Dimethylprolinol Versus Diphenylprolinol in CuBr$_2$-Catalyzed Enantioselective Allenylation of Terminal Alkynols

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Abstract The CuBr$_2$-catalyzed enantioselective allenylation of terminal alkynols with carbon chains of different lengths has been developed. Compared with (S)-α,α-dimethylprolinol, the reaction using (S)-α,α-diphenylprolinol as the chiral amine afforded optically active 1,3-disubstituted allenols with higher ee-values. Both aliphatic and aromatic aldehydes could be applied. The naturally occurring phlomic acid was synthesized in four steps from commercially available hex-5-yn-1-ol.

Key words CuBr$_2$, enantioselective allenylation, terminal alkynols, (S)-α,α-dimethylprolinol, (S)-α,α-diphenylprolinol, phlomic acid.

Optically active 1,3-disubstituted allenes$^1$ are the key unit in some natural products or bioactive compounds, such as marasin,$^2$ (R)-(-)-adenallene,$^3$ and (R)-(-)-cytalene.$^4$ Allenols are potential precursors for a series of 1,3-disubstituted allene natural products.$^5$ Owing to the rich reactivity of the alcohol functionality towards other synthetically useful functional groups, including aldehydes, esters, amides, amines, halides, malonates, etc., chiral allenols are very useful starting materials in organic synthesis. So far, transition metal-catalyzed cyclization of allenols has been a powerful tool for the construction of oxa-cyclic compounds.$^6$ In addition, the axial chirality of allenols may be transferred to central chirality under suitable reaction conditions.$^7$ Thus, the highly enantioselective synthesis of 1,3-disubstituted allenols is of high interest.

Recently, significant advances on the synthesis of axially chiral allenenes with functionalized groups such as boronates, alcohols, esters, amides, malonates, etc. have been achieved.$^{1,8}$ In 2015, we reported the CuBr$_2$-catalyzed highly enantioselective synthesis of optically active allenenes from terminal alkynes, aldehydes, and (R)- or (S)-α,α-diphenylprolinol (Scheme 1, Equation 1).$^9$ However, the enantioselectivity for some α-allenols with longer carbon chains between the allene moiety and alcohol functionality is not satisfactory (see also the data in Table 1). To our delight, when (S)-α,α-dimethylprolinol was used instead of (S)-α,α-diphenylprolinol, the enantioselectivity could be improved to a satisfactory level.$^{10}$ Reported methods for the preparation of optically active 1,3-disubstituted allenols usually suffered from lengthy steps, harsh conditions, limited scopes, and low enantioselectivity, etc.$^{10,11}$ Particularly, reports on the preparation of optically active allenols with longer carbon chains than γ-allenols are rare. Herein, we wish to report our recent investigations on developing a general access to 1,3-disubstituted allenenes with a practical enantioselectivity from the readily available terminal alkynols (Scheme 1, Equation 2).$^{12}$

Our previous work:

\[
\begin{array}{c}
\text{FG} \quad + \quad \text{RCHO} \\
\text{Ph} \quad \text{Ph} \quad \text{R} \quad \alpha, \alpha \text{-dimethylprolinol} \\
\text{cat. CuBr}_2 \\
\end{array}
\]

FG = CH$_2$OH, CH$_2$PHOH, (CH$_2$)$_2$OH
CH$_2$NH$_2$, CH$_2$NHBz, CH$_2$NHBOC
CH$_2$OH(CO$_2$Me)$_2$, carbohydrate

This work:

\[
\begin{array}{c}
\text{FG} \quad + \quad \text{RCHO} \\
\text{Ph} \quad \text{Ph} \quad \text{R} \quad \alpha, \alpha \text{-dimethylprolinol} \\
\text{cat. CuBr}_2 \\
\end{array}
\]

FG = MeOH, PhOH, (CH$_2$)$_2$OH

Scheme 1 CuBr$_2$-catalyzed enantioselective allenylation of terminal alkynols

Different terminal alkynols 1a–f were reacted with undecanal (2a) under CuBr$_2$ (20 mol%) in the presence of (S)-α,α-diphenylprolinol [(S)-3a] and (S)-α,α-dimethylprolinol [(S)-3b], respectively. As a result, the reactions promoted by (S)-3b afforded higher ee values (93–96% ee) than those by (S)-3a (85–93% ee) in all cases (Table 1, entries 1–6). When
n > 1, the difference in enantioselectivity is much larger. In most cases, the yields are also higher (entries 2–6). Besides \( n \)-alkyl aldehyde 2a, the bulkier sec-alkyl aldehydes could also be applied. The reactions using (S)-3b also gave chiral allenols in higher yields and ee than those using (S)-3a (entries 7–9).

Among the three reactants of the allenylation reaction, terminal alkynols 1 are usually not commercially available, and should be generally considered as the limiting reagent. At first, we attempted the reaction with the ratio of 1c/2a/(S)-3b being 1:1.5:1.1. As a result, the yield of (R)-4ca was 51% and the ee-value was 94% (Table 2, entry 2), both of which were slightly lower than that of reactions using 1c/2a/(S)-3b (ratio: 1.5:1:5:1) (entry1). On the basis of the results, the effect of the loading of 2a was screened (entries 2–5): When the ratio of 1c/2a/(S)-3b was 1:1.4:1.1, (R)-4ca was obtained in 46% yield with the highest ee of 95% (entry 3). Increasing the loading of (S)-3b to 1.2 equivalents led to an improved yield of 49% with the same ee (entry 6). Thus, the best conditions for this reaction could also be defined as 1 (1.0 equiv) and 2 (1.4 equiv) reacted with (S)-3b (1.2 equiv).

