Supporting Information

for

Catalytic Enantioselective Cr-Mediated Propargylation: Application to Halichondrin Synthesis

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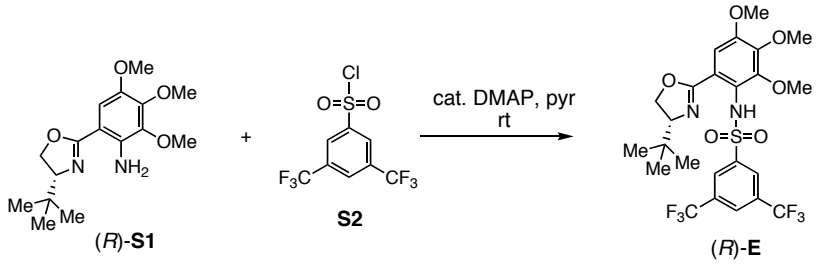
CONTENTS:

General Procedures and Methods:

^{1}H NMR spectra were recorded on a Varian Inova 600 or Varian Inova 500. ^{13}C NMR spectra were recorded on a Varian Inova 500. Chemical shifts were reported in parts per million (ppm). For ^{1}H NMR spectra ($CDCl_3$), the residual solvent peak was used as the internal reference (7.24 ppm in $CDCl_3$), while the central solvent peak as the reference (77.0 ppm in $CDCl_3$) for ^{13}C NMR spectra. Electrospray ionization experiments were performed on Micromass Inc., Platform II Atmospheric Pressure Ionization Mass Spectrometer. Optical rotations were measured at 25 °C using a Perkin-Elmer 241 polarimeter. Analytical thin layer chromatography (TLC) was performed with E. Merck precoated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Flash chromatography separations were performed on E. Merck kieselgel 60 (230-400) mesh silica gel.

Reagents and solvents are commercial grade and were used as supplied unless otherwise noted. THF (Baker, ultra low water, no preservative) for propargylation was freshly distilled with lithium aluminum hydride and degassed with argon. Propargyl bromide (Aldrich, 80 wt% in toluene) was purified by passing through a plug of basic alumina and degassed with argon. Toluene, ether, and dichloromethane were purified by glass contour solvent purification system. Et_3N (EMD, 99.5%) used for propargylation was distilled with calcium hydride and degassed with argon. 2,6-Lutidine (Aldrich, 99%), butane-1,4-diol (Alfa Aesar, 99%), $CrBr_3$ (Cerac, 99%), $Zr(Cp)_2Cl_2$ (Aldrich, 98%), Mn powder (Aldrich, 99.9%), and LiCl (Aldrich, anhydrous, 10 mesh) were used as supplied. All reactions were conducted under nitrogen atmosphere. Reaction vessels were flame-dried or oven-dried and cooled under an inert atmosphere.

1. Preparation of (*R*)-sulfonamide E

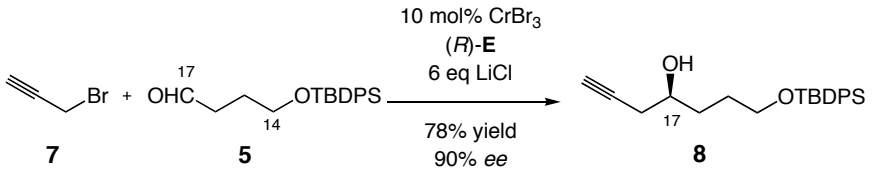


To a stirred solution of the previously reported amine (*R*)-**S1**[1] (1.5 g, 4.9 mmol) in pyridine (9.7 mL) was added DMAP (59 mg, 0.5 mmol) and sulfonyl chloride **S2** (Aldrich, 1.83 g, 5.8 mmol). The reaction mixture was stirred for 48 h at rt. The reaction was diluted with EtOAc (50 mL) and washed by 1 N HCl (50 mL). After evaporation of the solvent, the residue was purified by flash chromatography (silica gel, 30 g; eluent, hexanes/EtOAc/CH_2Cl_2=15:1:1) to give the sulfonamide as light yellow crystalline solid. The product was recrystallized from hexanes to furnish (*R*)-**E** (1.8 g, 63%) as greenish yellow crystal: mp 118-119 °C; $[\alpha]^{25}_D$ +27.0° (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; see the spectrum on page S-14): δ 12.23 (br, 1 H), 8.42 (s, 2 H), 8.03 (s, 1 H),

[1] Namba, K.; Cui, S.; Wang, J.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5417.

7.10 (s, 1 H), 4.30 (dd, J = 10, 8.5 Hz, 1 H), 4.18 (t, J = 8.5 Hz, 1 H), 4.11 (dd, J = 10, 8.5 Hz, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.18 (s, 3 H), 0.98 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$; see the spectrum on page S-15) δ 163.0, 150.1, 146.7, 145.6, 145.1, 132.0 (q, J = 33.8 Hz), 127.3 (d, J = 3.6 Hz), 127.0, 125.1 (p, J = 3.6 Hz), 122.7 (q, J = 271.3 Hz), 112.4, 107.3, 76.1, 68.0, 61.0, 59.4, 56.2, 34.0, 25.8; HRMS(ESI): calcd for $[M+H]^+$ $C_{24}H_{26}F_6N_2O_6S$ 585.1489, found 585.1485.

