Supporting Information

Enantioselective Organocatalytic Aldol Reaction of Ynones and its Synthetic Applications

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All solvents were purified prior to use by passing through a column of activated alumina under inert atmosphere. Chemicals were purchased from Aldrich and Lancaster. All reactions were carried out under inert atmosphere using flame-dried glassware. NMR spectra were recorded on a Bruker Avance AV400 or AV500. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane with the undeuterated solvent resonance as an internal standard. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Absorption bands are reported in wavenumbers (cm^{-1}). Mass spectra (m/z) and HRMS were recorded on a Micromass LCT in ElectronSpray Ionisation (ESI), Field Ionization (FI) mode or on a Micromass AutoSpec (CI^+). Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets precoated with Kieselgel 60F₂₅₄ and visualized with a UV lamp or by staining with KMnO_4 . Flash chromatography was carried out using silica gel (40-63 μm) and eluents as indicated. The enantiomeric excesses were determined by normal phase HPLC on a Waters HPLC system (626 Pump, 600S Controller, 996 Photodiode Array Detector, Millenium Software).

General procedure A: Synthesis of enantioenriched aldols :

To a solution of the corresponding aldehydes (2 mmol) and ketones (10 mmol) in DMSO (15 mL) was added water (2 mL) and the organocatalysts **1a¹-c** (0.4 mmol) in DMSO (1 mL). The mixture was stirred for 5 days at room temperature, then partitioned between water (60 mL), DCM (3 x 20 mL) and diethyl ether (3 x 20 mL). The combined organic extracts were dried with Na₂SO₄. After filtration, the solvent was removed *in vacuo*. The resulting residue was further purified by silica gel column chromatography.

General procedure B: Stereoselective carbonyl reduction with DIBAL-H :

To a solution of the aldol (0.1 mmol) in anhydrous THF (1.2 mL) was added DIBAL-H (1M in toluene, 800 μ L) dropwise at -78°C. The mixture was allowed to stir for 3h at -78°C, quenched with 4N HCl (0.4 mL) and dried with Na₂SO₄. The resulting slurry was filtered and washed with diethyl ether. The filtrate was concentrated under reduced pressure and the resulting crude oil was purified by silica gel column chromatography.

General procedure C: Deprotection with TFA :

To a solution of the aldol (0.05 mmol) in anhydrous DCM (0.5 mL) was slowly added trifluoroacetic acid (18 μ L, 0.25 mmol). The resulting solution was stirred at room temperature until completion as monitored by TLC. The mixture was then directly purified by silica gel column chromatography.

General procedure D: Cyclization with 1.3-di(diphenylphosphino)propane (dppp) :

To a solution of the aldol (0.2 mmol) in anhydrous toluene (20 mL) was added under argon acetic acid (4.6 μ L, 0.08 mmol) followed by dppp (7.95 mg, 0.02 mmol). The resulting mixture was stirred at 60°C for 3h, then it was directly purified by silica gel column chromatography as solvent removal resulted in product decomposition.

Synthesis of compounds 2-4.

1-hydroxy-1-(4-nitrophenyl)hept-4-yn-3-one (2)

2 was obtained from 4-nitrobenzaldehyde (76 mg, 0.5 mmol) and hex-3-yn-2-one (273 μ L, 2.5 mmol) according to general procedure A. Purification by silica gel column chromatography (hexane:EtOAc, 9:1) yielded the product (48 mg, 39% yield) as a pale yellow oil; R_f (hexane:ethyl acetate, 3:2) = 0.55. The enantiomeric excess of the product **2** was determined to be 74% ee by HPLC analysis [column, DAICEL CHIRALCEL OJ (0.46 cm Φ x 25 cm)]; eluent, hexane/ i PrOH = 85/15; flow rate, 1.0 mL/min; retention time: 21.1 min (major), 22.6 min (minor); δ_{1H} (400 MHz, CDCl₃) 1.22 (3H, t, J = 7.5 Hz), 2.40 (2H, q, J = 7.5 Hz), 2.99 (2H, d, J = 6.3 Hz), 3.34 (1H, d, J = 3.4 Hz), 5.33 (1H, td, J = 6.1, 3.4 Hz), 7.56 (2H, d, J = 8.8 Hz), 8.22 (2H, d, J = 8.6 Hz); δ_{13C} (100 MHz, CDCl₃) 12.5 (CH₂), 12.8 (CH₃), 53.5 (CH₂), 68.6 (CH), 79.3 (C), 97.8 (C), 123.8 (2 x CH), 126.4 (2 x CH), 147.4 (C), 149.5 (C), 186.1 (C); ν_{max} (film/cm⁻¹) 3454, 2983, 2213, 1670, 1605, 1520, 1347; m/z (HRMS, ESI) found 246.0755, ([M-H]⁻) C₁₃H₁₂NO₄ requires 246.0766.

(E)-1-(4-nitrophenyl)hept-1-en-4-yn-3-one (3).

Isolated side-product from the above reaction. Purification by silica gel column chromatography (petroleum ether 30-40°C:diethyl ether, 4:1) yielded the product (17.2 mg, 15% yield) as a pale yellow solid; mp = 138-142°C; R_f (petroleum ether 30-40°C:diethyl ether, 3:1) = 0.40. δ_{1H} (400 MHz, CDCl₃) 1.29 (3H, t, J = 7.6 Hz), 2.49 (2H, q, J = 7.6 Hz), 6.83 (1H, d, J = 16.0 Hz), 7.72 (2H, d, J = 8.8 Hz), 7.79 (1H, d, J = 16.2 Hz), 8.26 (2H, d, J = 8.8 Hz); δ_{13C} (100 MHz, CDCl₃) 12.85 (CH₃), 12.88 (CH₂), 78.6 (C), 97.3 (C), 124.2 (2 x CH), 129.1 (2 x CH), 131.8 (CH), 140.2 (C), 144.3 (CH), 148.8 (C), 177.7 (C); ν_{max} (film/cm⁻¹) 2215, 1640, 1619, 1515, 1342, 1265, 1110; m/z (HRMS, ESI) found 230.0816, ([M+H]⁺), C₁₃H₁₂NO₃ requires 230.0812.

7-(4-nitrophenyl)trideca-3,10-diyne-5,9-dione (4).

Isolated side-product of the above reaction. Purification by silica gel column chromatography (petroleum ether 30-40°C:diethyl ether, 3:1) yielded the product (17.9 mg, 11% yield) as a pale orange oil; R_f (petroleum ether 30-40°C:diethyl ether, 3:1) = 0.25. δ_{1H} (400 MHz, $CDCl_3$) 1.19 (6H, t, $J = 7.5$ Hz), 2.35 (4H, q, $J = 7.5$ Hz), 2.92 (2H, dd, $J = 17.0, 7.8$ Hz), 2.98 (2H, dd, $J = 17.0, 6.6$ Hz), 4.00 (1H, tt, $J = 6.6, 7.8$ Hz), 7.42 (2H, d, $J = 8.7$ Hz), 8.16 (2H, d, $J = 8.7$ Hz); δ_{13C} (100 MHz, $CDCl_3$) 12.64 (2 x CH_3), 12.71 (2 x CH_2), 36.2 (CH), 50.5 (2 x CH_2), 80.0 (2 x C), 96.8 (2 x C), 123.9 (2 x CH), 128.6 (2 x CH), 146.8 (C), 150.0 (C), 184.7 (2 x C); ν_{max} (film/ cm^{-1}) 2982, 2919, 2851, 2207, 164, 1515, 1343, 1244; m/z (HRMS, ESI) found 326.1387, ($[M+H]^+$) $C_{19}H_{20}NO_4$ requires 326.1387.