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>(R)-4 from (S)-3a</th>
<th>ee (%)</th>
<th>(R)-4 from (S)-3b</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1  (1a)</td>
<td>( n)-C(_1)H(_2)(_2)(2a)</td>
<td>60 ((\text{R}))-4aa</td>
<td>93</td>
<td>61 ((\text{R}))-4aa</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>2  (1b)</td>
<td>( n)-C(_1)H(_2)(_2)(2a)</td>
<td>49 ((\text{R}))-4ba</td>
<td>86</td>
<td>51 ((\text{R}))-4ba</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>3  (1c)</td>
<td>( n)-C(_1)H(_2)(_2)(2a)</td>
<td>56 ((\text{R}))-4ca</td>
<td>85</td>
<td>53 ((\text{R}))-4ca</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>4  (1d)</td>
<td>( n)-C(_1)H(_2)(_2)(2a)</td>
<td>51 ((\text{R}))-4da</td>
<td>88</td>
<td>57 ((\text{R}))-4da</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>5  (1e)</td>
<td>( n)-C(_1)H(_2)(_2)(2a)</td>
<td>46 ((\text{R}))-4ea</td>
<td>87</td>
<td>52 ((\text{R}))-4ea</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>6  (1f)</td>
<td>( n)-C(_1)H(_2)(_2)(2a)</td>
<td>53 ((\text{R}))-4fa</td>
<td>88</td>
<td>50 ((\text{R}))-4fa</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>4  (1d)</td>
<td>( n)-C(_1)H(_2)(_2)(2a)</td>
<td>45 ((\text{R}))-4db</td>
<td>93</td>
<td>46 ((\text{R}))-4db</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>4  (1d)</td>
<td>( n)-C(_1)H(_2)(_2)(2a)</td>
<td>53 ((\text{R}))-4dg</td>
<td>92</td>
<td>49 ((\text{R}))-4dg</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>4  (1d)</td>
<td>( n)-C(_1)H(_2)(_2)(2a)</td>
<td>34 ((\text{R}))-4dh</td>
<td>94</td>
<td>53 ((\text{R}))-4dh</td>
<td>99</td>
</tr>
</tbody>
</table>

* The reaction was conducted using 1 (1.5 mmol), 2 (1.5 mmol), \( n\)-3a or \( n\)-3b (1.0 mmol), and CuBr\(_2\) (20 mol%) in 1,4-dioxane (3 mL) at 130 °C for 12 h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1c/2a/(S)-3b</th>
<th>(R)-4ca</th>
<th>Yield (%)b</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5:1.5:1</td>
<td>53</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1:1.5:1.1</td>
<td>51</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1:1.4:1.1</td>
<td>46</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1:1.45:1.1</td>
<td>46</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1:1.6:1.1</td>
<td>50</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1:1.4:1.2</td>
<td>49</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>

* The reaction was conducted using 1c, 2a, \( n\)-3b, and CuBr\(_2\) (20 mol%) in 1,4-dioxane (3 mL) on 1 mmol scale at 130 °C for 12 h.

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**Table 1** Allenylation of Different Terminal Alkynols 1 with Aliphatic Aldehydes 2: \( n\)-3a vs \( n\)-3b.

**Table 2** Reaction of 2a with Pent-4-yn-1-ol (1c) as the Limiting Reagent.
equiv) catalyzed by CuBr₂ (20 mol%) at 130 °C in 1,4-dioxane when terminal alkynols were considered as the limiting reagent.

With the optimized conditions in hand, the reaction was then carried out on a gram scale. The allenol (R)-4da was obtained smoothly in 55% yield with 97% ee (Scheme 2).

The reactions of aromatic aldehydes were also tested. Pent-4-yn-1-ol (1c; 2 equiv) reacted with benzaldehyde (2c; 1.5 equiv) under CuBr₂ (50 mol%) in the presence of (S)-3a at 70 °C in 1,4-dioxane to give (R)-4cc in 45% yield with 95% ee. Under the same conditions, (S)-3b-promoted reaction afforded (R)-4cc in 37% yield with 98% ee (Table 3, entry 2). For 4-bromobenzaldehyde (2d), (S)-3b-promoted reaction gave better ee than (S)-3a. However, the yield was lower (entry 2). When 4-methylbenzaldehyde (2e) was applied under the same conditions, better yield and ee were obtained in the presence of (S)-3b. Nevertheless, the enantioselectivity for (R)-4ce was 90%, which was not satisfactory (entry 3). Gladly, the reaction using 1c/2e/(S)-3b (ratio 1:1:4:1.4) gave a better result, affording (R)-4ce with 93% ee albeit in a yield of 41% (entry 4). For 4-nitrobenzaldehyde (2f), the reaction using (S)-3b afforded (R)-4cf with a slightly better ee, but a lower yield than that using (S)-3a (entry 5). The reaction of o-chlorobenzaldehyde (2i) using (S)-3a and (S)-3b afforded the corresponding allenol (R)-4ci in 6% and 12% NMR yield, respectively (Scheme 3).

Several transformations were conducted to illustrate the synthetic potentials of these optically active allenols. Aerobic oxidation of (R)-4ca afforded chiral allenal (R)-5 with the same ee under the catalysis of 20 mol% each of Fe(No₃)₃·9H₂O, TEMPO, and NAc in DCE (Scheme 4A).13 Allenol (R)-4da could undergo a Mitsunobu reaction14 to afford chiral allenyl amide (R)-6 without any racemization (Scheme 4B).