2. Catalytic asymmetric propargylation of 4-(*tert*-butyldiphenylsilyloxy)butanal



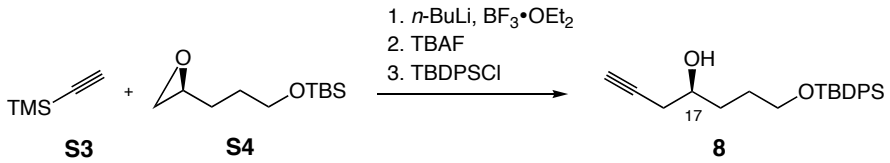
To a 50 mL round-bottomed flask with a stir bar was added (*R*)-sulfonamide **E** (197 mg, 0.34 mmol), $CrBr_3$ (89 mg, 0.31 mmol), Mn powder (505 mg, 9.3 mmol), LiCl (778 mg, 18.4 mmol) THF (distilled from $LiAlH_4$, 15.3 mL), and Et_3N (47.4 μL, 0.34 mmol) in a glove box. The mixture was stirred at rt for 1.5 h. After addition of 2,6-lutidine (86 μL, 0.74 mmol), the mixture was stirred at rt for 15 min. Propargyl bromide (80 wt % in toluene, 1.05 g, 7.0 mmol), aldehyde **5**[2] (degassed with freeze-pump-thaw procedure, 1.00 g, 3.1 mmol), and $Zr(Cp)_2Cl_2$ (1.07 g, 3.7 mmol) was added into the flask. After tightly capped with a septum, the flask was moved out of the glove box and placed in a 0 °C bath. The reaction was cooled in the 0 °C bath without stirring for 15 min and stirred for 28 h.

The mixture was then quenched by saturated aqueous serine (20 mL). The mixture was stirred for 30 min, extracted with EtOAc (3x20 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and purified by flash column chromatography (silica gel, 25 g; eluent: toluene/EtOAc = 20:1) to give **8** (880 mg, 78% yield) as light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$; see the spectrum on page S-16): δ 7.67-7.65 (m, 4 H), 7.43-7.36 (m, 6 H), 3.80-3.77 (m, 1 H), 3.69 (t, J = 6.0 Hz, 2 H), 2.43-2.33 (m, 2 H), 2.03 (t, J = 3.0 Hz, 1 H), 1.77-1.58 (m, 4 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$; see the spectrum on page S-17): δ 135.5, 133.5, 129.6, 127.6, 81.0, 70.6, 69.7, 63.9, 33.1, 28.7, 27.3, 26.8, 19.1; HRMS (ESI): Calcd for $[M+H]^+$ $C_{23}H_{30}O_2Si$ 367.2088, found 367.2095.

The enantiomeric excess (90% *ee*) was estimated from ^{1}H NMR analysis of the Mosher ester (see the spectrum on page S-18), obtained from **8** on treatment with (+)-Mosher acid chloride.

[2] **5** was prepared from 1,4-butanediol in 2 steps, following the procedure reported: (1) McDougal, P. G.; Rico, J. G.; Oh, Y.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388. (2) Freeman, F.; Kim, D. S. H. L.; Rodriguez, E. *J. Org. Chem.*, **1992**, *57*, 1722.

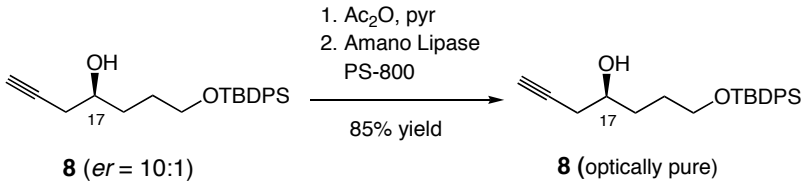
Based on the stereochemistry outcome observed in the asymmetric allylation and vinylation in the presence of Cr-catalyst derived from (*S*)- and (*R*)-sulfonamides, the absolute configuration of **8** was assigned as indicated, which was confirmed with correlation with the authentic sample prepared from the chiral epoxide **S4**.



To a solution of trimethylsilylacetylene (2.63 mL, 18.6 mmol) in THF (75 mL) at -78 °C was added dropwise *n*-BuLi (11.6 mL, 1.6 M in hexanes). After 0.5 h at -78 °C $BF_3 \cdot OEt_2$ (2.30 mL, 18.6 mmol) was added, followed by the addition of the epoxide[3] (2.0 g, 9.3 mmol) after 5 min. The reaction was allowed to stand for 1.5 h at -78 °C before quenched by 2 mL saturated aqueous NH_4Cl. The residue from the evaporation of the organic layer was purified by flash column chromatography (silica gel, 20 g; eluent, hexanes/EtOAc = 20:1) to give the alcohol (2.3 g, 82%) as colorless oil.

