}; HPLC (Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (major) = 6.5 min, t_R (minor) = 7.4 min.

(R,E)-6-(4-Chlorophenyl)-2-phenylhex-5-en-3-yn-2-ol (**3g**). Liquid; 50.8 mg, 90% yield; 88% ee; $[\alpha]_D^{20}$ = +8.5 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 5.7 Hz, 2H), 7.41 (t, *J* = 5.9 Hz, 2H), 7.37−7.28 (m, 5H), 6.96 (d, *J* = 16.3 Hz, 1H), 6.22 (d, *J* = 16.3 Hz, 1H), 2.58 (s, 1H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 140.6, 134.8, 134.6, 129.1, 128.5, 127.9, 127.6, 125.1, 108.3, 95.4, 83.9, 70.6, 33.3; HRMS (ESI) found m/z 305.0705 $[M + Na]^+$, calcd for $C_{18}H_{15}ClO$ + Na 305.0709; IR (KBr) ν 3131, 2960, 2927, 2866, 1592, 1489, 1401, 1261, 1091, 1019, 800, 698, 522 cm^{-1}, HPLC (Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (major) = 6.3 min, t_R (minor) = 6.9 min.

(R,E)-6-(Naphthalen-2-yl)-2-phenylhex-5-en-3-yn-2-ol (**3h**). White solid; mp 78−79 °C; 53.1 mg, 89% yield; 90% ee; $[\alpha]_D^{20}$ = +21.6 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.86−7.79 (m, 3H), 7.78−7.70 (m, 3H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.51−7.47 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 16.2 Hz, 1H), 6.38 (d, *J* = 16.2 Hz, 1H), 2.52 (s, 1H), 1.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.8, 142.1, 133.8, 133.7, 133.6, 128.7, 128.5, 128.4, 127.9, 127.9, 127.2, 126.7, 126.6, 125.2, 122.9, 107.9, 95.1, 84.4, 70.7, 33.4; HRMS (ESI) found m/z 321.1256 $[M + Na]^+$, calcd for $C_{22}H_{18}O$ + Na 321.1256; IR (KBr) ν 3382, 3056, 2983, 2929, 2860, 1598, 1492, 1447, 1263, 1235, 1097, 1067, 1028, 954, 810, 529 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 13.2 min, t_R (major) = 16.6 min.

(R,E)-6-(Naphthalen-1-yl)-2-phenylhex-5-en-3-yn-2-ol (**3i**). Liquid; 48.3 mg, 81% yield; 90% ee; $[\alpha]_D^{20}$ = +7.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* = 13.3, 7.5 Hz, 3H), 7.79−7.74 (m, 2H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 6.6 Hz, 2H), 7.44 (dd, *J* = 14.4, 7.4 Hz, 3H), 7.35 (d, *J* = 7.2 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 2.55 (s, 1H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 139.2, 133.9, 133.8, 131.1, 129.3, 128.8, 128.6, 128.0, 126.6, 126.2, 125.7, 125.2, 123.7, 123.7, 110.4, 94.7, 84.5, 70.7, 33.4; HRMS (ESI) found m/z 321.1251 $[M + Na]^+$, calcd for $C_{22}H_{18}O$ + Na 321.1256; IR (KBr) ν 3298, 3057, 2958, 2927, 2857, 1509, 1447, 1260, 1097, 1088, 1027, 949, 795, 774, 699 cm^{-1}; HPLC (Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (major) = 14.5 min, t_R (minor) = 27.3 min.

(R,E)-2-Phenyl-6-(thiophen-2-yl)hex-5-en-3-yn-2-ol (**3j**). Liquid; 50.8 mg, 90% yield; 92% ee; $[\alpha]_D^{20}$ = +12.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.1 Hz, 2H), 7.39 (t, *J* = 6.7 Hz, 2H), 7.32 (d, *J* = 6.8 Hz, 1H), 7.21 (d, *J* = 3.6 Hz, 1H), 7.10 (d, *J* = 15.9 Hz, 1H), 7.01 (d, *J* = 21.4 Hz, 2H), 6.05 (d, *J* = 15.9 Hz, 1H), 2.42 (s, 1H), 1.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.7, 141.3, 134.8, 128.5, 127.9, 127.4, 125.8, 125.1, 106.7, 95.0, 84.0, 70.6, 33.4; HRMS (ESI) found m/z 277.0663 $[M + Na]^+$, calcd for $C_{16}H_{14}OS$ + Na 277.0663; IR (KBr) ν 3399, 3031, 2954, 2861, 1597, 1492, 1445, 1264, 1075, 1027, 968, 809, 761, 700, 511 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 11.5 min, t_R (major) = 12.8 min.

(R)-5-Methyl-2-phenylhex-5-en-3-yn-2-ol (**3k**). Liquid; 33.5 mg, 90% yield; 94% ee; $[\alpha]_D^{20}$ = −0.5 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 5.33 (d, *J* = 49.9 Hz, 2H), 2.63 (d, *J* = 12.9 Hz, 1H), 1.95 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.8, 128.4, 127.8, 126.4, 125.1, 122.5, 91.5, 86.2, 70.4, 33.40, 23.6; HRMS (ESI) found m/z 209.0937 $[M + Na]^+$, calcd for $C_{13}H_{14}O$ + Na 209.0943; IR (KBr) ν 3427, 3035, 2984, 2931, 2833, 1604, 1511, 1490, 1253, 1178, 1028, 951, 813, 767, 699, 523 cm^{-1}; HPLC (Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, 0.8 mL/min, 254 nm) t_R (minor) = 12.2 min, t_R (major) = 12.7 min.