Table 3 Some Typical Examples with Aromatic Aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>(R)-4 from (S)-3a</th>
<th>(R)-4 from (S)-3b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1</td>
<td>Ph (2c)</td>
<td>46.5</td>
<td>45 [(R)-4cc]</td>
</tr>
<tr>
<td>2</td>
<td>4-BrC₆H₄(2d)</td>
<td>44.5</td>
<td>51 [(R)-4cd]</td>
</tr>
<tr>
<td>3</td>
<td>4-MeC₆H₄(2e)</td>
<td>46.5</td>
<td>49 [(R)-4ce]</td>
</tr>
<tr>
<td>4*</td>
<td>4-MeC₆H₄(2e)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>4-NO₂C₆H₄(2f)</td>
<td>43</td>
<td>47 [(R)-4cf]</td>
</tr>
</tbody>
</table>

* The reaction was conducted using 1c (2 mmol), 2 (1.5 mmol), (S)-3a or (S)-3b (1 mmol), and CuBr₂ (50 mol%) in 1,4-dioxane (3 ml) at 70 °C.

The reaction was conducted using 1c (2 mmol), 2 (1.4 mmol), (S)-3b (1.4 mmol), and CuBr₂ (50 mol%) in 1,4-dioxane (3 ml) at 70 °C.

Scheme 2 Gram-scale synthesis of allenol (R)-4da

Scheme 3 Reaction of o-chlorobenzaldehyde with pent-4-yn-1-ol

Finally, we applied this chemistry to the convenient synthesis of naturally occurring phlomic acid (R)-9.10,15 Starting from (R)-4da, iodide (R)-7 was obtained by the treatment of PPh3, imidazole, and I2.16 Then, the diester (R)-8 was formed in 61% yield with 96% ee by alkylation with diethyl malonate in the presence of NaOH as the base. By the treatment with aqueous NaOH in MeOH, followed by heating in AcOH at 120 °C, natural product phlomic acid [(R)-9] was obtained in 78% yield and 95% ee (Scheme 4C).

As proposed in our previous work,20 the reaction between the in situ generated alkynylmetal species IN-1 and the iminium ion 11 via 1,2-attack of the alkynyl entity from the back-side of the dimethylhydroxymethyl or diphenylhydroxymethyl group would generate propargylic amine (SS)-12, which undergoes highly stereoselective CuBr2-mediated intramolecular 1,5-hydride transfer followed by anti-β-elimination to deliver the R-allene unit. The reaction using (S)-dimethylprolinol may afford optically active propargylic amine (SS)-12 with higher de, resulting in higher ee for 1,3-disubstituted allenols (Scheme 5).

In conclusion, we have developed a general allenylation of terminal alkynes with aliphatic or aromatic aldehydes using (S)-α,α-dimethylprolinol instead of (S)-α,α-diphenylprolinol, affording a series of optically active 1,3-disubstituted allenols with high enantiospecificity in one-pot. The synthetic potentials of these allenols prepared have also been demonstrated by oxidation to aldehyde and conversion to amide, as well as a different approach for the naturally occurring phlomic acid.

1H and 13C NMR spectra were recorded with a Bruker AM 300 MHz spectrometer. IR spectra were recorded on a PerkinElmer 983G instrument. Elemental analyses were measured with a Carlo-Erba EA1110 elementary analysis instrument. Mass spectrometry was performed with an HP 5989A system. High-resolution mass spectrometry was taken with a Finnigan MAT 8430 or Bruker APEXIII instrument. CuBr2 was purchased from J & K. 1,4-Dioxane was distilled from Na using benzophenone as indicator under N2 before use. Et2O and THF were distilled from Na wire using benzophenone as indicator under N2 before use. CH2Cl2 and DMF were distilled from CaH2 under N2 before use. Petroleum ether (PE) used had a boiling range of 60–90 °C. All liquid aldehydes were freshly distilled before use. Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers. (S)-α,α-Dimethylprolinol17 and oct-7-yn-1-ol (1f)12 were prepared following the literature methods.

**Synthesis of Optically Active 1,3-Disubstituted Allenols via Enantioselective Allenylation of Terminal Alkyne (EATA) Reaction Using (S)-α,α-Diphenylprolinol and (S)-α,β-Dimethylprolinol**

**Synthesis of (R)-Pentadeca-2,3-dien-1-ol [(R)-4aa] Using (S)-3b; Typical Procedure**

To a flame-dried Schlenk tube with a polytetrafluoroethylene plug were added CuBr2 (0.0453 g, 0.2 mmol), (S)-3b (0.1299 g, 1.0 mmol), prop-2-yn-1-ol (1a; 0.0846 g, 1.5 mmol, dissolved in 1.5 mL of 1,4-dioxane), and dodecanal (2a; 0.2762 g, 1.5 mmol, dissolved in 1.5 mL of 1,4-dioxane).

![Scheme 4 Synthetic applications](image-url)
of 1,4-dioxane) sequentially under N₂. The Schlenk tube was then sealed by screwing the polytetrafluoroethylene plug tightly with the outlet being closed. The reaction mixture was heated in an oil bath preheated at 130 °C with stirring. After 12 h, the reaction was complete as monitored by TLC and the mixture was cooled to r.t. Afterwards, the resulting mixture was diluted with Et₂O (30 mL) and washed with aq HCl (3 M, 20 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried (anhdy Na₂SO₄). After filtration and evaporation, the residue was purified by chromatography on silica gel (eluent: CH₂Cl₂, 200 mL) was used for the first round to afford impure (R)-4aa, which was further purified by chromatography on silica gel (eluent: CH₂Cl₂, 200 mL for the second round): yield: 0.1161 g (49%); pale yellow liquid; [α]°D= -52.1 (c 0.97, CHCl₃).