The protecting group of this alcohol was adjusted in two steps. The alcohol was treated with TBAF (18.3 mL, 1.0 M in THF) at rt for 1 h. The reaction was quenched by 20 mL water and extracted with EtOAc (3x20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant diol was used without further purification. To solution of the diol in dichloromethane (50 mL) at rt was added TBDPSCl (1.92 mL, 7.4 mmol), Et_3N (1.24 mL, 8.9 mmol). The reaction mixture was stirred overnight at rt. The organic layer was washed by brine (3x20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 25 g; eluent, hexanes/EtOAc = 10:1) to give **8** (1.2 g, 43% overall yield). The Mosher ester prepared from **8** with (+)-Mosher acid chloride was confirmed to be identical with the product obtained via catalytic asymmetric propargylation.

3. Enrichment of the optical purity of 8 with Amano lipase PS-800



Step 1: Acetylation of the alcohol

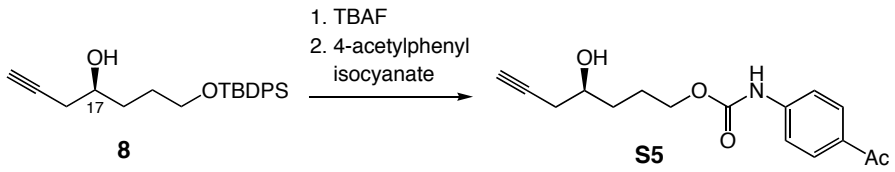
To a solution of chromatographically purified homopropargyl alcohol **8** (4.0 g, 10.9 mmol, *er* = 10:1) in CH_2Cl_2 (22 mL) was added acetic anhydride (2.06 mL, 21.8 mmol), pyridine (1.76 mL, 21.8 mmol), and DMAP (67 mg, 0.55 mmol) at rt. The mixture was

[3] Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

stirred overnight at rt. After dilution with EtOAc (100 mL), the reaction mixture was washed with brine (3x100 mL) and saturated aqueous $NaHCO_3$ (2x100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a silica gel pad (20 g) with hexanes/EtOAc (10:1) to give the acetate (4.4 g, quant.) as light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$; see the spectrum on page S-20): δ 7.66-7.64 (m, 4 H), 7.43-7.35 (m, 6 H), 4.96-4.91 (m, 1 H), 3.68-3.63 (m, 2 H), 2.46-2.44 (m, 2 H), 2.03 (s, 3 H), 1.97 (t, J = 3.0 Hz, 1 H), 1.86-1.52 (m, 4 H), 1.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$; see the spectrum on page S-21): δ 170.5, 135.5, 133.9, 129.6, 127.6, 79.6, 71.5, 70.4, 63.3, 29.4, 28.2, 26.8, 23.9, 21.1, 19.2.

Step 2: Amano lipase PS-800 hydrolysis of the acetate

To a 500 mL round-bottomed flask with a stir bar was added the acetate (4.4 g), acetone (Baker, 180 mL), buffer (VWR, pH = 7, sodium and potassium phosphate, 20 mL), and Amano lipase PS-800 (0.44 g). The reaction mixture was stirred at 50 °C for 43 h. The reaction mixture was filtered through a celite pad (10 g). After evaporation of acetone under reduced pressure, the residue was extracted with EtOAc (3x50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 40 g; eluent, hexanes/EtOAc = 30:1) to **8** (3.4 g, 85% for two steps) as light yellow oil: $[\alpha]^{25}_D$ -10.6° (*c* 1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$; see the spectrum on page S-16): δ 7.67-7.65 (m, 4 H), 7.43-7.36 (m, 6 H), 3.80-3.77 (m, 1 H), 3.69 (t, J = 6.0 Hz, 2 H), 2.43-2.33 (m, 2 H), 2.03 (t, J = 3.0 Hz, 1 H), 1.77-1.58 (m, 4 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$; see the spectrum on page S-17): δ 135.5, 133.5, 129.6, 127.6, 81.0, 70.6, 69.7, 63.9, 33.1, 28.7, 27.3, 26.8, 19.1; HRMS (ESI): Calcd for $[M+H]^+$ $C_{23}H_{30}O_2Si$ 367.2088, found 367.2095. The optical purity of **8** thus obtained was confirmed to be >99% from ^{1}H NMR analysis of its (+)-Mosher ester (see the spectrum on pages S-22 and S-23), as well as chiral HPLC analysis of its 4-acetylphenyl urethane **S5** derived from **8**.