Synthesis of ketones 5a-5c

Synthesis of ethyl 2-(methoxymethoxy)acetate

To a solution of ethyl glycolate (28 g, 270 mmol), LiBr (4.7 g, 54 mmol) in dimethoxymethane (500 mL) was added p-TSA (4.6 g, 27 mmol) under argon. The resulting mixture was stirred for 48h. Then, it was partitioned between brine (500 mL) and diethyl ether (3 x 150 mL). The combined organic extracts were dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The resulting residue was further purified by silica gel column chromatography (hexane:diethyl ether, 1:1) to give (21.5 g, 61% yield) as a pale yellow oil; R_f (hexane:diethyl ether, 1:1) = 0.50; δ_{1H} (400 MHz, CD_2Cl_2) 1.29 (3H, t, $J = 7.3$ Hz), 3.39 (3H, s), 4.15 (2H, s), 4.20 (2H, q, $J = 7.3$ Hz), 4.70 (2H, d); δ_{13C} (100 MHz, CD_2Cl_2) 14.4 (CH_3), 55.9 (CH_3), 61.2 (CH_2), 64.6 (CH_2), 96.7 (CH_2), 170.5 (C); ν_{max} (film/ cm^{-1}) 2939, 1756, 1446, 1062; m/z (HRMS, GCT Cl^+) found ($[M+H]^+$) 149.0813, $C_6H_{13}O_4$ requires 149.0814.

Synthesis of N-methoxy-2-(methoxymethoxy)-N-methylacetamide.

To N,O-dimethylhydroxylamine hydrochloride (14.6 g, 150 mmol) in anhydrous THF (250 mL) was added under argon at -78°C *n*-BuLi (2.5 M, 120 mL, 300 mmol) via cannula. The resulting solution was warmed up to room temperature and stirred for 30 mins. Then, the solution was cooled down to -78°C and the above ester (7.4 g, 50 mmol) in anhydrous THF (100 mL) was slowly added via cannula. The reaction mixture was allowed to warm at room temperature overnight. It was then cooled down to 0°C and a solution of saturated NH₄Cl (350 mL) was added. The organic layer was separated and the aqueous layer was partitioned with diethyl ether (3 x 130 mL) and DCM (2 x 100 mL). The combined organic extracts were dried over MgSO₄. After filtration, solvent was removed *in vacuo*. The resulting residue was purified by silica gel column chromatography (DCM:diethyl ether, 1:1) to give (7.23 g, 89% yield) as a pale yellow oil; *R*_f (DCM:diethyl ether, 1:1) = 0.3; δ_{1H} (400 MHz, CD₂Cl₂) 3.17 (3H, s), 3.39 (3H, s), 3.70 (3H, s), 4.35 (2H, s), 4.71 (2H, s); δ_{13C} (100 MHz, CD₂Cl₂) 32.5 (CH₃), 55.8 (CH₃), 61.8 (CH₃), 64.4 (CH₂), 96.8 (CH₂), 171.0 (C); ν_{max} (film/cm⁻¹) 2942, 1684, 1445, 1057, 990; *m/z* (HRMS, ESI) found ([M+Na]⁺) 186.0739, C₆H₁₃NNaO₄ requires 186.0737.

Synthesis of 1-(methoxymethoxy)pent-3-yn-2-one (5a)

To a solution of N-methoxy-2-(methoxymethoxy)-N-methylacetamide (6.52 g, 40 mmol) in anhydrous THF (250 mL) was added under argon at -78°C propynylmagnesium bromide (0.5 M in THF, 240 mL, 120 mmol) via cannula. The resulting solution was stirred at -78°C for 15 mins and allowed to slowly warm up to room temperature overnight. Then, it was quenched at 0°C with 1N HCl (250 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were dried over MgSO₄. After filtration, the solvent was removed *in vacuo*. The resulting residue was further purified by silica gel column chromatography (hexane:diethyl ether, 1:1) to give (4.74 g, 76% yield) as a pale yellow oil; *R*_f

(hexane:diethyl ether, 1:1) = 0.40; δ_{1H} (400 MHz, CD_2Cl_2) 2.07 (3H, s), 3.39 (3H, s), 4.27 (2H, s), 4.68 (2H, s); δ_{13C} (100 MHz, CD_2Cl_2) 4.3 (CH_3), 56.0 (CH_3), 73.4 (CH_2), 78.1 (C), 93.4 (C), 96.8 (CH_2), 184.6 (C); ν_{max} (film/ cm^{-1}) 2895, 2219, 1693, 1152, 1120, 1060; 957 m/z (HRMS, GCT Cl^+) found ($[M+NH_4]^+$) 160.0973, $C_7H_{14}NO_3$ requires 160.0974.

Synthesis of 1-(methoxymethoxy)-4-phenylbut-3-yn-2-one (5b)

To a solution of phenylacetylene (5.9 mL, 54 mmol) in anhydrous THF (210 mL) was added *n*-BuLi (2.5 M in hexanes, 21.6 mL) under argon at 0°C via cannula. After stirring for 15 mins at 0°C, the reaction was cooled down to -78°C and N-methoxy-2-(methoxymethoxy)-N-methylacetamide (8.0 g, 49.1 mmol) in THF (40 mL) was added via cannula. The mixture was stirred at -78°C for 30 mins and allowed to warm up to room temperature overnight. It was then quenched with NH_4Cl (100 mL) at 0°C. Water was added and the phases separated. The aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane:diethyl ether, 3:1) to yield the product (7.7 g, 73% yield) as a pale yellow oil; R_f (hexane:diethyl ether, 3:1) = 0.25; δ_{1H} (400 MHz, $CDCl_3$) 3.43 (3H, s), 4.43 (2H, s), 4.75 (2H, s), 7.36-7.43 (2H, m), 7.45-7.51 (1H, m), 7.56-7.61 (2H, m); δ_{13C} (100 MHz, $CDCl_3$) 55.9 (CH_3), 73.0 (CH_2), 85.6 (C), 93.6 (C), 96.5 (CH_2), 119.5 (C), 128.7 (2 x CH), 131.1 (2 x CH), 133.1 (CH), 184.1 (C); ν_{max} (film/ cm^{-1}) 2894, 2201, 1690, 1490, 1044; m/z (HRMS, GCT Cl^+) found ($[M+H]^+$) 205.0856, $C_{12}H_{13}O_3$ requires 205.0865.

Synthesis of 1-(methoxymethoxy)-4-(triethylsilyl)but-3-yn-2-one (5c).

To a solution of triethylsilylacetylene (5.50 mL, 30.7 mmol) in anhydrous THF (210 mL) was added under argon at 0°C *n*-BuLi (2.5 M in hexanes, 12.3 mL, 30.7 mmol) via cannula. After stirring for 15 mins at 0°C, the reaction was cooled down to -78°C and N-methoxy-2-

(methoxymethoxy)-N-methylacetamide (5.0 g, 30.7 mmol) in THF (30 mL) was added via cannula. The mixture was stirred at -78°C for 30 mins and allowed to warm up to room temperature overnight. It was then quenched with acetic acid (1.76 mL, 30.7 mmol) at 0°C. Water was added and the phases separated. The aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were dried over MgSO₄. After filtration, the solvent was removed *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane:diethyl ether, 5:1) to give (5.48 g, 74% yield) as a pale yellow oil; *R*_f (hexane:diethyl ether, 1:1) = 0.60; δ_{1H} (400 MHz, CD₂Cl₂) 0.72 (6H, q, *J* = 8.1 Hz), 1.05 (9H, t, *J* = 8.1 Hz), 3.40 (3H, s), 4.32 (2H, s), 4.69 (2H, s); δ_{13C} (100 MHz, CD₂Cl₂) 7.1 (3 x CH₃), 7.4 (3 x CH₂), 56.0 (CH₃), 73.5 (CH₂), 96.9 (CH₂), 99.6 (C), 101.3 (C), 184.3 (C); ν_{max} (film/cm⁻¹) 2958, 2879, 2150, 1698, 1048, 730; *m/z* (HRMS, GCT Cl⁺) found ([M+NH₄]⁺) 260.1685, C₁₂H₂₆NO₃Si requires 260.1682.

Synthesis of compounds 6a-6h

(4*S*,5*S*)- 1-Hydroxy-2-methoxymethoxy-1-(4-nitro-phenyl)-hex-4-yn-3-one (6a).