**Synthesis of (R)-Hexadeca-3,4-dien-1-ol [(R)-4ba]**

Using (S)-3a: Following the Typical Procedure I, the reaction of but-3-yn-1-ol [(1b); 0.1048 g, 1.5 mmol), dodecanal (2a; 0.2762 g, 1.5 mmol), (S)-3a (0.2585 g, 1 mmol), and CuBr₂ (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (R)-4ba (PE/EtOAc 8:1, 450 mL) was used for the first round to afford impure (R)-4ba, which was further purified by chromatography on silica gel (eluent: CH₂Cl₂, 200 mL for the second round): yield: 0.1161 g (49%); pale yellow liquid; [α]°D= -44.9 (c 1.01, CHCl₃).

**Synthesis of (R)-Heptadeca-4,5-dien-1-ol [(R)-4ca]**

Using (S)-3a: Following the Typical Procedure I, the reaction of pent-4-yn-1-ol [(1c); 0.1307 g, 1.5 mmol), dodecanal (2a; 0.2769 g, 1.5 mmol), (S)-3a (0.2589 g, 1 mmol), and CuBr₂ (0.0449 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (R)-4ca (PE/EtOAc 8:1, 450 mL) for the first round to afford impure (R)-4ca, which was fur-
ther purified by chromatography on silica gel (eluents: CH₂Cl₂, 200 ml for the first round); yield: 0.1405 g (56%); colorless liquid; MS (70 eV, EI):

1H NMR (300 MHz, CDCl₃): δ = 5.12–5.01 (m, 2 H, 2 × =CH), 3.65 (t, J = 6.3 Hz, 2 H, OCH₂), 2.08–1.91 (m, 4 H, 2 × CH₂), 1.71–1.56 (m, 2 H, CH₂), 1.56–1.19 (m, 21 H, 10 × CH₃ + OCH₂), 0.88 (t, J = 6.8 Hz, 3 H, CH₃).

13C NMR (75 MHz, CDCl₃): δ = 203.8, 91.2, 90.5, 62.8, 32.2, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.7, 25.3, 22.7, 14.1.

MS (70 eV, EI); m/z (S%): 267 [M + 1]⁺ (3.25), 266 (M⁺, 1.94), 82 (100). HRMS: m/z calcd for C₁₇H₃₂O (M⁺): 266.2610; found: 266.2613.

Synthesis of (R)-4da Using (S)-3b on a Gram-Scale
To a flame-dried Schlenk tube with a polytetrafluoroethylene plug was added CuBr₂ (0.4476 g, 2.0 mmol), (S)-3b (1.6336 g, 95% purity, 12 mmol), hex-5-yn-1-ol (1d; 1.0125 g, 97% purity, 10 mmol, dissolved in 15 ml of 1.4-dioxane), and dodecan dial (2a; 2.7202 g, 95% purity, 14 mmol, dissolved in 15 ml of 1.4-dioxane) sequentially under N₂. The Schlenk tube was then sealed by screwing the polytetrafluoroethylene plug tightly with the outlet being closed. Then the reaction mixture was heated in an oil bath preheated at 130 °C with stirring. After 12 h, the reaction was complete as monitored by TLC. The mixture was cooled to rt., diluted with Et₂O (150 mL), and washed with aq HCl (3 M, 150 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (2 × 100 ml). The combined organic layers were washed with brine (200 mL) and dried (anhyd Na₂SO₄). After filtration and evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 8:1, 1000 ml) to afford (R)-4da:

yield: 1.4561 g (55%); colorless liquid; [α]D20 = −47.1 (c 1.065, CHCl₃).

HPLC: Chiralpak PA-2 column, n-hexane/i-PrOH (200:1), 1.0 mL/min; λ = 214 nm; tᵣ (major) = 19.9 min, tᵣ (minor) = 23.0 min; 97% ee.

1H NMR (300 MHz, CDCl₃): δ = 5.11–5.00 (m, 2 H, 2 × =CH), 3.61 (t, J = 6.5 Hz, 2 H, OCH₂), 2.06–1.89 (m, 4 H, 2 × CH₂), 1.79–1.51 (m, 3 H, CH₂ + OCH₂), 1.49–1.17 (m, 22 H, 11 × CH₂), 0.88 (t, J = 6.8 Hz, 3 H, CH₃).


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Using (S)-2b. Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (1d; 0.1524 g, 1.5 mmol), isobutyrildehyde (2g; 0.1096 g, 1.5 mmol), (S)-3a (0.2582 g, 1 mmol), and CuBr2 (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (R)-4db (PE/EtOAc 8:1, 450 mL for the first round; CHCl3, 200 mL for the second round); yield: 0.1473 g (50%); colorless solid with a very low mp (0–20 °C); [α]D 29.30 – 36.22 (c 1.205, CHCl3).

HPLC: Chiralcel PA-2 column, n-hexane/i-PrOH (200:1), 0.7 mL/min, λ = 214 nm; tR (major) = 28.5 min, tR (minor) = 30.4 min; 88% ee.

1H NMR (300 MHz, CDCl3); δ = 5.10–5.00 (m, 2 H, 2 × =CH); 3.64 (t, J = 6.6 Hz, 2 H, OCH2); 2.04–1.90 (m, 4 H, 2 × CH2); 1.64–1.50 (m, 2 H, CH2); 1.48–1.17 (m, 25 H, 12 × CH2 + OH); 0.88 (t, J = 6.6 Hz, 3 H, CH3).

13C NMR (75 MHz, CDCl3); δ = 203.8, 91.0, 90.7, 63.0, 32.7, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 28.8, 25.6, 22.7, 14.1.

Using (S)-3b. Following the Typical Procedure I, the reaction of act-7-yn-1-ol (1F; 0.1894 g, 1.5 mmol), dodecanal (2a; 0.2760 g, 1.5 mmol), (S)-3b (0.1290 g, 1 mmol), and CuBr2 (0.0450 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (R)-4fa (PE/EtOAc 8:1, 450 mL for the first round; CHCl3, 200 mL for the second round); yield: 0.1473 g (50%); colorless solid with a very low mp (0–20 °C); [α]D 29.30–39.33 (c 1.000, CHCl3).