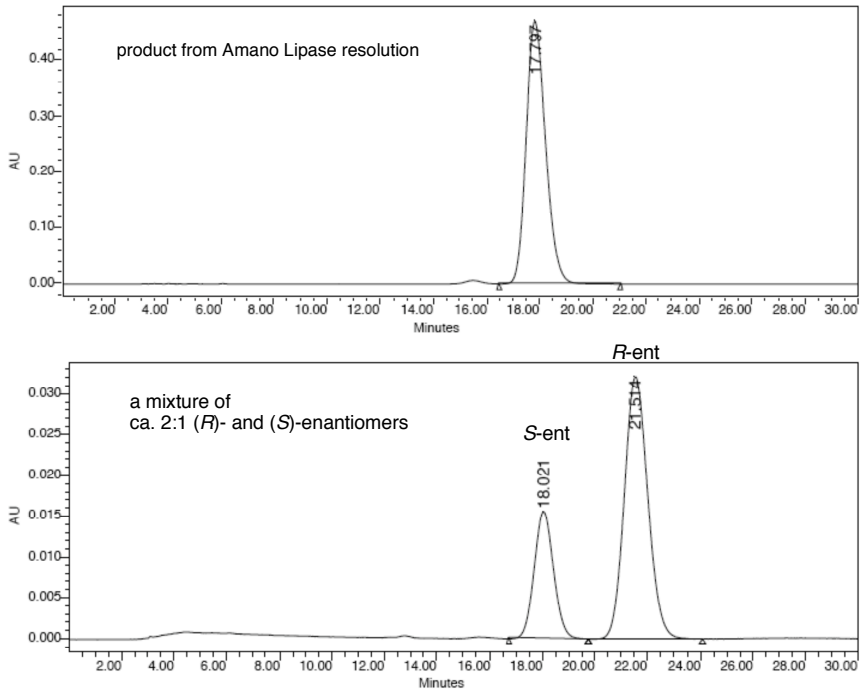
Step 1: Deprotection of the TBDPS

To **8** (37 mg, 0.1 mmol) in THF (1 mL) at rt was added TBAF (1.0 M in THF, 0.12 mmol). The reaction mixture was stirred overnight at rt and then diluted with brine (10 mL). The mixture was extracted with EtOAc (3x10 mL). The combined organic phase was dried over Na_2SO_4. After evaporation of the solvent, the residue was subjected to the next step without further purification.

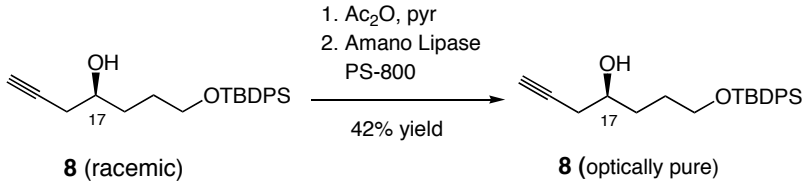
Step 2: 4-Acetylphenyl isocyanation of the diol

A solution of the resultant diol in CH_2Cl_2 (1 mL) was treated with 4-acetylphenyl isocyanate (16 mg, 0.1 mmol) and DMAP (2 mg, 0.016 mmol) at rt for 5 h. The crude product was purified by chromatography (silica gel; eluent, CH_2Cl_2/EtOAc = 4:1) to give **S5** (12 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$; see the spectrum on page S-24): δ 7.90 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 8.5 Hz, 2 H), 6.96 (br, 1 H), 4.21 (t, *J* = 6.5 Hz, 2 H), 3.83-3.77 (m, 1 H), 2.55 (s, 3 H), 2.45-2.31 (m, 2 H), 2.11 (d, *J* = 5.0 Hz, 1 H), 2.05 (t, *J* = 3.0 Hz, 1 H), 1.87-1.59 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$; see the spectrum on page S-25): δ 196.9, 153.1, 142.4, 132.2, 129.9, 117.6, 80.5, 71.2, 69.4, 65.4, 32.4, 27.6, 26.4, 25.1; HRMS (ESI): Calcd for $[M+H]^+$ $C_{16}H_{19}NO_4$ 290.1387, found 290.1388.

HPLC Conditions. Column: chiralcel OD; solvent system: hexanes/IPA/DEA = 85%/15%/ 0.1%; flow rate: 1.0 mL/min; detector: UV at 277 nm; retention time: 21.5 and 18.0 min for (*R*)- and (*S*)-enantiomers, respectively.



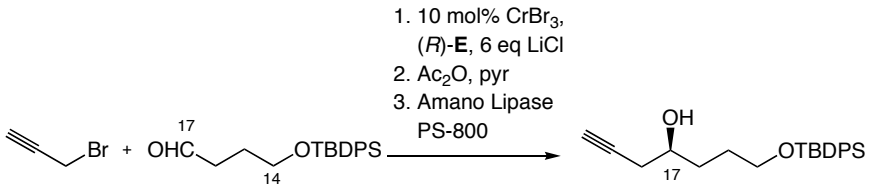
4. Optical resolution of racemic 8 with Amano lipase PS-800



8 (racemic) **8** (optically pure)

Racemic **8** (2.01 g, prepared via catalytic non-asymmetric propargylation[4]: $CrCl_3$· 3,3'-dimethyl-2,2'-bipyridine (21 mg, 0.061 mmol), CoPC (6 mg, 0.0104 mmol), LiCl (517 mg, 12.2 mmol), Mn (1.01 g, 18.3 mmol), $ZrCp_2Cl_2$ (2.135 g, 7.32 mmol), **5** (2.00 g, 6.1 mmol), propargyl bromide (80 wt % in toluene, 2.074 g, 14.03 mmol) in THF (30.5 mL)) was subjected to the two step procedure, to furnish **8** (846 mg, 42%, >99% ee) along with the recovered acetate (1.21 g, 47%) as a ca. 6:1 (*R*)- and (*S*)-enantiomers.