(R,E)-2,8-Diphenyloct-5-en-3-yn-2-ol (**3m**). Liquid; 47.0 mg, 85% yield; 88% ee; $[\alpha]_D^{20}$ = +1.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 6.5 Hz, 3H), 7.23−7.16 (m, 3H), 6.31−6.08 (m, 1H), 5.59 (d, *J* = 15.9 Hz, 1H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.44 (dd, *J* = 13.7, 5.3 Hz, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 144.3, 141.3, 128.6, 128.5, 128.4, 127.8, 126.2, 125.1, 109.8, 91.5, 70.5, 35.2, 34.9, 33.4; HRMS (ESI) found m/z 299.1407 $[M + Na]^+$, calcd for $C_{20}H_{20}O$ + Na 299.1412; IR (KBr) ν 3345, 3061, 3027, 2982, 2929, 2860, 1601, 1494, 1450, 1260, 1179, 1028, 801, 764, 699, 583 cm^{-1}; HPLC (Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 92/8, 1.0 mL/min, 254 nm) t_R (major) = 6.2 min, t_R (minor) = 6.5 min.

(R,E)-2-(3-Methoxyphenyl)-6-(4-methoxyphenyl)hex-5-en-3-yn-2-ol (**3n**). Liquid; 56.13 mg, 91% yield; 94% ee; $[\alpha]_D^{20}$ = +17.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.32−7.25 (m, 5H), 6.92 (d, *J* = 16.2 Hz, 1H), 6.84 (t, *J* = 8.7 Hz, 3H), 6.07 (d, *J* = 16.2 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.57 (s, 1H), 1.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 159.7, 147.7, 141.6, 129.5, 129.1, 127.8, 117.6, 114.3, 113.2, 111.1, 105.1, 93.9, 84.5, 70.5, 55.5, 33.4; HRMS (ESI) found m/z 331.1305 $[M + Na]^+$, calcd for $C_{20}H_{20}O_3$ + Na 331.1310; IR (KBr) ν 3446, 3032, 2982, 2960, 2934, 2836, 1603, 1510, 1252,

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1175, 1034, 957, 812, 701, 530 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 92/8, 1.0 mL/min, 254 nm) t_R (minor) = 24.4 min, t_R (major) = 32.5 min.

(R,E)-6-(4-Methoxyphenyl)-2-(p-tolyl)hex-5-en-3-yn-2-ol (**3o**). White solid; mp 72−74 °C; 52.6 mg, 90% yield; 92% ee; $[\alpha]_D^{20}$ = +15.4 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 2H), 6.95 (d, *J* = 16.2 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.10 (d, *J* = 16.2 Hz, 1H), 3.82 (s, 3H), 2.48 (s, 1H), 2.37 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 143.1, 141.5, 137.5, 129.1, 127.8, 125.1, 114.4, 105.3, 94.2, 84.4, 70.5, 55.5, 33.3, 21.2; HRMS (ESI) found *m/z* 315.1357 $[M + Na]^+$, calcd for $C_{20}H_{20}O_2$ + Na 315.1361; IR (KBr) ν 3432, 3031, 2983, 2932, 2837, 1605, 1511, 1251, 1175, 1032, 957, 817, 533 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 21.2 min, t_R (major) = 23.6 min.

(S,E)-2-(2-Chlorophenyl)-6-(4-methoxyphenyl)hex-5-en-3-yn-2-ol (**3p**). Liquid; 53.1 mg, 85% yield; 91% ee; $[\alpha]_D^{20}$ = +10.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 9.4 Hz, 3H), 7.17−7.14 (m, 1H), 6.82 (d, *J* = 16.2 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 5.96 (d, *J* = 16.2 Hz, 1H), 3.71 (s, 3H), 3.04 (s, 1H), 1.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 141.7, 141.6, 132.1, 131.5, 129.2, 129.1, 127.8, 127.1, 126.9, 114.3, 105.2, 93.0, 84.3, 69.5, 55.5, 29.9; HRMS (ESI) found *m/z* 335.0812 $[M + Na]^+$, calcd for $C_{19}H_{17}ClO_2$ + Na 335.0815; IR (KBr) ν 3446, 3032, 3002, 2959, 2933, 2837, 1604, 1510, 1250, 1177, 1077, 1035, 955, 813, 759, 71, 533 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 20.4 min, t_R (major) = 37.2 min.

(R,E)-2-(3-Chlorophenyl)-6-(4-methoxyphenyl)hex-5-en-3-yn-2-ol (**3q**). Liquid; 53.7 mg, 86% yield; 90% ee; $[\alpha]_D^{20}$ = +28.2 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.21−7.15 (m, 2H), 6.85 (d, *J* = 16.3 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 5.98 (d, *J* = 16.3 Hz, 1H), 3.71 (s, 3H), 2.58 (s, 1H), 1.71 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 148.1, 141.9, 134.4, 129.8, 129.0, 127.9, 127.9, 125.6, 123.4, 114.4, 104.9, 93.2, 85.0, 70.2, 55.5, 33.5; HRMS (ESI) found *m/z* 335.0814 $[M + Na]^+$, calcd for $C_{19}H_{17}ClO_2$ + Na 335.0815; IR (KBr) ν 3401, 3033, 2984, 2932, 2837, 1604, 1511, 1468, 1420, 1250, 1175, 1032, 956, 812, 735, 696, 529 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 15.9 min, t_R (major) = 24.7 min.