6a was obtained from 4-nitrobenzaldehyde (302 mg, 2.0 mmol) and **5a** (1.42 g, 10.0 mmol) according to general procedure A. Purification by silica gel column chromatography (hexane:diethyl ether, 1:1) yielded the product (398 mg, 68% yield, dr = 9:1) as a pale yellow oil; *R*_f(hexane:diethyl ether, 1:1) = 0.20; The enantiomeric excess of the product **6a** was determined to be 93% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cmΦ x 25 cm)]; eluent, hexane/^{*i*}PrOH = 85/15; flow rate, 0.8 mL/min; retention time: 17.1 min (major), 21.0 min (minor); [*a*]_D²⁰ -69.1 (c 1.0, CH₂Cl₂); δ_{1H} (400 MHz, CD₂Cl₂) 2.04 (3H, s), 3.20 (3H, s), 3.71 (1H, d, *J* = 3.7 Hz), 4.26 (1H, d, *J* = 6.1 Hz), 4.56 (1H, d, *J* = 6.8 Hz), 4.61 (1H, d, *J* = 6.8 Hz), 5.21 (1H, m), 7.62 (2H, d, *J* = 8.8 Hz), 8.19 (2H, d, *J* = 8.8 Hz); δ_{13C} (100 MHz, CD₂Cl₂) 4.5 (CH₃), 56.5 (CH₃), 73.5 (CH), 79.3 (C), 86.0 (CH), 96.0 (C), 97.1 (CH₂), 123.6 (2 x CH), 128.5 (2 x CH), 147.7 (C),

148.0 (C), 186.2 (C); $\nu_{\max}$ (film/cm⁻¹) 3462, 2898, 2213, 1675, 1606, 1522, 1348, 859, 735; m/z (HRMS, ESI) found ([M-H]⁻) 292.0817, C₁₄H₁₅NO₆ requires 292.0816.

(4*S*,5*S*)-5-hydroxy-4-(methoxymethoxy)-5-(4-nitrophenyl)-1-phenylpent-1-yn-3-one (6b). **6b** was obtained from 4-nitrobenzaldehyde (75.6 mg, 0.50 mmol) and **5b** (510 mg, 2.5 mmol) according to general procedure A. Purification by silica gel column chromatography (petroleum ether (30-40°C):diethyl ether, 1:1) yielded the product (160 mg, 90% yield, dr = 9:1) as a pale yellow solid; mp = 105°C; R_f (petroleum ether (30-40°C):diethyl ether, 1:1) = 0.30; The enantiomeric excess of the product **6b** was determined to be 94% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cmΦ x 25 cm)]; eluent, hexane/EtOH = 9/1; flow rate, 0.5 mL/min; retention time: 25.4 min (major), 29.3 min (minor); $[\alpha]_D^{20}$ -73.4 (c 1.0, CHCl₃); δ_{1H} (400 MHz, CDCl₃) 3.28 (3H, s), 3.39 (1H, br s), 4.46 (1H, d, J = 5.6 Hz), 4.67 (1H, d, J = 6.8 Hz), 4.72 (1H, d, J = 6.8 Hz), 5.29 (1H, d, J = 5.6 Hz), 7.35-7.40 (2H, m), 7.45-7.50 (3H, m), 7.64 (2H, d, J = 8.5 Hz), 8.18 (2H, d, J = 8.9 Hz); δ_{13C} (100 MHz, CDCl₃) 56.4 (CH₃), 73.4 (CH), 85.6 (CH), 86.9 (C), 96.0 (C), 96.9 (CH₂), 119.1 (C), 123.4 (2 x CH), 128.0 (2 x CH), 128.8 (2 x CH), 131.4 (CH), 133.2 (2 x CH), 146.5 (C), 147.7 (C), 185.6 (C); $\nu_{\max}$ (film/cm⁻¹) 3463, 2898, 2202, 1672, 1521, 1347; m/z (HRMS, ESI) found ([M-H]⁻) 354.0976, C₁₉H₁₆NO₆ requires 354.0972.

(4*S*,5*S*)- 5-Hydroxy-4-methoxymethoxy-5-(4-nitro-phenyl)-1-triethylsilanyl-pent-1-yn-3-one (6c). **6c** was obtained from 4-nitrobenzaldehyde (60 mg, 0.40 mmol) and **5c** (484 mg, 2 mmol) according to general procedure A (dr crude = 4:1). Purification by silica gel column chromatography (hexane:diethyl ether, 2:1) yielded the product (130 mg, 87% yield, dr = 7:1) as a pale yellow oil; R_f (hexane:diethyl ether, 2:1) = 0.25; The enantiomeric excess of the product **6c** was determined to be 77% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cmΦ x 25 cm)]; eluent, hexane/ⁱPrOH = 19:1; flow rate, 0.7 mL/min; retention time: 15.3 min (major), 18.4 min (minor); $[\alpha]_D^{20}$ -50.5 (c 1.0, CH₂Cl₂); δ_{1H} (400 MHz, CDCl₃) 0.64 (6H, q, J = 7.8 Hz),

0.98 (9H, t, $J = 7.8$ Hz), 3.22 (1H, br s), 3.26 (3H, s), 4.37 (1H, d, $J = 5.6$ Hz), 4.64 (1H, d, $J = 6.8$ Hz), 4.69 (1H, d, $J = 6.8$ Hz), 5.22 (1H, d, $J = 5.6$ Hz), 7.59 (2H, d, $J = 8.8$ Hz), 8.20 (2H, d, $J = 8.8$ Hz); $\delta_{13\text{C}}$ (100 MHz, CDCl_3) 3.7 (3 x CH_3), 7.3 (3 x CH_2), 56.4 (CH_3), 73.3 (CH), 85.4 (CH), 96.9 (CH_2), 101.8 (C), 102.5 (C), 123.4 (2 x CH), 128.1 (2 x CH), 146.3 (C), 147.7 (C), 185.2 (C); ν_{max} (film/ cm^{-1}) 3449, 2958, 2912, 2152, 1680, 1523, 1348, 1024; m/z (HRMS, ESI) found ($[\text{M}+\text{Na}]^+$) 416.1495, $\text{C}_{19}\text{H}_{27}\text{NNaO}_6\text{Si}$ requires 416.1500

((4*S*,5*S*)- 1-Hydroxy-2-methoxymethoxy-1-(4-trifluoromethyl-phenyl)-hex-4-yn-3-one (6d).

6d was obtained from 4-trifluoromethylbenzaldehyde (348 mg, 2 mmol) and **5a** (1.42 g, 10 mmol) according to general procedure A. Purification by silica gel column chromatography (hexane :diethyl ether, 1:1) yielded the product (425 mg, 67% yield, dr = 19:1) as a pale yellow oil; R_f (hexane :diethyl ether, 1:1) = 0.15; The enantiomeric excess of the product **6d** was determined to be 95% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/EtOH = 9/1; flow rate, 0.7 mL/min; retention time: 14.0 min (major), 15.7 min (minor); $[\alpha]_{\text{D}}^{18}$ -65.6 (c 1.0, CH_2Cl_2); $\delta_{1\text{H}}$ (400 MHz, CD_2Cl_2) 2.02 (3H, s), 3.21 (3H, d, $J = 5.6$ Hz), 3.22 (3H, s), 4.30 (1H, d, $J = 6.1$ Hz), 4.58 (1H, d, $J = 6.8$ Hz), 4.63 (1H, d, $J = 6.8$ Hz), 5.20 (1H, app t, $J = 5.3$ Hz), 7.58 (2H, d, $J = 8.1$ Hz), 7.66 (2H, d, $J = 8.1$ Hz); $\delta_{13\text{C}}$ (100 MHz, CD_2Cl_2) 4.4 (CH_3), 56.4 (CH_3), 73.8 (CH), 79.3 (C), 86.1 (CH), 95.6 (C), 97.1 (CH_2), 124.0 (C, $^1J(\text{C},\text{F}) = 271.6$ Hz), 125.4 (2 x CH , $^3J(\text{C},\text{F}) = 4.0$ Hz), 127.9 (2 x CH), 130.3 (C, $^2J(\text{C},\text{F}) = 32.0$ Hz), 144.3 (C), 186.1 (C); $\delta_{19\text{F}}$ (376 MHz, CD_2Cl_2) -62.8 (3F, s); ν_{max} (film/ cm^{-1}) 3392, 2927, 2204, 1651, 1418, 1326, m/z (HRMS, ESI) found ($[\text{M}+\text{Na}]^+$) 339.0808, $\text{C}_{15}\text{H}_{15}\text{F}_3\text{NaO}_4$ requires 339.0815.