5. Catalytic asymmetric propargylation: Procedure coupled with Amano-lipase workup



Step 1: Catalytic asymmetric propargylation

To a 200 mL round-bottomed flask with a stir bar was added the ligand (984 mg, 1.68 mmol), $CrBr_3$ (444 mg, 1.53 mmol), Mn powder (2.53 g, 45.9 mmol), LiCl (3.89 g, 91.8 mmol) THF (Baker, ultra lower water, distilled with $LiAlH_4$, 76.5 mL), and Et_3N (237 μL, 1.68 mmol) in a glove box. The mixture was stirred at rt for 1.5 h. After addition of 2,6-lutidine (429 μL, 3.67 mmol), the mixture was stirred at rt for 15 min. Propargyl bromide (80wt% in toluene, 5.25 g, 35.2 mmol), aldehyde (5.00 g, 15.3 mmol), and $Zr(Cp)_2Cl_2$ (5.35 g, 18.3 mmol) was added into the flask. After tightly capped with a septum, the flask was moved out of the glove box and placed in a 0 °C bath. The reaction was cooled in the 0 °C bath without stirring for 15 min and stirred for 28 h.

The reaction was then diluted with EtOAc (50 mL), filtered through a pad of celite (5 g). After evaporation of the solvent, the residue was added saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3x50 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and passed through a pad of silica gel (25 g, hexanes/EtOAc = 1:1) to give the light yellow oil which was subjected to acetylation directly. The enantiomeric excess (*ee*) of this product was estimated to be 90% from ^1H NMR analysis of its (+)-Mosher ester.

Step 2: Acetylation of the alcohol

To a solution of the crude propargyl alcohol in CH_2Cl_2 (76.5 mL) was added acetic anhydride (2.89 mL, 30.6 mmol), pyridine (2.47 mL, 30.6 mmol), and DMAP (94 mg, 0.77 mmol) at rt. The mixture was stirred overnight at rt. The reaction mixture was washed with 1 N HCl (50 mL), saturated aqueous NH_4Cl (50 mL) and saturated aqueous

[4] Namba, K.; Wang, J.; Cui, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5421.

$NaHCO_3$ (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a silica gel pad (50 g) with hexanes/EtOAc = 20:1 → 5:1, to give the crude acetate (5.53 g; light yellow oil) and (*R*)-**E** (798 mg, 81%; 500 mg, 51% after recrystallization from hexanes).[5]

Step 3: Amano lipase PS-800 hydrolysis

To a 500 mL round-bottomed flask with a stir bar was added the acetate (5.53 g), acetone (Baker, 226 mL), buffer (VWR, pH=7, sodium and potassium phosphate, 25 mL), and Amano lipase PS-800 (553 mg). The reaction mixture was stirred at 50 °C for 43 h. The reaction mixture was filtered through a celite pad (5g). After evaporation of acetone under reduced pressure, the residue was extracted with EtOAc (3x50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 50 g; eluent: hexanes/EtOAc = 20:1 → 2:1) to give the homopropargyl alcohol (4.10 g, 73% for three steps) as light yellow oil: $[\alpha]^{25}_{D}$ -10.6° (*c* 1.0, MeOH).

The optical purity of **8** thus obtained was confirmed to be >99% from chiral HPLC analysis of its 4-acetylphenyl urethane **S5** derived from **8**, as well as from ^{1}H NMR analysis of its (+)-Mosher ester.

6. Catalytic asymmetric propargylations listed in Table 1

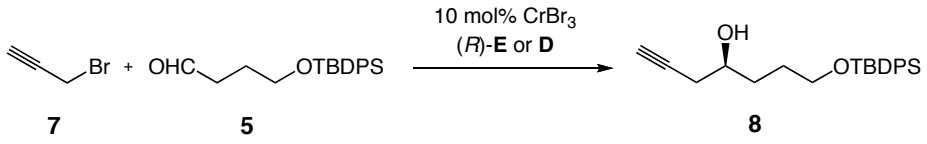
Catalytic asymmetric propargylation listed in Table 1 was conducted in a 0.2 mmol scale. For the coupling with the Cr-catalyst derived from (*R*)-sulfonamide **E**, the procedure given in page S-3 was employed. For the coupling with the Cr-catalyst derived from (*R*)-sulfonamide **D**, the procedure given below was adopted. Based on the previous examples, the absolute configuration of the major product was predicted as indicated and then confirmed from the ^{1}H NMR analysis of Mosher esters.

Coupling procedure with the Cr-catalyst derived from sulfonamide D

To a vial charged with a stir bar were added ligand **D** (8.8 mg, 0.022 mmol), $CrBr_3$ (5.8 mg, 0.020 mmol), Mn (33 mg, 0.60 mmol), THF (distilled from $LiAlH_4$, 1 mL), and Et_3N (3.1 μL 0.022 mmol) in a glove box. After tightly capped with a septum, the vial was moved out from the glove box and the mixture was stirred at 42 °C for 1.5 h. The vial was placed into the glove box and the serum cap was removed. After addition of 2,6-lutidine (2.8 μL, 0.024 mmol), the mixture was stirred for 15 min at rt. Then, without stirring, propargyl bromide (80wt% in toluene, 68 mg, 0.46 mmol), the aldehyde (0.20 mmol), and $Zr(Cp)_2Cl_2$ (70 mg, 0.24 mmol) were successively introduced into the mixture. Once again, after tightly capped with a septum, the vial was moved out from the glove box and placed in a 0 °C bath and stirred for 15 h.