(R,E)-2-(4-Chlorophenyl)-6-(4-methoxyphenyl)hex-5-en-3-yn-2-ol (**3r**). Liquid; 55.0 mg, 88% yield; 89% ee; $[\alpha]_D^{20}$ = +8.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.36−7.31 (m, 4H), 6.94 (d, *J* = 16.3 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.07 (d, *J* = 16.3 Hz, 1H), 3.81 (s, 3H), 2.68 (s, 1H), 1.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 144.5, 141.8, 133.6, 129.0, 128.5, 127.8, 126.7, 114.4, 104.9, 93.5, 84.9, 70.2, 55.5, 33.5; HRMS (ESI) found *m/z* 335.0815 $[M + Na]^+$, calcd for $C_{19}H_{17}ClO_2$ + Na 335.0815; IR (KBr) ν 3406, 3033, 2984, 2837, 1604, 1511, 1488, 1250, 1175, 1091, 1032, 956, 829, 720, 534 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 18.0 min, t_R (major) = 23.3 min.

(R,E)-2-(4-Fluorophenyl)-6-(4-methoxyphenyl)hex-5-en-3-yn-2-ol (**3s**). White solid; mp 79−81 °C; 53.3 mg, 90% yield; 89% ee; $[\alpha]_D^{20}$ = +10.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.62−7.58 (m, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.01−6.97 (m, 2H), 6.88 (d, *J* = 16.3 Hz, 1H), 6.82−6.80 (m, 2H), 6.02 (d, *J* = 16.3 Hz, 1H), 3.75 (s, 3H), 2.53 (s, 1H), 1.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.4 (q, *J* = 244.5 Hz), 160.4, 141.8, 129.0, 127.8, 127.0 (q, *J* = 8.1 Hz), 115.2 (q, *J* = 21.2 Hz), 114.4, 105.0, 93.7, 84.8, 70.2, 55.5, 33.6; ^{19}F NMR (377 MHz, $CDCl_3$) δ −115.20; HRMS (ESI) found *m/z* 319.1103 $[M + Na]^+$, calcd for $C_{19}H_{17}FO_2$ + Na 319.1111; IR (KBr) ν 3417, 3034, 2984, 2838, 1602, 1505, 1462, 1250, 1175, 1031, 956, 920, 837, 653, 573, 533 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 15.9 min, t_R (major) = 22.0 min.

(S,E)-2-(2-Fluorophenyl)-6-(4-methoxyphenyl)hex-5-en-3-yn-2-ol (**3t**). Liquid; 54.5 mg, 92% yield; 88% ee; $[\alpha]_D^{20}$ = +11.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.72 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 10.0 Hz, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.09 (dd, *J* = 11.7, 8.3 Hz, 1H), 6.93 (d, *J* = 16.3 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.06 (d, *J* = 16.3 Hz, 1H), 3.80 (s, 3H), 2.92 (s, 1H), 1.96 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3 (q, *J* = 246.5 Hz), 160.3, 141.7, 132.3 (q, *J* = 10.5 Hz), 129.6 (q, *J* = 8.4 Hz), 129.1, 127.8, 126.9 (q, *J* = 3.2 Hz), 124.1 (q, *J* = 3.3 Hz), 116.4 (q, *J* = 22.2 Hz), 114.3, 105.1, 93.0, 84.0, 68.3, 55.4, 30.7 (q, *J* = 2.4 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ −112.77; HRMS (ESI) found *m/z* 319.1107 $[M + Na]^+$, calcd for $C_{19}H_{17}FO_2$ + Na 319.1111; IR (KBr) ν 3435, 3034, 2985, 2960, 2935, 2837, 1604, 1511, 1486, 1250, 1175, 1084, 1031, 956, 811, 760, 529 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 17.5 min, t_R (major) = 29.0 min.

(R,E)-6-(4-Methoxyphenyl)-2-[4-(trifluoromethyl)phenyl]hex-5-en-3-yn-2-ol (**3u**). White solid; mp 84−86 °C; 58.8 mg,; 85% yield; 85% ee; $[\alpha]_D^{20}$ = +22.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 16.3 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.07 (d, *J* = 16.3 Hz, 1H), 3.81 (s, 3H), 2.78 (s, 1H), 1.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 149.9, 142.1, 130.0 (q, *J* = 32.1 Hz), 129.0, 127.9, 125.6, 125.5 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 270.5 Hz), 114.4, 104.7, 93.1, 85.1, 70.3, 55.5, 33.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.40; HRMS (ESI) found *m/z* 369.1076 $[M + Na]^+$, calcd for $C_{20}H_{17}F_3O_2$ + Na 369.1079; IR (KBr) ν 3400, 3034, 2986, 2935, 2839, 1755, 1605, 1511, 1410, 1327, 1251, 1174, 1125, 1033, 845, 532 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 14.4 min, t_R (major) = 19.9 min.