((4*S*,5*S*)-5-hydroxy-4-(methoxymethoxy)-1-phenyl-5-(4-(trifluoromethyl)phenyl)pent-1-yn-3-one (6e).

6e was obtained from 4-trifluoromethylbenzaldehyde (273 μL , 2 mmol) and **5b** (2.04 g, 10 mmol) according to general procedure A. Purification by silica gel column chromatography (petroleum ether (30-40°C):diethyl ether, 1:1) yielded the product (635 mg, 84% yield, dr = 9:1) as

a pale yellow oil; R_f (petroleum ether (30-40°C):diethyl ether, 1:1) = 0.35; The enantiomeric excess of the product **6e** was determined to be 93% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/EtOH = 99/1; flow rate, 1.0 mL/min; retention time: 41.5 min (major), 57.4 min (minor); $[\alpha]_D^{18}$ -76.5 (c 1.0, CHCl₃); δ_{1H} (400 MHz, CDCl₃) 3.17 (1H, br s), 3.28 (3H, s), 4.48 (1H, d, J = 5.6 Hz), 4.66 (1H, d, J = 6.8 Hz), 4.72 (1H, d, J = 6.8 Hz), 5.23 (1H, d, J = 5.6 Hz), 7.35-7.42 (2H, m), 7.44-7.50 (3H, m), 7.57-7.64 (4H, m); δ_{13C} (100 MHz, CDCl₃) 56.3 (CH₃), 73.7 (CH), 85.7 (CH), 86.9 (C), 95.7 (C), 96.8 (CH₂), 119.3 (C), 124.0 (C, 1J (C,F) = 272.0 Hz), 125.2 (2 x CH, 3J (C,F) = 3.6 Hz), 127.5 (2 x CH), 128.7 (2 x CH), 130.2 (C, 2J (C,F) = 32.4 Hz), 131.2 (CH), 133.2 (2 x CH), 143.2 (C), 185.8 (C); δ_{19F} (376 MHz, CDCl₃) -62.6 (3F, s); ν_{max} (film/cm⁻¹) 3457, 2998, 2955, 2898, 2203, 1673, 1418, 1326; m/z (HRMS, ESI) found ([M-H]⁻) 377.0995, C₂₀H₁₆F₃O₄ requires 377.0995.

(4S,5S)- 5-Hydroxy-4-methoxymethoxy-1-triethylsilanyl-5-(4-trifluoromethyl-phenyl)-pent-1-yn-3-one (6f). **6f** was obtained from 4-trifluoromethylbenzaldehyde (174 mg, 1 mmol) and **5c** (1.21 g, 5 mmol) according to general procedure A. Purification by silica gel column chromatography (hexane:diethyl ether, 7:3) yielded the product (312 mg, 75% yield, dr = 3:1) as a pale yellow oil; R_f (hexane:diethyl ether, 7:3) = 0.25; The enantiomeric excess of the product **6f** could not be determined due to low polarity of the product; $[\alpha]_D^{20}$ -58.0 (c 1.0, CH₂Cl₂); δ_{1H} (400 MHz, CD₂Cl₂) 0.70 (6H, q, J = 7.6 Hz), 1.03 (9H, t, J = 7.6 Hz), 3.26 (3H, s), 3.28 (1H, br s), 4.34 (1H, d, J = 5.6 Hz), 4.62 (1H, d, J = 6.8 Hz), 4.67 (1H, d, J = 6.8 Hz), 5.18 (1H, d, J = 5.6 Hz), 7.57 (2H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.8 Hz); δ_{13C} (100 MHz, CD₂Cl₂) 4.1 (3 x CH₃), 7.4 (3 x CH₂), 56.5 (CH₃), 73.9 (CH), 86.1 (CH), 97.2 (CH₂), 101.8 (C), 102.0 (C), 124.6 (C, 1J (C,F) = 271.6 Hz), 125.5 (2 x CH, 3J (C,F) = 4.0 Hz), 128.0 (2 x CH), 130.4 (C, 2J (C,F) = 32.0 Hz), 144.1 (C), 186.0 (C); δ_{19F} (376MHz, CD₂Cl₂) -62.8 (3F, s); ν_{max} (film/cm⁻¹) 3461, 2960, 2879, 2151,

1678, 1460, 1327; m/z (HRMS, ESI) found ($[M+Na]^+$) 439.1522, $C_{20}H_{27}F_3NaO_4Si$ requires 439.1523.

(4*S*,5*S*)-5-hydroxy-4-(methoxymethoxy)-1,5-diphenylpent-1-yn-3-one (6g).

6g was obtained from benzaldehyde (51 μ L, 0.5 mmol) and **5b** (510 mg, 2.5 mmol) according to general procedure **A**. Purification by silica gel column chromatography (petroleum ether (30-40°C):diethyl ether, 3:2) yielded the product (40 mg, 26% yield, dr = 13:1) as a pale yellow oil; R_f (petroleum ether (30-40°C):diethyl ether, 3:2) = 0.40; The enantiomeric excess of the product **6g** was determined to be 93% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/EtOH = 99/1; flow rate, 1.0 mL/min; retention time: 42.7 min (major), 53.2 min (minor); $[\alpha]_D^{23}$ -52.4 (c 1.0, $CHCl_3$); δ_{1H} (400 MHz, $CDCl_3$) 2.96 (1H, br s), 3.22 (3H, s), 4.45 (1H, d, J = 6.3 Hz), 4.60 (1H, d, J = 6.8 Hz), 4.68 (1H, d, J = 6.9 Hz), 5.15 (1H, d, J = 6.1 Hz), 7.28-7.40 (5H, m), 7.44-7.55 (5H, m); δ_{13C} (100 MHz, $CDCl_3$) 56.2 (CH₃), 74.2 (CH), 85.8 (CH), 87.0 (C), 95.0 (C), 96.7 (CH₂), 119.6 (C), 127.1 (2 x CH), 128.3 (CH), 128.4 (2 x CH), 128.6 (2 x CH), 131.1 (CH), 133.3 (2 x CH), 139.5 (C), 186.5 (C); ν_{max} (film/cm⁻¹) 3457, 2953, 2895, 2203, 1672, 1490, 1286; m/z (HRMS, ESI) found ($[M+Na]^+$) 333.1096, $C_{19}H_{18}NaO_4$ requires 333.1097.

(4*S*,5*S*)-5-(4-bromophenyl)-5-hydroxy-4-(methoxymethoxy)-1-phenylpent-1-yn-3-one (6h).