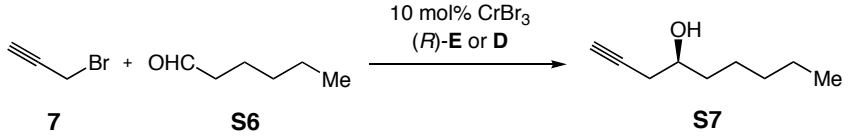
[5] The recovered (*R*)-**E** was tested for the catalytic asymmetric propargylation in a 65 mg scale, to demonstrate its quality (78% yield; 90% *ee*).

The mixture was then diluted with ethyl acetate, filtered through a silica gel pad, washed with $NaHCO_3$ (20 mL) and extracted with ethyl acetate (20 mL, 3 times). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give the crude product which was purified by flash column chromatography (20:1 → 5:1 hexanes/EtOAc) to give the product. The enantiomeric excess was determined from ^1H NMR analysis of its (+)-Mosher ester.



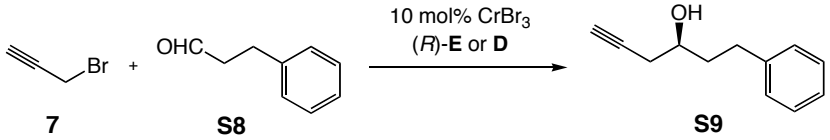
7 **5** **8**

Coupling with the Cr-catalyst derived from (*R*)-**E**: 78% and 90% *ee* (see page S-18).
Coupling with the Cr-catalyst derived from (*R*)-**D**: 85% and 83% *ee* (see page S-19).



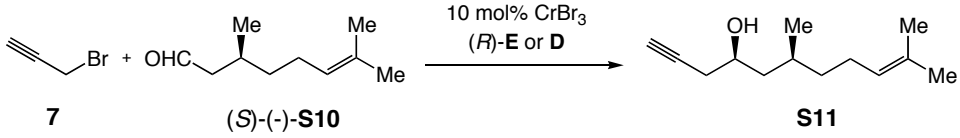
7 **S6** **S7**

Coupling with the Cr-catalyst derived from (*R*)-**E**: 82% and 81% *ee* (see page S-26).
Coupling with the Cr-catalyst derived from (*R*)-**D**: 81% and 67% *ee* (see page S-27).



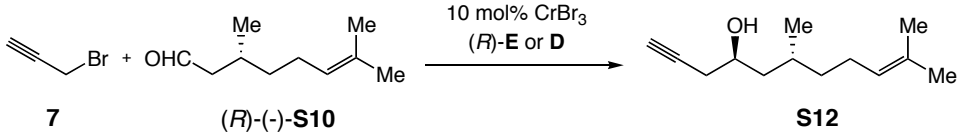
7 **S8** **S9**

Coupling with the Cr-catalyst derived from (*R*)-**E**: 91% and 89% *ee* (see page S-28).
Coupling with the Cr-catalyst derived from (*R*)-**D**: 94% and 72% *ee* (see page S-29).



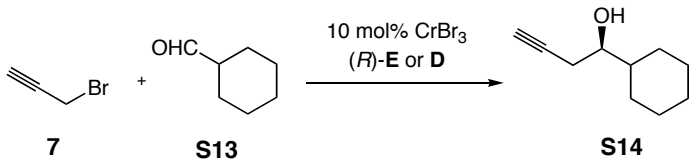
7 (*S*)-(-)-**S10** **S11**

Coupling with the Cr-catalyst derived from (*R*)-**E**: 70% and 93% *ee* (see page S-30).
Coupling with the Cr-catalyst derived from (*R*)-**D**: 81% and 93% *ee* (see page S-31).



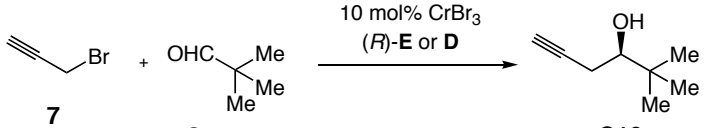
7 (*R*)-(-)-**S10** **S12**

Coupling with the Cr-catalyst derived from (*R*)-**E**: 73% and 80% *ee* (see page S-32).
Coupling with the Cr-catalyst derived from (*R*)-**D**: 86% and 84% *ee* (see page S-33).



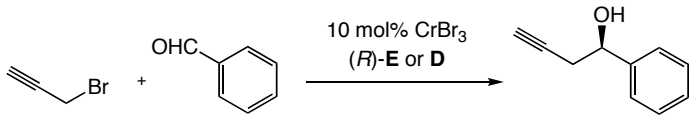
7 S13 S14

Coupling with the Cr-catalyst derived from (*R*)-**E**: 67% and 78% *ee* (see page S-34).
Coupling with the Cr-catalyst derived from (*R*)-**D**: 88% and 90% *ee* (see page S-35).