(E)-4-(2-Hydroxy-6-(4-methoxyphenyl)hex-5-en-3-yn-2-yl)-benzonitrile (**3v**). White solid; mp 118−119 °C; 50 mg, 83% yield; 81% ee; $[\alpha]_D^{20}$ = +22.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 16.3 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.04 (d, *J* = 16.3 Hz, 1H), 3.80 (s, 3H), 2.84 (s, 1H), 1.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 151.1, 142.2, 132.3, 128.8, 127.9, 126.0, 118.9, 114.4, 111.5, 104.56, 92.6, 85.4, 70.4, 55.5, 33.6; HRMS (ESI) found *m/z* 304.1337 $[M + H]^+$, calcd for $C_{20}H_{17}NO_2$ + H 304.1338; IR (KBr) ν 3520, 2988, 2954, 2932, 2834, 2223, 1604, 1509, 1454, 1439, 1340, 1310, 1249, 1178, 1095, 1030, 977, 839, 822, 592, 571, 532 cm^{-1}; HPLC (Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 25.5 min, t_R (major) = 21.6 min.

Methyl (E)-4-[2-Hydroxy-6-(4-methoxyphenyl)hex-5-en-3-yn-2-yl]benzoate (**3w**). White solid; mp 119−120 °C; 60 mg, 89% yield; 89% ee; $[\alpha]_D^{20}$ = +14 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (s, 2H), 6.92 (d, *J* = 16.3 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.05 (d, *J* = 16.3 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 2.95 (s, 1H), 1.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 160.3, 151.0, 141.8, 129.8, 129.5, 129.0, 127.8, 125.2, 114.3, 104.8, 93.3, 84.9, 70.3, 55.4, 52.3, 33.5; HRMS (ESI) found *m/z* 337.1438 $[M + H]^+$, calcd for $C_{21}H_{20}O_4$ + H 337.1440; IR (KBr) ν 3483, 2992, 2952, 2937, 2842, 1700, 1604, 1512, 1433, 1313, 1289, 1247, 1176, 1121, 1033, 1017, 976, 855, 813, 774, 705, 543 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 31.0 min, t_R (major) = 38.7 min.

(R,E)-2-[(1,1′-Biphenyl)-4-yl]-6-(4-methoxyphenyl)hex-5-en-3-yn-2-ol (**3x**). White solid; mp 78−80 °C; 57.4 mg, 81% yield; 92% ee; $[\alpha]_D^{20}$ = +11.4 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.62 (dd, *J* = 7.7, 3.1 Hz, 4H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.36 (dd, *J* = 16.4, 8.1 Hz, 3H), 6.98 (d, *J* = 16.3 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.12 (d, *J* = 16.2 Hz, 1H), 3.82 (s, 3H), 2.54 (s, 1H), 1.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 145.0, 141.7, 140.9, 140.8, 129.1, 129.0, 127.8, 127.5, 127.3, 127.3, 125.7, 114.4, 105.1, 93.9, 84.7, 70.5, 55.5, 33.4; HRMS (ESI) found *m/z* 377.1512 $[M + Na]^+$, calcd for $C_{25}H_{22}O_2$ + Na 377.1518; IR (KBr) ν 3301, 3030, 2987, 2957, 2931, 2836, 1604, 1510, 1250, 1175, 1091, 1031, 957, 812, 531 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 27.0 min, t_R (major) = 34.7 min.

(R,E)-6-(4-Methoxyphenyl)-2-(naphthalen-2-yl)hex-5-en-3-yn-2-ol (**3y**). White solid; mp 68−70 °C; 52.5 mg, 80% yield; 89% ee;

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$[\alpha]_D^{20}$ = +36.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, CDCl3) δ 8.17 (s, 1H), 7.90−7.85 (m, 3H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.52−7.49 (m, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 16.3 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.13 (d, *J* = 16.2 Hz, 1H), 3.82 (s, 3H), 2.67 (s, 1H), 1.93 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 143.2, 141.7, 133.2, 133.0, 129.1, 128.5, 128.3, 127.8, 127.7, 126.4, 126.2, 123.8, 123.5, 114.4, 105.1, 94.0, 84.8, 70.7, 55.5, 33.3; HRMS (ESI) found *m*/*z* 351.1361 $[M + Na]^+$, calcd for $C_{23}H_{20}O_2$ + Na 351.1361; IR (KBr) ν 3408, 3032, 2932, 2836, 1604, 1510, 1462, 1251, 1175, 1032, 955, 816, 533 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 29.2 min, t_R (major) = 34.6 min.

(S,E)-6-(4-Methoxyphenyl)-2-(thiophen-2-yl)hex-5-en-3-yn-2-ol ***(3z)***. Liquid; 51.7 mg, 91% yield; 90% ee; $[\alpha]_D^{20}$ = +12.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.19 (d, *J* = 8.6 Hz, 3H), 7.14 (d, *J* = 4.5 Hz, 1H), 6.81 (d, *J* = 16.3 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 5.95 (d, *J* = 16.3 Hz, 1H), 3.67 (s, 3H), 2.89 (s, 1H), 1.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1, 147.4, 141.5, 128.9, 127.7, 126.3, 125.8, 120.9, 114.2, 104.9, 93.7, 83.6, 67.8, 55.4, 32.2; HRMS (ESI) found *m*/*z* 285.0953 $[M + H]^+$, calcd for $C_{17}H_{16}O_2S$ + H 285.0950; IR (KBr) ν 3523, 3056, 2959, 2933, 2907, 2836, 1600, 1510, 1251, 1144, 1029, 960, 817, 532 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 18.8 min, t_R (major) = 24.7 min.