HPLC: Chiralcel PA-2 column, n-hexane/i-PrOH (200:1), 0.7 mL/min, λ = 214 nm; tR (major) = 22.1 min, tR (minor) = 24.7 min; 95% ee. IR (neat): 3334, 2925, 2854, 1962, 1464, 1377, 1056 cm−1.

Using (S)-3c. Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (1d; 0.1524 g, 1.5 mmol), isobutyraldehyde (2g; 0.1096 g, 1.5 mmol), (S)-3c (0.2582 g, 1 mmol), and CuBr2 (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (R)-4dc (PE/EtOAc 8:1, 450 mL for the first round; CHCl3, 200 mL for the second round); yield: 0.1473 g (50%); colorless solid with a very low mp (0–20 °C); [α]D 29.30–39.33 (c 1.000, CHCl3).

HPLC: Chiralcel PA-2 column, n-hexane/i-PrOH (200:1), 0.7 mL/min, λ = 214 nm; tR (major) = 22.1 min, tR (minor) = 24.7 min; 95% ee. IR (neat): 3334, 2925, 2854, 1962, 1464, 1377, 1056 cm−1.

Using (S)-3d. Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (1d; 0.1524 g, 1.5 mmol), isobutyraldehyde (2g; 0.1096 g, 1.5 mmol), (S)-3d (0.2582 g, 1 mmol), and CuBr2 (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (R)-4dd (PE/EtOAc 8:1, 450 mL for the first round; CHCl3, 200 mL for the second round); yield: 0.1473 g (50%); colorless solid with a very low mp (0–20 °C); [α]D 29.30–39.33 (c 1.000, CHCl3).

HPLC: Chiralcel PA-2 column, n-hexane/i-PrOH (200:1), 0.7 mL/min, λ = 214 nm; tR (major) = 22.1 min, tR (minor) = 24.7 min; 95% ee. IR (neat): 3334, 2925, 2854, 1962, 1464, 1377, 1056 cm−1.

Using (S)-3e. Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (1d; 0.1524 g, 1.5 mmol), isobutyraldehyde (2g; 0.1096 g, 1.5 mmol), (S)-3e (0.2582 g, 1 mmol), and CuBr2 (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (R)-4de (PE/EtOAc 8:1, 450 mL for the first round; CHCl3, 200 mL for the second round); yield: 0.1473 g (50%); colorless solid with a very low mp (0–20 °C); [α]D 29.30–39.33 (c 1.000, CHCl3).

HPLC: Chiralcel PA-2 column, n-hexane/i-PrOH (200:1), 0.7 mL/min, λ = 214 nm; tR (major) = 22.1 min, tR (minor) = 24.7 min; 95% ee. IR (neat): 3334, 2925, 2854, 1962, 1464, 1377, 1056 cm−1.

Using (S)-3f. Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (1d; 0.1524 g, 1.5 mmol), isobutyraldehyde (2g; 0.1096 g, 1.5 mmol), (S)-3f (0.2582 g, 1 mmol), and CuBr2 (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (R)-4df (PE/EtOAc 8:1, 450 mL for the first round; CHCl3, 200 mL for the second round); yield: 0.1473 g (50%); colorless solid with a very low mp (0–20 °C); [α]D 29.30–39.33 (c 1.000, CHCl3).

HPLC: Chiralcel PA-2 column, n-hexane/i-PrOH (200:1), 0.7 mL/min, λ = 214 nm; tR (major) = 22.1 min, tR (minor) = 24.7 min; 95% ee. IR (neat): 3334, 2925, 2854, 1962, 1464, 1377, 1056 cm−1.
1,4-dioxane (3 mL) at 130 °C for 12 h afforded (S)-4dh (PE/EtOAc 10:1, 495 mL); yield: 0.0619 g (34%); colorless liquid; [α]D20 = −66.7 (c 0.780, CHCl3).

HPLC: Chiralcel OJ-H column, n-hexane/i-PrOH (200:1), 1.0 mL/min, λ = 214 nm; tR (minor) = 11.3 min, tR (major) = 11.9 min; 94% ee.

1H NMR (300 MHz, CDCl3): δ = 5.08 (qd, J1 = 6.5 Hz, J2 = 1.5 Hz, 1 H, =CH), 4.95–4.84 (m, 1 H, =CH), 3.66 (t, J = 6.5 Hz, 2 H, OCH3), 2.07–1.97 (m, 2 m, 2 H, CH + OH), 1.70–1.20 (m, 2 H, 4 × CH2), 0.894 (t, J = 7.5 Hz, 3 H, CH3).

13C NMR (75 MHz, CDCl3): δ = 203.7, 94.9, 90.4, 62.8, 42.9, 32.2, 28.9, 27.7, 27.5, 25.4, 11.7, 11.5.

Using (S)-3b: Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (1d; 0.1592 g, 1.5 mmol), 2-ethylbutan-1-ol (2b; 0.1502 g, 1.5 mmol), and CuBr2 (0.0455 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (S)-4dh (PE/EtOAc 10:1, 495 mL); yield: 0.0980 g (53%); colorless liquid; [α]D20 = −73.6 (c 0.975, CHCl3).

HPLC: Chiralcel OJ-H column, n-hexane/i-PrOH (200:1), 1.0 mL/min, λ = 214 nm; tR (minor) = 12.2 min; 99% ee.