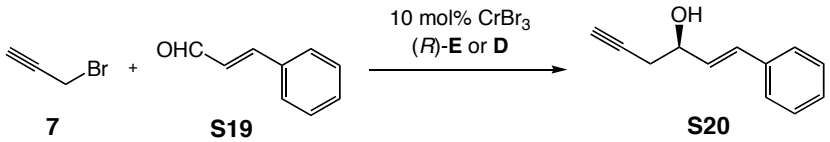
7 S15 S16

Coupling with the Cr-catalyst derived from (*R*)-**E**: 55% and 92% *ee* (page S-36).
Coupling with the Cr-catalyst derived from (*R*)-**D**: 75% and 73% *ee* (page S-37).



7 S17 S18

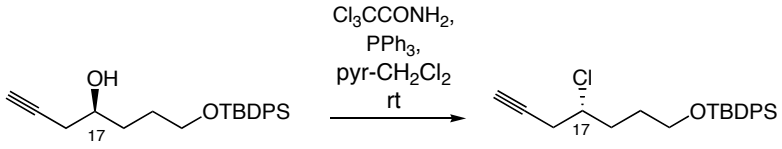
Coupling with the Cr-catalyst derived from (*R*)-**E**: 80% and 46% *ee* (page S-38).
Coupling with the Cr-catalyst derived from (*R*)-**D**: 92% and 73% *ee* (page S-39).



7 S19 S20

Coupling with the Cr-catalyst derived from (*R*)-**E**: 84% and 51% *ee* (page S-40).
Coupling with the Cr-catalyst derived from (*R*)-**D**: 89% and 70% *ee* (page S-41).

7. Chlorination of homopropargyl alcohol 8[6]

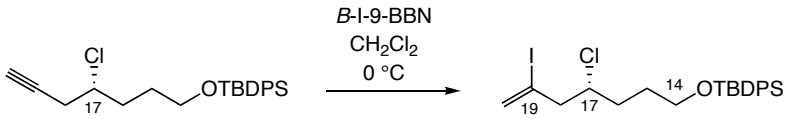


8 9

[6] Pluempanupat, W.; Chavasiri, W. *Tetrahedron Lett.* **2006**, *47*, 6821.

To a solution of homopropargyl alcohol **8** (16.4 g, 44.7 mmol) in CH_2Cl_2 (224 mL) was sequentially added pyridine (10.9 mL, 134 mmol), triphenylphosphine (17.6 g, 67.1 mmol) and trichloroacetamide (10.9 g, 67.1 mmol) at rt. After stirring at rt for 24 h, the reaction mixture was washed with brine (3x100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a silica gel pad (82 g) with hexanes/EtOAc (30:1) to give **9** (16.2 g, 94%) as light yellow oil: $[\alpha]^{25}_D$ +10.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; see the spectrum on page S-42): δ 7.67-7.65 (m, 4 H), 7.42-7.36 (m, 6 H), 4.03-3.98 (m, 1 H), 3.71-3.68 (m, 2 H), 2.71-2.60 (m, 2 H), 2.13-2.07 (m, 2 H), 1.86-1.64 (m, 3 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$; see the spectrum on page S-43): δ 135.5, 133.8, 129.6, 127.6, 79.9, 71.0, 63.0, 59.7, 33.6, 29.2, 28.6, 26.8, 19.2; HRMS (ESI): Calcd for $[M+H]^+$ $C_{23}H_{29}ClOSi$ 385.1749, found 385.1749.

8. Iodoboration of homopropargyl chloride 9[7]

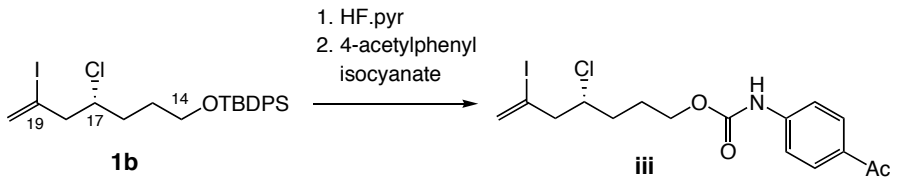


9 **1b**

To a solution of homopropargyl chloride **9** (3.0 g, 7.8 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added dropwise *B*-iodo-9-BBN (Aldrich, 8.2 mL, 1.0 M in hexanes). The reaction mixture was stirred for 1 h at 0 °C before addition of acetic acid (1mL, 15.6 mmol). The reaction was allowed to stand further for 0.5 h at 0 °C. The reaction mixture was titrated to red with 30% aqueous hydrogen peroxide and then to colorless with aqueous sodium thiosulfate. The organic layer was washed with saturated aqueous sodium bicarbonate (3x40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 45 g; eluent, hexanes/EtOAc = 30:1) to give **1b** (3.4 g, 85%) as light yellow oil: $[\alpha]^{25}_D$ +1.7° (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; see the spectrum on page S-44): δ 7.66-7.63 (m, 4 H), 7.43-7.35 (m, 6 H), 6.14 (d, *J* = 1.5 Hz, 1 H), 5.82 (d, *J* = 1.5 Hz, 1 H), 4.15-4.10 (m, 1 H), 3.71-3.65 (m, 2 H), 2.73 (d, *J* = 7.0 Hz, 2 H), 1.97-1.66 (m, 4 H), 1.03 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$; see the spectrum on page S-45): δ 135.6, 133.8, 129.6, 128.8, 127.6, 106.3, 63.1, 61.0, 53.5, 33.8, 29.3, 26.9, 19.2; HRMS (ESI): Calcd for $[M+H]^+$ $C_{23}H_{30}ClIOSi$ 513.0872, found 513.0867.