(R,E)-7-(4-Methoxyphenyl)-3-phenylhept-6-en-4-yn-3-ol ***(3a′)***. Liquid; 53.2 mg, 91% yield; 84% ee; $[\alpha]_D^{20}$ = +16.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.35−7.29 (m, 3H), 6.97 (d, *J* = 16.3 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.12 (d, *J* = 16.3 Hz, 1H), 3.82 (s, 3H), 2.54 (s, 1H), 2.06 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.98 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 144.8, 141.5, 129.1, 128.3, 127.8, 127.8, 125.8, 114.4, 105.2, 92.9, 85.7, 74.6, 55.5, 38.6, 9.3; HRMS (ESI) found *m*/*z* 315.1358 $[M + Na]^+$, calcd for $C_{20}H_{20}O_2$ + Na 315.1361; IR (KBr) ν 3450, 3031, 2968, 2935, 2837, 1603, 1511, 1448, 1251, 1174, 1031, 958, 813, 759, 700, 533 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 17.0 min, t_R (major) = 24.9 min.

(R,E)-8-(4-Methoxyphenyl)-4-phenyloct-7-en-5-yn-4-ol ***(3b′)***. Liquid; 54.0 mg, 88% yield; 86% ee; $[\alpha]_D^{20}$ = +27.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 16.2 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.12 (d, *J* = 16.2 Hz, 1H), 3.82 (s, 3H), 2.46 (s, 1H), 1.99 (td, *J* = 12.8, 4.6 Hz, 1H), 1.95−1.87 (m, 1H), 1.54 (dt, *J* = 12.2, 7.1 Hz, 1H), 1.45−1.40 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 145.2, 141.5, 129.2, 128.3, 127.8, 127.8, 125.7, 114.46, 105.3, 93.2, 85.7, 74.0, 55.5, 47.9, 18.3, 14.2; HRMS (ESI) found *m*/*z* 329.1515 $[M + Na]^+$, calcd for $C_{21}H_{22}O_2$ + Na 329.1518; IR (KBr) ν 3447, 3031, 2959, 2933, 2872, 2832, 1604, 1511, 1250, 1175, 1031, 956, 813, 767, 701, 533 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 16.0 min, t_R (major) = 21.0 min.

(R,E)-1-(4-Methoxyphenyl)-5-phenyldec-1-en-3-yn-5-ol ***(3c′)***. Liquid; 62.8 mg, 94% yield; 89% ee; $[\alpha]_D^{20}$ = +23.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.36−7.27 (m, 3H), 6.96 (d, *J* = 16.2 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.13 (d, *J* = 16.2 Hz, 1H), 3.81 (s, 3H), 2.58 (s, 1H), 2.07−1.99 (m, 1H), 1.98−1.89 (m, 1H), 1.53 (s, 1H), 1.44−1.38 (m, 1H), 1.31 (s, 4H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 145.2, 141.5, 129.1, 128.3, 127.8, 127.7, 125.7, 114.3, 105.3, 93.3, 85.6, 74.0, 55.4, 45.6, 31.9, 24.6, 22.7, 14.2; HRMS (ESI) found *m*/*z* 357.1829 $[M + Na]^+$, calcd for $C_{23}H_{26}O_2$ + Na 357.1831; IR (KBr) ν 3437, 3031, 2954, 2861, 1604, 1511, 1448, 1250, 1175, 1032, 955, 813, 767, 701, 533 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 13.6 min, t_R (major) = 20.5 min.

(R,E)-2-Cyclohexyl-6-(4-methoxyphenyl)hex-5-en-3-yn-2-ol ***(3d′)***. Liquid; 46.6 mg, 82% yield; 70% ee; $[\alpha]_D^{20}$ = +12.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.86 (t, *J* = 12.7 Hz, 3H), 6.03 (d, *J* = 16.2 Hz, 1H), 3.80 (s, 3H), 2.12 (s, 1H), 2.01 (d, *J* = 11.9 Hz, 1H), 1.90 (d, *J* = 12.2 Hz, 1H), 1.82 (d, *J* = 9.1 Hz, 2H), 1.69 (d, *J* = 12.2 Hz, 1H), 1.49 (s, 3H), 1.29−1.22 (m, 2H), 1.22−1.10 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1, 140.9, 129.2, 127.7, 114.3, 105.5, 94.2, 83.6, 71.8, 55.4, 49.1, 28.0, 27.6, 27.5, 26.5, 26.4; HRMS (ESI) found *m*/*z* 307.1673 $[M + Na]^+$, calcd for $C_{19}H_{24}O_2$ + Na 307.1674; IR (KBr) ν 3440, 3032, 2931, 2853, 1605, 1511, 1451, 1251, 1175, 1033, 955, 813, 531 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 11.7 min, t_R (major) = 17.5 min.