6h was obtained from 4-bromobenzaldehyde (92 mg, 0.5 mmol) and **5b** (510 mg, 2.5 mmol) according to general procedure **A**. Purification by silica gel column chromatography (petroleum ether (30-40°C):diethyl ether, 3:1) yielded the product (65% yield, dr = 9:1) as a pale yellow oil; R_f (petroleum ether (30-40°C):diethyl ether, 1:1) = 0.52; The enantiomeric excess of the product **6h** was determined to be 93% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/EtOH = 99/1; flow rate, 1.0 mL/min; retention time: 42.7 min (major), 53.2 min (minor); $[\alpha]_D^{23}$ -56.0 (c 1.0, $CHCl_3$); δ_{1H} (400 MHz, $CDCl_3$) 3.07 (1H, br s), 3.28

(3H, s), 4.43 (1H, d, $J = 5.8$ Hz), 4.64 (1H, d, $J = 6.9$ Hz), 4.70 (1H, d, $J = 6.9$ Hz), 5.13 (1H, d, $J = 5.8$ Hz), 7.34 (2H, d, $J = 8.5$ Hz), 7.35-7.42 (2H, m), 7.45-7.52 (3H, m), 7.49 (2H, d, $J = 8.2$ Hz); $\delta_{13\text{C}}$ (100 MHz, CDCl_3) 56.3 (CH_3), 73.7 (CH), 85.7 (CH), 87.0 (C), 95.5 (C), 96.8 (CH_2), 119.4 (C), 122.3 (2 x CH), 128.7 (2 x CH), 128.8 (2 x CH), 131.2 (CH), 131.4 (2 x CH), 133.3 (2 x CH), 138.3 (C), 186.0 (C); ν_{max} (film/ cm^{-1}) 3452, 2210, 1634; m/z (HRMS, ESI) found ($[\text{M-H}]^-$) 387.0227, $\text{C}_{19}\text{H}_{16}\text{BrO}_4$ requires 387.0226.

Synthesis of compounds **7e**, **8e**

((4S,5S,6R)- 2-Methoxymethoxy-5-phenyl-1-(4-trifluoromethyl-phenyl)-pent-4-yne-1,3-diol (7e). **7e** was obtained from **6e** (76 mg, 0.2 mmol) according to general procedure **B**. Purification by silica gel column chromatography (hexane:diethyl ether, 1:2) yielded the product (68 mg, 89% yield, dr = 92:8) as a white oil; R_f (hexane:diethyl ether, 1:2) = 0.4; The enantiomeric excess of the product **7e** was determined to be 93% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/EtOH = 98/2; flow rate, 1.0 mL/min; retention time: 49.4 min (minor), 70.4 min (major); $[\alpha]_{\text{D}}^{18}$ -39.7 (c 1.0, CH_2Cl_2); $\delta_{1\text{H}}$ (400 MHz, CD_2Cl_2) 3.25 (2H, br s), 3.39 (3H, s), 3.84 (1H, dd, $J = 7.6, 3.8$ Hz), 4.45 (1H, d, $J = 7.1$ Hz), 4.63 (1H, d, $J = 7.1$ Hz), 4.83 (1H, d, $J = 3.8$ Hz), 4.97 (1H, d, $J = 7.6$ Hz), 7.33-7.40 (3H, m), 7.46-7.50 (2H, m), 7.62 (2H, d, $J = 8.3$ Hz), 7.66 (2H, d, $J = 8.3$ Hz); $\delta_{13\text{C}}$ (125 MHz, CD_2Cl_2) 56.5 (CH_3), 63.9 (CH), 73.9 (CH), 86.7 (C), 87.4 (CH), 87.7 (C), 98.6 (CH), 122.9 (C), 124.7 (C, $^1J(\text{C},\text{F}) = 271.8$ Hz), 125.5 (2 x CH, $^3J(\text{C},\text{F}) = 3.8$ Hz), 128.1 (2 x CH), 128.8 (2 x CH), 129.0 (CH), 130.1 (C, $^2J(\text{C},\text{F}) = 31.5$ Hz), 132.1 (C), 145.9 (C); $\delta_{19\text{F}}$ (376 MHz, CDCl_3) -62.5 (3F, s); ν_{max} (film/ cm^{-1}) 3406, 2900, 2231, 1620, 1419, 1325, 1121; m/z (HRMS, ESI) found ($[\text{M}+\text{Na}]^+$) 403.1129, $\text{C}_{20}\text{H}_{19}\text{F}_3\text{NaO}_4$ requires 403.1128.

((4S,5S,6R)- 5-Phenyl-1-(4-trifluoromethyl-phenyl)-pent-4-yne-1,2,3-triol (8e). **8e** was obtained from **7e** (19 mg, 0.05 mmol) according to general procedure **C**. Reaction time was 12h.

Purification by silica gel column chromatography (hexane:diethyl ether, 1:2) yielded the product (10 mg, 60% yield, dr > 99:1) as a white oil; R_f (hexane:diethyl ether, 1:2) = 0.35; The enantiomeric excess of the product **8e** was determined to be 88% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/EtOH = 9/1; flow rate, 0.8 mL/min; retention time: 16.8 min (minor), 19.9 min (major); $[\alpha]_D^{18}$ -38.4 (c 1.0, CH₃CN); δ_{1H} (400 MHz, CD₃CN) 3.32 (1H, br s), 3.76 (1H, dd, J = 7.8, 4.6 Hz), 3.86 (2H, br s), 4.73 (1H, d, J = 4.6 Hz), 4.78 (1H, d, J = 7.8 Hz), 7.37-7.42 (3H, m), 7.48-7.52 (2H, m), 7.63 (2H, d, J = 8.3 Hz), 7.69 (2H, d, J = 8.3 Hz); δ_{13C} (125 MHz, CD₃CN) 64.4 (CH), 74.2 (CH), 77.0 (CH), 85.3 (C), 88.0 (C), 122.8 (C), 123.5 (C, 1J (C,F) = 271.0 Hz), 124.7 (2 x CH, 3J (C,F) = 3.9 Hz), 128.2 (2 x CH), 128.56 (CH), 128.57 (2 x CH), 128.8 (C, 2J (C,F) = 32.0 Hz), 131.6 (2 x CH), 147.1 (C); δ_{19F} (376 MHz, CD₃CN) -62.8 (3F, s); ν_{max} (film/cm⁻¹) 3368, 2924, 2255, 1619, 1324, 1120, 1066, 834; m/z (HRMS, ESI) found ($[M+Na]^+$) 359.0865, C₁₈H₁₅F₃NaO₃ requires 359.0866.

Synthesis of compounds **9a**, **9b**, **9d**, **9e**.

(4S,5S,E)- 2-Ethylidene-4-methoxymethoxy-5-(4-nitro-phenyl)-dihydro-furan-3-one (9a). **9a** was obtained from **6a** (88 mg, 0.3 mmol) according to general procedure **D**. Purification by silica gel column chromatography (DCM:hexane, 2:1) yielded the product (46 mg, 63% yield, E:Z = 97:3) as a pale yellow oil ; R_f (DCM:hexane, 2:1) = 0.25; The enantiomeric excess of the product **9a** was determined to be 94% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/^{*i*}PrOH = 9/1; flow rate, 0.8 mL/min; retention time: 12.1 min (minor), 14.3 min (major); $[\alpha]_D^{20}$ +7.4 (c 1.0, CH₂Cl₂); δ_{1H} (400 MHz, CD₂Cl₂) 1.86 (3H, d, J = 7.6 Hz), 3.27 (3H, s), 4.32 (1H, d, J = 8.3 Hz), 4.65 (1H, d, J = 6.8 Hz), 5.02 (1H, d, J = 6.8 Hz), 5.26 (1H, d, J = 8.3 Hz), 5.78 (1H, q, J = 7.6 Hz), 7.72 (2H, d, J = 8.3 Hz), 8.31 (2H, d, J = 8.3 Hz); δ_{13C} (100 MHz, CD₂Cl₂) 10.8 (CH₃), 56.3 (CH₃), 80.5 (CH), 81.4 (CH), 96.7 (CH₂), 106.8

(CH), 124.3 (2 x CH), 127.3 (2 x CH), 145.9 (C), 148.4 (C), 148.6 (C), 196.2 (C); $\nu_{\max}$ (film/cm⁻¹) 2901, 1748, 1664, 1607, 1349, 1111; m/z (HRMS, ESI) found ([M-H]⁻) 292.0816, C₁₄H₁₄NO₆ requires 292.0816.

(4*S*,5*S*,*E*)-2-benzylidene-4-(methoxymethoxy)-5-(4-nitrophenyl)dihydrofuran-3(2*H*)-one (9b).