The optical purity of **1b** thus obtained was confirmed to be >99% from chiral HPLC analysis of its 4-acetylphenyl urethane **iii** derived from **1b**.

[7] Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.



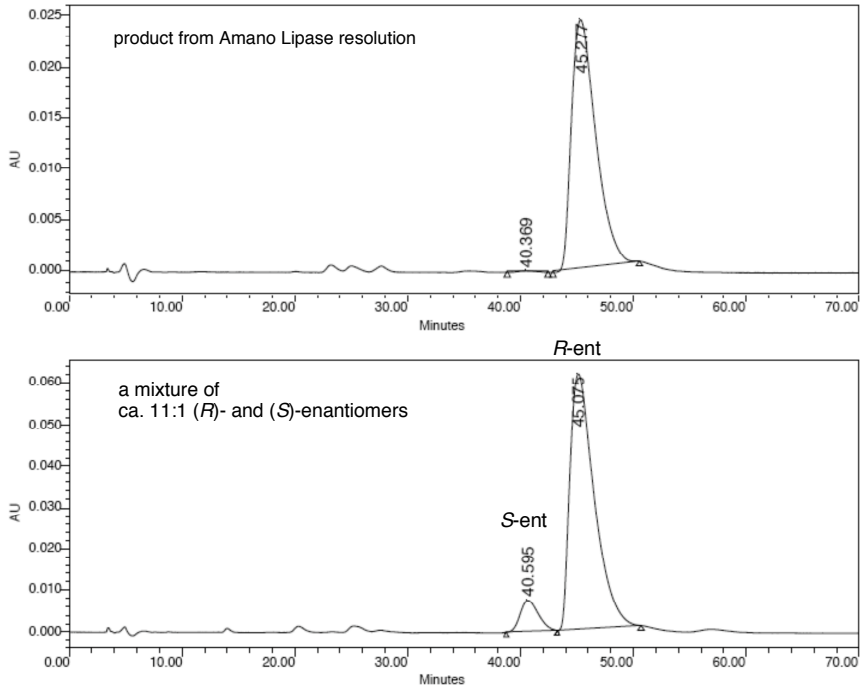
Step 1: Deprotection of the TBDPS

To **1b** (51 mg, 0.1 mmol) in MeCN (1 mL) at rt was added pyridine (162 μL, 2 mmol) and HF.pyr (7.3 μL, 0.4 mmol). The reaction mixture was stirred overnight at rt and then quenched with saturated aqueous sodium bicarbonate (10 mL). The mixture was extracted with EtOAc (3x10 mL). The combined organic phase was dried over Na_2SO_4. After evaporation of the solvent, the residue was subjected to the next step without further purification.

Step 2: 4-Acetylphenyl isocyanation of the alcohol

A solution of the resultant alcohol in CH_2Cl_2 (1 mL) was treated with 4-acetylphenyl isocyanate (19 mg, 0.12 mmol) and DMAP (2 mg, 0.016 mmol) at rt for 5 h. The crude product was purified by chromatography (silica gel; eluent, hexanes/EtOAc = 2:1) to give **iii** (36 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$; see the spectrum on page S-46): δ 7.91-7.89 (m, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 7.14 (br, 1 H), 6.14 (d, *J* = 1.0 Hz, 1 H), 5.82 (d, *J* = 1.0 Hz, 1 H), 4.20 (t, *J* = 6.5 Hz, 2 H), 4.15-4.09 (m, 1 H), 2.72 (d, *J* = 7.0 Hz, 2 H), 2.54 (s, 3 H), 1.99-1.70 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$; see the spectrum on page S-47): δ 197.0, 153.0, 142.4, 132.1, 129.8, 129.0, 117.6, 105.8, 64.8, 60.4, 53.3, 33.6, 26.4, 25.8; HRMS (ESI): Calcd for $[M+H]^+$ $C_{16}H_{19}ClINO_3$ 436.0171, found 436.0175.

HPLC Condition. Column: chiralpak OJ-H; solvent system: hexanes/IPA/DEA = 85%/15%/ 0.1%; flow rate = 1.0 mL/min; detector=UV at 277 nm; retention time: 45.1 and 40.6 min for (*R*)- and (*S*)-enantiomers, respectively.


product from Amano Lipase resolution
45.277
40.369
AU
Minutes
a mixture of
ca. 11:1 (R)- and (S)-enantiomers
R-ent
45.075
S-ent
40.595
AU
Minutes