(R,E)-7-(4-Methoxyphenyl)-2,3-dimethylhept-6-en-4-yn-3-ol ***(3e′)***. White solid; mp 28−30 °C; 39.1 mg, 80% yield; 70% ee; $[\alpha]_D^{20}$ = +0.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.86 (t, *J* = 13.1 Hz, 3H), 6.03 (d, *J* = 16.2 Hz, 1H), 3.80 (s, 3H), 2.08 (d, *J* = 7.0 Hz, 1H), 1.86 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.50 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.2, 141.0, 129.2, 127.7, 114.3, 105.5, 93.7, 83.6, 72.3, 55.4, 39.3, 27.4, 18.1, 17.7; HRMS (ESI) found *m*/*z* 267.1358 $[M + Na]^+$, calcd for $C_{16}H_{20}O_2$ + Na 267.1361; IR (KBr) ν 3408, 3032, 2932, 2836, 1604, 1510, 1462, 1251, 1175, 1032, 955, 816, 533 cm^{-1}; HPLC (Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 12.0 min, t_R (major) = 14.8 min.

Syntheses of Aliphatic Enyne 2l[6] and Their Direct Application to Enantioselective Addition to Ketone. To a solution of triphenyl[3-(trimethylsilyl)prop-2-yn-1-yl]phosphonium bromide (22.6 g, 50 mmol) in THF was added potassium *t*-butoxide (7.3 g, 65 mmol) at 0 °C. The mixture was warmed to 25 °C, stirred for 1 h, and cooled to 0 °C again. Cyclopropanecarbaldehyde (3.5 g, 50 mmol) was added via syringe. After 15 min, the reaction was warmed to room temperature. The aqueous layer was extracted three times with Et_2O (90 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded (*E*)-(4-cyclopropylbut-3-en-1-yn-1-yl)trimethylsilane (enyne-TMS).

(E)-(4-Cyclopropylbut-3-en-1-yn-1-yl)trimethylsilane (Enyne-TMS). Liquid; 5.10 g, 62% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (dd, *J* = 15.7, 9.3 Hz, 1H), 5.55 (d, *J* = 15.8 Hz, 1H), 1.48−1.45 (m, 1H), 0.80 (d, *J* = 7.4 Hz, 2H), 0.47 (d, *J* = 4.5 Hz, 2H), 0.16 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 150.2, 106.8, 104.5, 92.7, 14.9, 7.9, 0.2; HRMS (ESI) found *m*/*z* 187.0915 $[M + Na]^+$, calcd for $C_{10}H_{16}Si$ + Na 187.0919; IR (KBr) ν 3085, 3009, 2960 2899, 1626, 1456, 1409, 1249, 1076, 949, 843, 759, 698, 649 cm^{-1}.

Then tetra-*n*-butylammonium fluoride (TBAF) (125.4 mg, 0.48 mmol, 1.0 M solution in Et_2O) was added to the cooled (0 °C) solution of (*E*)-(4-cyclopropylbut-3-en-1-yn-1-yl)trimethylsilane (66 mg, 0.4 mmol) in Et_2O. The reaction was stirred for half an hour, quenched with saturated aqueous NH_4Cl, and extracted twice with Et_2O (20 mL). The organic layer was combined, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography with hexane as eluent to give the corresponding enyne **2l** for the next step.

The above-obtained enyne **2l** and ligand **L10** (23.6 mg, 0.04 mmol) in THF were stirred at −78 °C for 20 min under Ar_2. *n*-BuLi (2.5 M in hexane, 0.16 mL, 0.4 mmol) was slowly dropped into the mixture and stirred for 20 min. Acetophenone (23.5 μL, 0.2 mmol) was added, and the mixture was stirred for 5 days at −78 °C. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted by ether (5 mL × 3). The organic layer was washed with $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified via flash column chromatography (silica gel) with 5% ethyl acetate in petroleum ether as eluent to give adduct **3l**. The enantiomeric excess was determined by HPLC analysis on a Chiralcel column.

(R,E)-6-Cyclopropyl-2-phenylhex-5-en-3-yn-2-ol ***(3l)***. Liquid; 34.0 mg, 80% yield; 80% ee; $[\alpha]_D^{20}$ = +9.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 6.7 Hz, 2H), 7.30 (d, *J* = 6.6 Hz, 1H), 5.66 (dt, *J* = 29.5, 12.5 Hz, 2H), 2.64 (s, 1H), 1.78 (s, 3H), 1.50 (s, 1H), 0.83 (d, *J* = 6.5 Hz, 2H), 0.50 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.5, 146.0, 128.3, 127.7, 125.1, 106.0, 91.1, 83.9, 70.4, 33.4, 14.9, 7.8; HRMS (ESI) found *m*/*z* 235.1094 $[M + Na]^+$, calcd for $C_{15}H_{16}O$ + Na 235.1099; IR (KBr) ν 3518, 3058, 3026,

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2984, 2962, 2927, 2855, 1625, 1601, 1495, 1427, 1236, 1170, 1095, 1027, 949, 764, 699, 812, 500 cm^{-1}; HPLC (Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (major) = 4.9 min, t_R (minor) = 5.4 min.

Procedure for Allylation of Adduct 4. To a cooled suspension (0 °C) of NaH (57% dispersion in oil, 17.5 mg, 0.416 mmol) in anhydrous THF (4 mL) under argon atmosphere was added a solution of **3a** (99.3 mg, 0.4 mmol) in anhydrous THF (1 mL). The resulting gray suspension was stirred for 20 min, and allyl bromide (136 μL, 1.58 mmol) was added. The mixture was stirred for 30 min at 0 °C, and then the ice bath was removed and the mixture was stirred at room temperature overnight. The mixture was cooled to 0 °C and quenched with water (15 mL). The solution was warmed to 25 °C and extracted with ether (3 × 10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (petroleum ether) to yield the allylation product **4**.