IR (neat): 3328, 2962, 2933, 2874, 1961, 1456, 1377, 1341, 1283, 1065, 1036 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 5.07 (qd, J1 = 6.6 Hz, J2 = 1.5 Hz, 1 H, =CH), 4.92–4.85 (m, 1 H, =CH), 3.66 (t, J = 6.5 Hz, 2 H, OCH3), 2.07–1.97 (m, 2 m, 2 H, CH + OH), 1.70–1.20 (m, 2 H, 4 × CH2), 0.893 (t, J = 7.5 Hz, 3 H, CH3), 0.886 (t, J = 7.5 Hz, 3 H, CH3).

13C NMR (75 MHz, CDCl3): δ = 202.3, 94.9, 90.4, 62.8, 42.9, 32.2, 28.9, 27.7, 27.5, 25.4, 11.7, 11.5.

MS (70 eV, EI): m/z (%) = 174 (M⁺, 16.58), 130 (100).

HRMS: m/z calc for C12H14O (M⁺): 174.1045; found: 174.1051.

Synthesis of (R)-4cc Using (S)-3b: Typical Procedure III
To a flame-dried Schlenk tube were added CuBr2 (0.1132 g, 0.5 mmol), (S)-3b (0.1296 g, 1.0 mmol, dissolved in 1 mL of 1,4-dioxane), prop-2-yn-1-ol (1c; 0.1733 g, 2 mmol, dissolved in 1 mL of 1,4-dioxane), and benzaldehyde (2c; 0.1596 g, 1.5 mmol, dissolved in 1 mL of 1,4-dioxane) sequentially under N2. The resulting mixture was heated in an oil bath preheated at 70 °C with stirring. After 46.5 h, the reaction was complete as monitored by TLC. The mixture was cooled to r.t. and diluted with Et2O (30 mL) and washed with aq HCl (3 M, 20 mL). The organic layer was separated and the aqueous layer was extracted with Et2O (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried (anhyd Na2SO4). After filtration and evaporation, the residue was purified by chromatography on silica gel (CH2Cl2/CHCl3/PrOH 40:1, 280 mL) to afford (R)-4cc: yield: 0.0644 g (37%); pale yellow liquid; [α]D20 = +245.2 (c 1.100, CHCl3).

HPLC: Chiralcel OJ-H column, n-hexane/i-PrOH (90:1), 0.8 mL/min, λ = 214 nm; tR (major) = 60.8 min, tR (minor) = 66.4 min; 98% ee.

1H NMR (300 MHz, CDCl3): δ = 7.32–7.23 (m, 4 m, 4 H, ArH), 7.22–7.12 (m, 2 m, 2 H, ArH), 6.17–6.10 (m, 1 m, 1 H, =CH), 5.59 (q, J = 6.6 Hz, 1 H, =CH), 3.67 (t, J = 6.5 Hz, 2 H, OCH3), 2.25–2.14 (m, 2 m, 2 H, CH2), 1.96–1.67 (m, 3 m, 3 H, =CH + CH2).

13C NMR (75 MHz, CDCl3): δ = 201.5, 134.8, 128.5, 126.7, 126.5, 95.0, 94.4, 62.1, 31.8, 24.8.
MS (70 eV; EI): m/z (%) = 254 (M⁺), 177, 252 (M⁺, 78Br), 154 (100).
HRMS: m/z calc'd for C₁₉H₁₇BrO₂ (M⁺): 252.0150; found: 252.0145.

**Synthesis of ([R]-6-[3-Nitrophenyl]hexa-4,5-dien-1-ol ([R]-4ce)**

Using (S)-3a: Following the Typical Procedure II, the reaction of pent-4-yn-1-ol (1c; 0.1732 g, 2 mmol), 4-methylbenzaldehyde (2e; 0.1278 g, 1.0 mmol), and CuBr₂ (0.1130 g, 0.5 mmol) in 1,4-dioxane (3 mL) at 70 °C for 47.5 h afforded ([R]-4ce) (0.1293 g, 1.0 mmol), 4-methylbenzaldehyde (2f; 0.2332 g, 1.5 mmol), and CuBr₂ (0.1114 g, 0.5 mmol) in 1,4-dioxane (3 mL) at 70 °C for 43 h afforded ([R]-4cf) (CH₂Cl₂/Et₂O 80:1, 400 mL); yield: 0.0852 g (39%); pale yellow liquid; [α]₂⁰ = 225.7 (c 1.055, CHCl₃).

HPLC: Chiralcel OJ-H column, n-hexane/i-PrOH (80:1), 1.0 mL/min, λ = 214 nm; tₚ (minor) = 59.4 min, tₚ (major) = 41.2 min; 90% ee.

1H NMR (300 MHz, CDCl₃): δ = 8.15 (d, J = 8.7 Hz, 2 H, ArH), 7.40 (d, J = 8.7 Hz, 2 H, ArH), 6.27–6.19 (m, 1 H, =CH), 5.74 (q, J = 6.6 Hz, 1 H, =CH), 3.72 (t, J = 6.5 Hz, 2 H, OH), 2.33–2.23 (m, 2 H, CH₂), 1.85–1.65 (m, 2 H, CH₂), 1.50 (s, 1 H, OH).

13C NMR (75 MHz, CDCl₃): δ = 207.1, 146.3, 142.3, 126.9, 94.5, 94.2, 62.1, 31.7, 24.6.

**Synthetic Applications**

**Synthesis of ([R]-Heptadeca-4,5-dienial ([R]-5)) via Fe-Catalyzed Aerobic Oxidation of ([R]-4ca)**

To a flame-dried Schlenk tube were added Fe(NO₃)₃·9H₂O (0.0703 g, 0.30 mmol), Fe(III)-salen (0.1507 g, 0.30 mmol), and CuBr₂ (0.1142 g, 0.5 mmol) in 1,4-dioxane (3 mL) at 70 °C for 43 h, afforded ([R]-4ca) (CH₂Cl₂/Et₂O 80:1, 400 mL); yield: 0.0852 g (39%); pale yellow liquid; [α]₂⁰ = 31.7 (c 1.025, CHCl₃).