9b was obtained from **6b** (77 mg, 0.22 mmol) according to general procedure **D**. Purification by silica gel column chromatography (petroleum ether (40-60°C):diethyl ether, 3:1) yielded the product (70 mg, 90% yield, dr > 99:1) as a pale yellow oil; R_f (petroleum ether (40-60°C):diethyl ether, 1:1) = 0.62; The enantiomeric excess of the product **9b** was determined to be 94% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/EtOH = 19/1; flow rate, 1.0 mL/min; retention time: 17.1 min (minor), 18.4 min (major); $[\alpha]_D^{20}$ +45.2 (c 1.0, CHCl₃); δ_{1H} (400 MHz, CDCl₃) 3.33 (3H, s), 4.39 (1H, d, J = 8.0 Hz), 4.71 (1H, d, J = 6.7 Hz), 5.10 (1H, d, J = 6.7 Hz), 5.45 (1H, d, J = 7.9 Hz), 6.54 (1H, s), 7.32-7.43 (3H, m), 7.73 (2H, d, J = 8.5 Hz), 7.80 (2H, m), 8.33 (2H, d, J = 8.8 Hz); δ_{13C} (100 MHz, C₆D₆) 55.6 (CH₃), 79.3 (CH), 82.0 (CH), 96.1 (CH₂), 108.1 (CH), 123.8 (2 x CH), 126.7 (2 x CH), 129.2 (2 x CH), 129.3 (CH), 131.0 (2 x CH), 133.5 (C), 144.6 (C), 146.4 (C), 148.3 (C), 196.6 (C); $\nu_{\max}$ (film/cm⁻¹) 2971, 1725, 1631, 1523, 1145; m/z (HRMS, ESI) found ([M-H]⁻) 354.0968, C₁₉H₁₆NO₆ requires 354.0972.

(4*S*,5*S*,*E*)- 2-Ethylidene-4-methoxymethoxy-5-(4-trifluoromethyl-phenyl)-dihydro-furan-3-one (9d).

9d was obtained from **6d** (32 mg, 0.1 mmol) according to general procedure **D**. Purification by silica gel column chromatography (DCM:hexane, 2:1) yielded the product (17 mg, 53% yield, E/Z= 99:1) as a pale yellow oil; R_f (DCM:hexane, 2:1) = 0.5; The enantiomeric excess of the product **9d** was determined to be 95% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/*i*PrOH = 98/2; flow rate, 1.0 mL/min; retention time: 7.0 min (minor), 8.6 min (major); $[\alpha]_D^{20}$ -42.1 (c 1.0, CH₂Cl₂); δ_{1H} (500 MHz, C₆D₆) 1.66 (3H, d, J = 7.3 Hz), 3.04 (3H, s), 4.16 (1H, d, J = 8.2 Hz), 4.45 (1H, d, J = 6.6 Hz),

4.90 (1H, d, $J = 8.2$ Hz), 5.03 (1H, d, $J = 6.6$ Hz), 5.77 (1H, q, $J = 7.3$ Hz), 7.19 (2H, d, $J = 8.2$ Hz), 7.42 (2H, d, $J = 8.2$ Hz), $\delta_{13\text{C}}$ (125 MHz, C_6D_6) 10.2 (CH_3), 55.3 (CH_3), 79.9 (CH), 81.3 (CH), 95.9 (CH_2), 105.2 (CH), 124.5 (C, $^1J(\text{C},\text{F}) = 272.8$ Hz), 125.5 (2 x CH, $^3J(\text{C},\text{F}) = 3.8$ Hz), 126.6 (2 x CH), 130.6 (C, $^2J(\text{C},\text{F}) = 32.4$ Hz), 142.4 (C), 148.5 (C), 195.7 (C); $\delta_{19\text{F}}$ (376 MHz, C_6D_6) -62.2 (3F, s); ν_{max} (film/ cm^{-1}) 2941, 1847, 1663, 1326, 1126; m/z (HRMS, ESI) found ($[\text{M}+\text{Na}]^+$) 339.0811, $\text{C}_{15}\text{H}_{15}\text{F}_3\text{NaO}_4$ requires 339.0815.

(4*S*,5*S*,*E*)-2-benzylidene-4-(methoxymethoxy)-5-(4-(trifluoromethyl)phenyl)dihydrofuran-

3(2H)-one (9e). **9e** was obtained from **6e** (85 mg, 0.22 mmol) according to general procedure **D**. Purification by silica gel column chromatography (petroleum ether (40-60°C):diethyl ether, 3:2) yielded the product (64 mg, 77% yield, dr > 99:1) as a pale yellow oil; R_f (petroleum ether (40-60°C):diethyl ether, 3:2) = 0.42; The enantiomeric excess of the product **9e** was determined to be 93% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ x 25 cm)]; eluent, hexane/EtOH = 99/1; flow rate, 1.0 mL/min; retention time: 9.1 min (minor), 10.6 min (major); $[\alpha]_{\text{D}}^{20} +49.4$ (c 1.0, CHCl_3); $\delta_{1\text{H}}$ (400 MHz, C_6D_6) 3.06 (3H, s), 4.21 (1H, d, $J = 8.1$ Hz), 4.48 (1H, d, $J = 6.6$ Hz), 5.00 (1H, d, $J = 8.0$ Hz), 5.05 (1H, d, $J = 6.7$ Hz), 6.75 (1H, s), 7.11-7.16 (1H, m), 7.19 (2H, d, $J = 8.1$ Hz), 7.24 (2H, m), 7.40 (2H, d, $J = 8.1$ Hz), 7.84 (2H, m); $\delta_{13\text{C}}$ (100 MHz, C_6D_6) 55.5 (CH_3), 79.4 (CH), 82.5 (CH), 96.1 (CH_2), 107.8 (CH), 124.4 (C, $^1J(\text{C},\text{F}) = 272.0$ Hz), 125.9 (2 x CH, $^3J(\text{C},\text{F}) = 3.8$ Hz), 126.7 (2 x CH), 128.9 (2 x CH), 129.1 (CH), 130.9 (C, $^2J(\text{C},\text{F}) = 32.4$ Hz), 131.0 (2 x CH), 133.8 (C), 142.1 (C), 146.6 (C), 196.5 (C); $\delta_{19\text{F}}$ (376 MHz, C_6D_6) -62.2 (3F, s); ν_{max} (film/ cm^{-1}) 2961, 1740, 1636, 1325, 1155; m/z (HRMS, ESI) found ($[\text{M}+\text{Na}]^+$) 401.0973, $\text{C}_{20}\text{H}_{17}\text{F}_3\text{NaO}_4$ requires 401.0971.

Synthesis of compounds **10b**, **10e**.

(4*S*,5*S*,*E*)-2-benzylidene-4-hydroxy-5-(4-nitrophenyl)dihydrofuran-3(2*H*)-one (10b). **10b** was obtained from **9b** (47 mg, 0.13 mmol) according to general procedure **C**. Purification by silica gel column chromatography (petroleum ether (40-60°C) :diethyl ether, 3:1) yielded the product (37.6 mg, 93% yield, dr > 99:1) as a white solid; mp = 128°C; R_f (petroleum ether (40-60°C):diethyl ether, 1:1) = 0.32; The enantiomeric excess of the product **10b** was determined to be 94% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cmΦ x 25 cm)]; eluent, hexane/EtOH = 19/1; flow rate, 1.0 mL/min; retention time: 28.6 min (major), 32.4 min (minor); [α]_D²⁰ +135.0 (c 1.0, CHCl₃); δ_{1H} (400 MHz, CDCl₃) 3.14 (1H, br s), 4.37 (1H, d, *J* = 8.9 Hz), 5.36 (1H, d, *J* = 9.0 Hz), 6.59 (1H, s), 7.36-7.46 (3H, m), 7.80 (2H, d, *J* = 8.9 Hz), 7.82-7.85 (2H, m), 8.35 (2H, d, *J* = 8.7 Hz); δ_{13C} (100 MHz, CDCl₃) 77.6 (CH), 82.9 (CH), 109.7 (CH), 124.1 (2 x CH), 126.5 (2 x CH), 128.9 (2 x CH), 129.5 (CH), 130.9 (2 x CH), 132.6 (C), 144.8 (C), 145.2 (C), 148.2 (C), 198.6 (C); ν_{max} (film/cm⁻¹) 3467, 2923, 2853, 1737, 1634, 1521, 1348; *m/z* (HRMS, ESI) found ([*M*-H]⁻) 310.0717, C₁₇H₁₂NO₅ requires 310.0710.