*(R,E)-[5-(Allyloxy)hex-1-en-3-yne-1,5-diyl]dibenzene (**4**).* Faint yellow oil; 110 mg, 95% yield; $[\alpha]_D^{20}$ = +3.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 2H), 7.52−7.36 (m, 8H), 7.15 (d, *J* = 16.3 Hz, 1H), 6.40 (d, *J* = 16.3 Hz, 1H), 6.08 (ddt, *J* = 16.0, 10.6, 5.5 Hz, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.3 Hz, 1H), 4.29 (dd, *J* = 12.2, 5.4 Hz, 1H), 3.84 (dd, *J* = 12.2, 5.5 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.4, 140.0, 134.3, 133.2, 126.9, 126.9, 126.5, 125.9, 124.5, 124.1, 114.6, 105.7, 89.8, 84.8, 74.7, 64.5, 31.1; HRMS (ESI) found *m*/*z* 311.1411 [M + Na]$^+$, calcd for $C_{21}H_{20}O$ + Na 311.1412; IR (KBr) ν 3649, 3060, 2986, 2930, 2859, 1647, 1599, 1491, 1446, 1233, 1082, 953, 898, 748, 699, 519 cm^{-1}.

Procedure for Pauson−Khand Cycloaddition of 5. $Co_2(CO)_8$ (208.7 mg, 0.61 mmol) was added to a solution of **4** (80 mg, 0.28 mmol) in CH_2Cl_2 (4 mL) at room temperature under strict exclusion of light, and the stirring was maintained for 2 h under an atmosphere of CO. Then *N*-methylmorpholine-*N*-oxide (NMO) (519 mg, 4.43 mmol) was added. After the mixture was stirred for another 2 h, TLC monitoring indicated the reaction was complete. The solvent was removed in vacuo, and the crude product was subjected to column chromatography on silica gel to afford cyclopentenone **5**.

*(1R,3aS)-1-Methyl-1-phenyl-6-[(E)-styryl]-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one (**5**).* Pale yellow powder; 59.6 mg, 68% yield; mp 132−133 °C; $[\alpha]_D^{20}$ +124.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 16.3 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.35 (dd, *J* = 16.6, 8.9 Hz, 3H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 16.2 Hz, 1H), 4.42 (t, *J* = 8.0 Hz, 1H), 3.56 (dd, *J* = 10.5, 8.3 Hz, 1H), 3.37 (d, *J* = 6.8 Hz, 1H), 2.73 (dd, *J* = 17.6, 6.5 Hz, 1H), 2.31 (dd, *J* = 17.6, 3.7 Hz, 1H), 1.91 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.0, 180.2, 143.6, 137.3, 135.4, 131.3, 129.0, 128.8, 128.5, 128.1, 126.9, 125.3, 116.3, 83.0, 70.3, 43.8, 40.2, 26.3; HRMS (ESI) found *m*/*z* 317.1542 [M + H]$^+$, calcd for $C_{22}H_{20}O_2$ + H 317.1537; IR (KBr) ν 3649, 3025, 2977, 2931, 2854, 1598, 1493, 1446, 1267, 1175, 1091, 1031, 957, 812, 531 cm^{-1}; HPLC (Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm) t_R (minor) = 9.2 min, t_R (major) = 10.0 min.

Synthetic Procedure for 1-(5-Chloro-2-nitrophenyl)-2,2,2-trifluoroethanone (6). To a solution of 5-chloro-2-nitrobenzaldehyde (3.00 g, 20.6 mmol) in dry CH_2Cl_2/PhMe (2:1) (100 mL) cooled to −20 °C were added $CF_3Si(CH_3)_3$ (10.0 mL, 61.8 mmol) and tetra-*n*-butylammonium bromide (TBAB) [10 mL, 1.0 M in dry CH_2Cl_2/PhMe (2:1)]. After the mixture was stirred for 2 h, CsF (31.9 mg, 0.2 mmol) was added and the mixture was stirred for another 6 h. Aqueous 2 N HCl was added and the mixture was stirred for 15 min, and then TBAF (33 mL, 1.0 M in dry THF) was added and the mixture was stirred for one night. The reaction was quenched with water (50 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with water and brine and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent in vacuo gave the residue 1-(5-chloro-2-nitrophenyl)-2,2,2-trifluoroethan-1-ol, which was used for the next step without further purification.

MnO_2 (20.30 g, 234.0 mmol) was added to the solution of 1-(5-chloro-2-nitrophenyl)- 2,2,2-trifluoroethan-1-ol (3.00 g, 11.7 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred for 16 h at 38 °C. After filtration and removal of CH_2Cl_2 in vacuo, the residue was purified by column chromatography (petroleum ether/ethyl acetate 50/1) to give **6** as a yellow solid.

*1-(5-Chloro-2-nitrophenyl)-2,2,2-trifluoroethanone (**6**).* Yellow solid; 2.80 g, 94% yield; mp 38−39 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 1H), 7.76 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.50 (d, *J* = 2.2 Hz, 1H) ;^{13}C NMR (150 MHz, $CDCl_3$) δ 182.7 (q, *J* = 39.2 Hz), 144.6, 142.7, 132.9, 131.9, 128.8, 126.1, 115.5 (q, *J* = 288.6 Hz); ^{19}F NMR (565 MHz, $CDCl_3$) δ −75.74; HRMS (ESI) found *m*/*z* 253.9830 [M + H]$^+$, calcd for $C_8H_3ClF_3NO_3$ + H 253.9832; IR (KBr) ν 3107, 1754, 1657, 1604, 1533, 1345, 1193, 966, 852, 801, 727, 690, 538 cm^{-1}.