HPLC: Chiralcel OJ-H column, n-hexane/i-PrOH (90:10), 1.0 mL/min, λ = 214 nm; tₚ (major) = 23.0 min; tₚ (minor) = 23.0 min; 96% ee.

1H NMR (300 MHz, CDCl₃): δ = 8.15 (d, J = 8.7 Hz, 2 H, ArH), 7.40 (d, J = 8.7 Hz, 2 H, ArH), 6.27–6.19 (m, 1 H, =CH), 5.74 (q, J = 6.6 Hz, 1 H, =CH), 3.73 (t, J = 6.5 Hz, 2 H, OH), 2.33–2.23 (m, 2 H, CH₂), 1.85–1.65 (m, 2 H, CH₂), 1.50 (s, 1 H, OH).

13C NMR (75 MHz, CDCl₃): δ = 207.1, 146.3, 142.3, 126.9, 94.5, 94.2, 62.1, 31.7, 24.6.
To a flame-dried Schlenk tube were added LiAlH₄ (0.0235 g, 0.6 mmol) and anhyd Et₂O (1 mL) under N₂. Then the resulting mixture was cooled to 0 °C in an ice-water bath with stirring. After that, (R)-5 (0.1008 g, 0.4 mmol) and anhyd Et₂O (1 mL) were added. Then the reaction mixture was warmed up to rt. After 16.5 h, the reaction was complete as monitored by TLC. The mixture was cooled to 0 °C in an ice-water bath, quenched with H₂O (3 mL), and extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried (anhyd Na₂SO₄). After filtration and evaporation, the residue was purified by chromatography on silica gel [PE (distilled)/EtOAc 8:1, 450 mL] to afford (R)-4ca; yield: 0.0896 g (88%); colorless liquid; [α]₂⁰ = −50.1 (c 1.02, CHCl₃).

HPLC: Chiralcel IC column, n-hexane-i-PrOH (400:1), 0.6 mL/min, λ = 214 nm; tₓ (minor) = 44.5 min, tₓ (major) = 47.6 min; 95% ee.

1H NMR (300 MHz, CDCl₃); δ = 5.17–5.04 (m, 2 H, =CH), 3.69 (t, J = 6.6 Hz, 2 H, OCH₂), 2.13–2.02 (m, 2 H, 2 H, OCH₂), 2.02–1.91 (m, 2 H, CH₂), 1.76–1.63 (m, 2 H, CH₂), 1.61 (s, 1 H, OH), 1.44–1.19 (m, 18 H, 9 × CH₂), 0.88 (t, J = 6.6 Hz, 3 H, CH₃).

13C NMR (75 MHz, CDCl₃); δ = 203.8, 191.5, 90.1, 62.3, 31.90, 31.88, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 28.4, 28.0, 26.3, 22.6, 14.1.

Synthesis of (R)-2-(Octadeca-5,6-dien-1-yloxy)isoindoline-1,3-dione ([R]-6) via Mitsunobu Reaction; Typical Procedure IV

To a flame-dried Schlenk tube were added (R)-4da (0.2661 g, 1 mmol) and anhyd THF (5 mL) under N₂. Then PPh₃ (0.5240 g, 2 mmol) and phthalimide (0.2970 g, 2 mmol) were added. The reaction mixture was cooled to 0 °C in an ice-water bath with stirring. After that, DEAD (320 μL, d = 1.106 g/cm³, 0.3554 g, 2 mmol) was added dropwise over 2 min. The reaction mixture was then warmed up to rt. After 12 h, the reaction was complete as monitored by TLC. After evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 15:1, 480 mL) to afford (R)-6; yield: 0.3611 g (91%); colorless liquid; [α]₂⁰ = −42.1 (c 1.10, CHCl₃).

HPLC: Chiralcel PC-4 column, n-hexane-i-PrOH (400:1), 1.0 mL/min, λ = 214 nm; tₓ (minor) = 28.6 min, tₓ (major) = 30.7 min; 95% ee.

IR (neat): 2923, 2853, 1961, 1771, 1714, 1467, 1435, 1393, 1372, 1361, 1337, 1232, 1212, 1188, 1171, 1116, 1088, 1071, 1039 cm⁻¹.

MS (70 eV, EI); m/z (%): 396 [(M + 1)⁺, 6.28], 395 (M⁺, 1.24), 108 (100).

HRMS: m/z calc'd for C₂₀H₁₇NO₃(M⁺): 395.2824; found: 395.2827.

Scheme 6 Synthesis of rac-6

Synthesis of rac-6 for ee Determination (Scheme 6)

Following the Typical Procedure IV, the reaction of rac-4da (0.2666 g, 1 mmol), PPh₃ (0.5243 g, 2 mmol), phthalimide (0.2970 g, 2 mmol), and DEAD (320 μL, d = 1.106 g/cm³, 0.3554 g, 2 mmol) in THF (5 mL) at r.t. for 8.5 h afforded rac-6 (PE/EtOAc 15:1, 480 mL); yield: 0.3126 g (79%); colorless liquid.

IR (neat): 2923, 2853, 1961, 1771, 1714, 1615, 1467, 1435, 1394, 1372, 1232, 1212, 1188, 1171, 1116, 1088, 1071, 1039 cm⁻¹.

HRMS: m/z calc'd for C₂₀H₁₇NO₃(M⁺): 395.2824; found: 395.2831.