(4*S*,5*S*,*E*)-2-benzylidene-4-hydroxy-5-(4-(trifluoromethyl)phenyl)dihydrofuran-3(2*H*)-one (10e). **10e** was obtained from **9e** (50 mg, 0.13 mmol) according to general procedure **C**. Purification by silica gel column chromatography (hexane:diethyl ether, 3:1) yielded the product (39.1 mg, 90% yield, dr > 99:1) as a pale yellow solid; mp = 166°C; R_f (hexane:diethyl ether, 3:1) = 0.32; The enantiomeric excess of the product **10e** was determined to be 93% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cmΦ x 25 cm)]; eluent, hexane/EtOH = 99/1; flow rate, 1.0 mL/min; retention time: 46.3 min (major), 56.3 min (minor); [α]_D²³ +79.8 (c 1.0, CHCl₃); δ_{1H} (400 MHz, CD₂Cl₂) 3.23 (1H, br s), 4.43 (1H, d, *J* = 8.8 Hz), 5.35 (1H, d, *J* = 8.9 Hz), 6.56 (1H, s), 7.35-7.47 (3H, m), 7.79 (4H, s), 7.85-7.89 (2H, m); δ_{13C} (100 MHz, CD₂Cl₂) 78.1 (CH), 83.8 (CH), 108.7 (CH), 124.5 (C, ¹*J* (C,F) = 272.0 Hz), 126.2 (2 x CH, ³*J* (C,F) = 3.6 Hz), 126.6 (2 x CH), 129.1 (2 x CH), 129.5 (CH), 131.12 (C, ²*J* (C,F) = 32.3 Hz), 131.13 (2 x

CH), 133.4 (C), 142.4 (C), 146.2 (C), 199.2 (C); $\delta_{19\text{F}}$ (376 MHz, CD_2Cl_2) -62.9 (3F, s); ν_{max} (film/ cm^{-1}) 3424, 1735, 1635, 1332, 1240, 1131; m/z (HRMS, ESI) found ($[\text{M-H}]^-$) 333.0738, $\text{C}_{18}\text{H}_{12}\text{F}_3\text{O}_3$ requires 333.0733.

Assignment of absolute configuration

The absolute configuration was determined by ^1H NMR shift observation after acylation of the free hydroxyl from **6e** with (S)-(+)- α -methoxyphenylacetic acid affording compound **11a**. Compound **11b** was obtained from the other enantiomer by reaction of a racemic **6e** with the acyl chloride. According to Trost's paper ⁶, the S configuration correlates with a high-fielding shift of the protons from the ynone part of the aldol. This can be observed for H_a (4.46 ppm in **11a**, 4.49 ppm in **11b**), H_b (4.36 ppm in **11a**, 4.56 ppm in **11b**), H_c (4.56 ppm in **11a**, 4.66 ppm in **11b**) and H_d (3.11 ppm in **11a** and 3.21 ppm in **11b**).

Synthesis of compounds 11a-11b.

(S)-((1S,2S)-2-(methoxymethoxy)-3-oxo-5-phenyl-1-(4-(trifluoromethyl)phenyl)pent-4-ynyl) 2-methoxy-2-phenylacetate (11a). A solution of (S)-(+)- α -methoxyphenylacetic acid (50 mg, 0.28 mmol) in thionyl chloride (1 mL) was stirred at RT for 2h. The solvent was then removed *in vacuo*. To the corresponding acyl chloride was added dropwise at -20°C a solution of **6e** (52 mg, 0.14 mmol) in THF (5 mL) and pyridine (44 μL , 0.54 mmol). The reaction mixture was warmed up to RT and stirred for 1h. The mixture was then partitioned between H_2O (10 mL) and diethyl ether (3 x 10 mL). The combined organic extracts were dried over MgSO_4 . After filtration, solvent was removed *in vacuo*. Purification of the residue by silica gel column chromatography (hexane:diethyl ether, 3:1) yielded the product (**S,S,S**)-**11a** (30 mg, 42% yield) as a pale yellow oil;

R_f (hexane:diethyl ether, 3:1) = 0.34; δ_{1H} (400 MHz, $CDCl_3$) 3.11 (3H, s), 3.36 (3H, s), 4.36 (1H, d, $J = 6.9$ Hz), 4.46 (1H, d, $J = 6.2$ Hz), 4.56 (1H, d, $J = 6.8$ Hz), 4.83 (1H, s), 6.32 (1H, d, $J = 6.1$ Hz), 7.31-7.36 (3H, m), 7.38-7.45 (4H, m), 7.48-7.54 (5H, m), 7.56-7.61 (2H, m); δ_{13C} (100 MHz, $CDCl_3$) 56.1 (CH_3), 57.4 (CH_3), 74.6 (CH), 82.5 (CH), 83.2 (CH), 86.0 (C), 95.6 (C), 96.5 (CH_2), 119.2 (C), 124.0 (C, $^1J(C,F) = 272.0$ Hz), 125.3 (2 x CH, $^3J(C,F) = 3.6$ Hz), 127.2 (2 x CH), 128.1 (2 x CH), 128.69 (2 x CH), 128.73 (2 x CH), 129.0 (CH), 130.9 (C, $^2J(C,F) = 32.8$ Hz), 131.3 (CH), 133.4 (2 x CH), 135.4 (C), 139.5 (C), 169.3 (C), 183.6 (C); δ_{19F} (376 MHz, $CDCl_3$) -62.7 (3F, s); ν_{max} (film/ cm^{-1}) 2934, 2203, 1759, 1675, 1490, 1445, 1326; m/z (HRMS, ESI) found ($[M+Na]^+$) 549.1491, $C_{29}H_{25}F_3NaO_6$ requires 549.1495.

(S)-((1R,2R)-2-(methoxymethoxy)-3-oxo-5-phenyl-1-(4-(trifluoromethyl)phenyl)pent-4-ynyl) 2-methoxy-2-phenylacetate (11b). (S,R,R)-11b was obtained from the racemic *anti* **6e** (150 mg, 0.37 mmol) according to the above procedure. Purification by silica gel column chromatography (hexane:diethyl ether, 3:2) yielded the product (36 mg, 20% yield) as a pale yellow oil; R_f (hexane:diethyl ether, 3:1) = 0.25; δ_{1H} (400 MHz, $CDCl_3$) 3.21 (3H, s), 3.38 (3H, s), 4.49 (1H, d, $J = 6.3$ Hz), 4.56 (1H, d, $J = 7.0$ Hz), 4.66 (1H, d, $J = 7.0$ Hz), 4.85 (1H, s), 6.29 (1H, d, $J = 6.3$ Hz), 7.14 (2H, d, $J = 8.2$ Hz), 7.32-7.37 (5H, m), 7.38-7.43 (4H, m), 7.48-7.53 (1H, m), 7.54-7.57 (2H, m); δ_{13C} (100 MHz, $CDCl_3$) 56.2 (CH_3), 57.4 (CH_3), 74.5 (CH), 82.2 (CH), 83.3 (CH), 86.3 (C), 95.8 (C), 96.4 (CH_2), 119.2 (C), 124.0 (C, $^1J(C,F) = 272.0$ Hz), 125.1 (2 x CH, $^3J(C,F) = 3.6$ Hz), 127.5 (4 x CH), 128.8 (4 x CH), 129.0 (CH), 130.5 (C, $^2J(C,F) = 32.8$ Hz), 131.4 (CH), 133.9 (2 x CH), 135.5 (C), 139.4 (CH), 168.9 (C), 183.9 (C); δ_{19F} (376 MHz, $CDCl_3$) -62.7 (3F, s); ν_{max} (film/ cm^{-1}) 2935, 2203, 1762, 1676, 1326, 1120, 1068; m/z (HRMS, ESI) found ($[M+Na]^+$) 549.1494, $C_{29}H_{25}F_3NaO_6$ requires 549.1495.