Enantioselective Addition of (*E*)-But-1-en-3-yn-1-ylcyclopropane to Trifluoromethylketones (6). A solution of (*E*)-but-1-en-3-yn-1-ylcyclopropane (37.0 mg, 0.4 mmol) and ligand **L10** (23.6 mg, 0.04 mmol) in THF (1 mL) was stirred at −78 °C for 20 min under Ar_2. *n*-BuLi (2.5 M in hexane, 0.16 mL, 0.4 mmol) was slowly dropped into the above solution via syringe and the homogeneous solution was stirred for 20 min, and then trifluoromethylketone **6** (50.6 mg, 0.2 mmol) in THF (1 mL) was added. The mixture was allowed to stir at −78 °C for 5 days. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted by ether (5 mL × 3). The organic layer was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified via flash column chromatography (silica gel) with 5% ethyl acetate in petroleum ether as eluent to give addition product **7**.

*(E)-2-(5-Chloro-2-nitrophenyl)-6-cyclopropyl-1,1,1-trifluorohex-5-en-3-yn-2-ol (**7**).* Liquid; 55.3 mg, 80% yield; *E*/*Z* 8/1; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.47 (dd, *J* = 23.1, 8.0 Hz, 2H), 5.81 (dd, *J* = 15.6, 9.7 Hz, 1H), 5.55 (d, *J* = 15.8 Hz, 1H), 3.81 (s, 1H), 1.51 (d, 1H), 0.87 (d, *J* = 6.4 Hz, 2H), 0.54 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 148.7, 137.2, 130.8, 130.3, 129.8, 125.8, 122.9 (q, *J* = 285.2 Hz), 104.0, 89.0, 80.5, 72.6 (q, *J* = 33.6 Hz), 15.3, 8.3; ^{19}F NMR (565 MHz, $CDCl_3$) δ −78.09, −78.16; HRMS (ESI) found *m*/*z* 368.0282 [M + Na]$^+$, calcd for $C_{15}H_{11}ClF_3NO_3$ + Na 368.0277; IR (KBr) ν 3476, 3010, 1627, 1542, 1478, 1366, 1179, 1117, 942, 852, 750, 580 cm^{-1}.

Preparation of Efavirenz Analogue 8. Fe (532.0 mg, 9.5 mmol) and CH_3CO_2H (0.48 mL) were added into a solution of **7** (200.0 mg, 0.58 mmol) in THF/MeOH (2/1, 6.5 mL) at room temperature under nitrogen atmosphere. After the reaction mixture was stirred for one night, the resulting mixture was filtrated through Celite, and washed with AcOEt (5 mL). The filtrate was evaporated under reduced pressure, and the residue was dissolved in AcOEt (30 mL). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give the corresponding amino alcohol for the next step.

To a solution of the corresponding amino alcohol and $KHCO_3$ (87 mg, 0.87 mmol) in MTBE/H_2O (1/2, 1.2 mL) was added 4-nitrophenyl chloroformate (122.8 mg, 0.61 mmol), and the reaction mixture was stirred for 1 h at ambient temperature. Then the pH of the reaction mixture was adjusted to 12 by addition of 2 N KOH aqueous until the carbamate dissolved. The resulting mixture was neutralized by addition of saturated aqueous solution NH_4Cl. The whole mixture was extracted with AcOEt (10 mL × 3), and the combined organic layers was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by a single recrystallization (petroleum ether/CH_2Cl_2) to give the product **8**.

*(E)-6-Chloro-4-(4-cyclopropylbut-3-en-1-yn-1-yl)-4-(trifluoromethyl)-1H-benzo[d][1,3]oxazin-2(4H)-one (**8**).* White solid; mp 177−178 °C; 158.2 mg, 80% yield; ^1H NMR (600 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.49 (s, 1H), 7.35 (d, *J* = 6.8 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 5.88 (dd, *J* = 14.4, 10.2 Hz, 1H), 5.63 (d, *J* = 15.6 Hz, 1H), 1.54 (s, 1H), 0.90 (d, *J* = 4.6 Hz, 2H), 0.57 (s, 2H); ^{13}C NMR (150

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MHz, $CDCl_3$) δ 154.6, 149.6, 133.6, 132.0, 129.4, 127.9, 122.4 (q, J = 286.5 Hz), 116.7, 115.2, 104.0, 90.3, 79.7 (q, J = 35.0 Hz), 77.9, 15.4, 8.5; ^{19}F NMR (565 MHz, $CDCl_3$) δ −80.67; HRMS (ESI) found m/z 364.0327 $[M + Na]^+$, calcd for $C_{16}H_{11}ClF_3NO_2$ + Na 364.0328; IR (KBr) ν 3151, 2962, 1735, 1599, 1496, 1402, 1340, 1255, 1192, 1034, 937, 867, 824, 743, 692, 656, 560 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra, ^{13}C NMR spectra, and/or HPLC analytic results for **2a−j**, **3a−z**, **3a′−e′**, and **4−8** (PDF), as well as crystallographic data for compounds **3u** and **5** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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