Synthesis of Pholic Acid ([R]-9)

Step 1: Synthesis of Dimethyl (R)-2-(Octadeca-5,6-dien-1-yl)malonate ([R]-8) (Scheme 7)

To a flame-dried Schlenk tube were added (R)-4da (0.8790 g, 3.3 mmol) and CH₂Cl₂ (30 mL) under N₂. Then PPh₃ (0.10390 g, 3.96 mmol) and imidazole (0.2725 g, 3.96 mmol) were added sequentially. After cooling the reaction mixture to 5 °C, B, (1.0060 g, 3.96 mmol) and CH₂Cl₂ (3 mL) were added. Then the resulting mixture was stirred at this temperature for 20 min until the reaction was complete as monitored by TLC. Filtration through a short column of silica gel [elucent: PE (3 × 20 mL)] for the first time, evaporation, and filtration through a...
short column of silica gel [eluent: pet (3 × 50 mL)] for the second time afforded (R)-7 as a liquid, which was used directly in the next step without further purification.

To a flame-dried Schlenk flask were added NaH (0.1586 g, 3.96 mmol) and anhyd DMF (17 mL) under N2 and the reaction mixture was stirred at rt. Dimethyl malonate (507 μL, d = 1.14 g/cm², 0.5783 g, 4.29 mmol) was added dropwise in 5 min. After that, the reaction mixture was stirred at rt. for another 10 min. A solution of 0.5783 g, 4.29 mmol) was added dropwise in 5 min. After that, the reaction mixture was stirred at rt. for another 30 min and treated with H2O (15 mL), brine (20 mL), and dried (anhyd Na2SO4). After filtration and evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 40:1, 1200 mL) to afford (R)-8; yield: 0.7706 g (61% over two steps); colorless liquid.

IR (neat): 2952, 2925, 2854, 1961, 1759, 1739, 1462, 1435, 1343, 1269, 1252, 1228, 1200, 1150, 1077, 1014 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 5.12–4.99 (m, 2 H, 2 × =CH), 3.74 (s, 6 H, 2 × OCH3), 3.36 (t, J = 7.5 Hz, 1 H, CH), 2.03–1.86 (m, 6 H, 3 × CH2), 1.50–1.19 (m, 22 H, 11 × CH2), 0.88 (t, J = 6.8 Hz, 3 H, CH3).

13C NMR (75 MHz, CDCl3): δ = 203.8, 169.8, 91.2, 90.3, 52.4, 51.6, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 28.7, 28.6, 26.8, 22.7, 14.1.

MS (70 eV, EI): m/z (%) = 380 (M⁺, 1.11), 148 (100). HRMS: m/z calc for C18H33I (M⁺): 376.1627; found: 376.1623.

Synthesis of rac-8 for ee Determination ¹⁰ (Scheme 8)

Scheme 8 Synthesis of rac-8

rac-7

To a flame-dried Schlenk tube were added rac-4da (0.3989 g, 1.5 mmol), CH2Cl2 (12 mL), PPh3 (0.4725 g, 1.8 mmol), and imidazole (0.1239 g, 1.8 mmol) sequentially under N2. I2 (0.4568 g, 1.8 mmol) and CH2Cl2 (3 mL) were added at rt. with stirring. The resulting mixture was kept stirring at rt. for 35 min until the reaction was complete as monitored by TLC. After filtration through a short column of silica gel (eluent: PE; 20 mL) and evaporation of the solvent, the residue was purified by chromatography on silica gel (eluent: PE, 400 mL) to afford rac-7; yield: 0.4982 g (88%); colorless liquid.

IR (neat): 2955, 2923, 2852, 1962, 1463, 1456, 1435, 1377, 1367, 1340, 1278, 1243, 1224, 1207, 1166, 1120 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 5.15–4.99 (m, 2 H, 2 × =CH), 3.19 (t, J = 7.1 Hz, 2 H, CH2), 2.07–1.92 (m, 4 H, 2 × CH2), 1.92–1.81 (m, 2 H, CH2), 1.58–1.45 (m, 2 H, CH2), 1.45–1.20 (m, 18 H, 9 × CH2), 0.88 (t, J = 6.8 Hz, 3 H, CH3).

13C NMR (75 MHz, CDCl3): δ = 203.9, 91.4, 91.0, 32.9, 31.9, 29.9, 29.6, 29.5, 29.4, 29.2, 29.1, 29.0, 27.8, 22.7, 14.1.

MS (70 eV, EI): m/z (%) = 376 (M⁺, 6.53), 109 (100). HRMS: m/z calc for C18H33I (M⁺): 376.1627; found: 376.1623.

Step 2: Hydrolysis of (R)-8 to Phlomic Acid (Scheme 9)

Scheme 9 Hydrolysis of (R)-8 to phlomic acid
**Phlomic Acid ([R]-9)**

To a flame-dried Schlenk tube were added ([R]-8) (0.2669 g, 0.7 mmol), MeOH (2 mL), andaq 2.2 N NaOH (1.3 mL) under N\(_2\). The resulting mixture was stirred in a pre-heated (100 °C) oil bath. After 2.5 h, the reaction was complete as monitored by TLC. The reaction mixture was cooled to r.t., acidified to pH 1 withaq 1 N HCl, and extracted with Et\(_2\)O (3 × 15 mL). The combined organic layers were washed with brine (5 mL) and dried (anhyd Na\(_2\)SO\(_4\)). After filtration and evaporation, the residue was used in the next step without further purification.

To a flame-dried Schlenk tube were added the product prepared as above and AcOH (4.2 mL) under N\(_2\). The resulting mixture was stirred in a pre-heated (120 °C) oil bath. After 29 h, the reaction was complete as monitored by TLC. After evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 30:1, 360 mL) to afford ([R]-9) (Scheme 10).

**References**