Assignment of relative configuration

NOE experiments were performed on cyclised products.

	Irradiated protons		
	H ₅	H ₈	H ₁₀
H ₅	-100%	2.9%	4.2%
H ₈	2.7%	-100%	1.8%
H ₁₀	3.8%	8.4%	-100%

	Irradiated protons		
	H ₅	H ₈	H ₁₀
H ₅	-100%	2.9%	4.2%
H ₈	2.6%	-100%	2.4%
H ₁₀	3.5%	7.8%	-100%

Synthesis of compound 12.

((4*S*,5*S*,6*R*)- 5-Methoxymethoxy-2,2-dimethyl-4-phenylethynyl-6-(4-trifluoromethyl-phenyl)-[1,3]dioxane (12). To a solution of **8e** (19 mg, 0.05 mmol) was added dimethoxypropane (120 μ L,

1 mmol), acetone (120 μ L) and *p*-TSA (0.43 mg, 2.5 μ mol). The resulting solution was stirred under argon at room temperature for 3h. The mixture was then directly purified by silica gel column chromatography (hexane:diethyl ether, 4:1) yielded the product (16 mg, 76% yield, dr = 92:8:0) as a white oil; R_f (hexane:diethyl ether, 4:1) = 0.4; δ_{1H} (400 MHz, C_6D_6) 1.36 (3H, s), 1.63 (3H, s), 2.81 (3H, s), 3.94 (1H, app t, $J = 9.4$ Hz), 4.22 (1H, d, $J = 6.6$ Hz), 4.66 (1H, d, $J = 9.6$ Hz), 4.86 (1H, d, $J = 6.6$ Hz), 4.98 (1H, d, $J = 9.4$ Hz), 7.02 (1H, d, $J = 2.0$ Hz), 7.04 (2H, d, $J = 2.0$ Hz), 7.39 (2H, d, $J = 8.1$ Hz), 7.46 (2H, d, $J = 8.1$ Hz), 7.53 (2H, m); δ_{13C} (125 MHz, C_6D_6) 18.9 (CH_3), 29.6 (CH_3), 55.5 (CH_3), 66.1 (CH), 75.9 (CH), 76.6 (CH), 86.1 (C), 87.6 (C), 97.0 (CH_2), 99.8 (C), 122.9 (C), 124.9 (2 x CH, $^3J(C,F) = 3.8$ Hz), 125.3 (C, $^1J(C,F) = 271.8$ Hz), 128.7 (2 x CH), 128.9 (CH), 129.0 (2 x CH), 130.5 (C, $^2J(C,F) = 32.4$ Hz), 132.0 (CH), 142.0 (C), δ_{19F} (376 MHz, C_6D_6) -62.0 (3F, s); ν_{max} (film/ cm^{-1}) 2995, 2255, 1326, 1073, 902, 842; m/z (HRMS, ESI) found ($[M+Na]^+$) 443.1444, $C_{23}H_{23}F_3NaO_4$ requires 443.1441

Assignment of *E*-geometry for 10b and 10e

To confirm the geometry of the exocyclic double bond in **9a-e**, we synthesized the product **14** via our phosphine-mediated cyclisation. This product is known in the literature in both *E* and *Z* geometries. Comparison of the ¹H NMR shifts allowed us to conclude that we obtained the *E*-isomer. The *E*-geometry of compounds **9a-e** has been assigned by analogy.

Synthesis of compounds 13, 14.

5-hydroxy-1,5-diphenylpent-1-yn-3-one (13). **13** was obtained from benzaldehyde (203 μL, 2 mmol) and 4-phenylbut-3-yn-2-one ² (374 mg, 2.6 mmol) according to known procedure ³. Purification by silica gel column chromatography (hexane:diethyl ether, 3:2) yielded the product (420 mg, 84% yield) as a colorless oil; *R*_f (hexane:diethyl ether, 3:2) = 0.50.; δ_{1H} (400 MHz, CDCl₃) 3.09 (1H, dd, *J* = 17.3, 3.4 Hz), 3.10 (1H, d, *J* = 3.3 Hz), 3.19 (1H, dd, *J* = 17.3, 9.1 Hz), 5.32 (1H, ddd, *J* = 9.1, 3.4, 3.3 Hz), 7.28-7.34 (1H, m), 7.36-7.44 (6H, m), 7.46-7.52 (1H, m), 7.56-7.61 (2H, m); δ_{13C} (100 MHz, CDCl₃) 54.2 (CH₂), 69.9 (CH), 87.8 (C), 92.3 (C), 119.6 (C), 125.8 (2 x CH), 127.9 (CH), 128.65 (2 x CH), 128.71 (2 x CH), 131.0 (CH), 133.2 (2 x CH), 142.4 (C), 186.6 (C); ν_{max} (film/cm⁻¹) 3442, 2203, 1665, 1490, 1093; *m/z* (HRMS, ESI) found 273.0878, ([M+Na]⁺), C₁₇H₁₄NaO₂ requires 273.0886.

(E)-2-benzylidene-5-phenyldihydrofuran-3(2H)-one (14) ⁴. **14** was obtained from **13** (83.7 mg, 0.34 mmol) according to general procedure **D**. Purification by silica gel column chromatography (petroleum ether 30-40°C:diethyl ether, 9:1) yielded the product (55 mg, 66% yield) as a yellow solid. The NMR data is in agreement with the literature ⁴.

Screening and optimization of the organocatalytic addition of 3-hexyn-2-one to *p*-nitrobenzaldehyde.

Entry	Catalyst	Solvent	Ketone (eq)	H ₂ O (%)	Reaction time (h)	Yield 2 (ee)	Yield 3 (%)	Yield 4 (%)
1	a	THF	5	10	24	19 (23)	0	nd
2	b	THF	5	10	24	17 (57)	5	nd
3	c	EtOH	5	10	24	52 (28)	6	nd
4	a	DMSO	5	10	24	65 (28)	4	nd
5	b	DMSO	5	10	24	21 (57)	10	nd
6	b	DMSO	5	10	72	21 (64)	9	9
7	d	DMSO	5	10	72	36 (72)	12	8
8	d	DMSO	5	10	120	39 (74)	15	11
9	d	DMSO	2.5	10	72	38 (72)	12	4
10	d	DMSO	7.5	10	72	46 (70)	15	9
11	d	DMSO	5	20	72	32 (58)	14	5
12 ^a	d	DMSO	5	10	72	36 (70)	14	10

^a catalyst loading of 30 mol%

References:

1. Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.
2. Wessig, P.; Mueller, G.; Kuehn, A.; Herre, R.; Blumenthal, H.; Troelenberg, S. *Synthesis*, **2005**, *9*, 1445.
3. Silva, F. A.; Gouverneur, V. *Tetrahedron Lett.* **2005**, *46*, 8705.
4. Xu, C.; Zhang, Y.; Yuan, C. *Eur. J. Org. Chem.*, **2004**, *10*, 2253.
5. Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron*, **2002**, *58*, 8167.
- 6.

(S,S)-(-) 6a

(S,S)-(-) 6a

(S,S)-(-) 6b

(S,S)-(-) 6b

(S,S)-(-)-6c
major:minor (7:1)

(S,S)-(-)6c
major:minor (7:1)

(S,S)-(-) 6e

(S,S)-(-)6f

(S,S)-(-)6f

(S,S)-(-)-6h

(S,S,R)-(-) 7e
major : minor (92:8)

(S,S,R)-(-) 7e
major:minor (92:8)

(S,S,E)-(+)-10e

(S,S,R) 12