Diversity-Oriented Enantioselective Synthesis of Highly Functionalized Cyclic and Bicyclic Alcohols

Bin Mao,[a] Martín Fañanás-Mastral,[a] Martin Lutz,[b] and Ben L. Feringa*[a]

Abstract: The copper-catalyzed hetero-allylic asymmetric alkylation (h-AAA) of functionalized Grignard reagents that contain alkene or alkyne moieties has been achieved with excellent regio- and enantioselectivity. The corresponding alkylation products were further transformed into a variety of highly functionalized cyclic and bicyclic alcohols with excellent control over the chemo-, regio-, and stereoselectivity.

Introduction

Cyclic and bicyclic alcohols are present in a large number of natural products and pharmaceuticals (Figure 1). For instance, these structural features are often found in the sesquiterpenoid family, which possess important biological activities, such as antitumor and antimicrobial properties. The rapid construction of highly functionalized ring structures and control over the regio- and stereochemistry of single- or fused-ring systems continue to offer important synthetic challenges. Methods for the asymmetric synthesis of cyclic alcohols, including chiral synths, chiral auxiliaries, and Corey–Bakshi–Shibata (CBS) reduction, have been described; however, the formation of enantiopure bicyclic alcohols in a concise and efficient manner is still highly challenging. The development of fully catalytic and highly stereoselective short synthetic procedures for cyclic and bicyclic alcohols is of particular interest in the context of the diversity-oriented synthesis of stereochemically complex structures.

The copper-catalyzed asymmetric allylic alkylation (AAA) reaction represents a very powerful tool for the enantioselective construction of optically active molecules. Recently, a highly regio- and enantioselective synthesis of optically active allylic esters through copper-catalyzed hetero-allylic asymmetric alkylation (h-AAA) with Grignard reagents has been developed by our group (Scheme 1).[6] One of the major features of this method is that it provides access to protected chiral allyl alcohols, in combination with other functional groups, which allow for further transformations into a variety of important structures.[6,7]

Keywords: alcohols · asymmetric synthesis · copper · cyclization · cycloaddition

We envisioned that the use of functionalized Grignard reagents that contain alkene or alkyne moieties in the Cu-catalyzed h-AAA reaction, in combination with several stereoselective cyclization and cycloaddition reactions, could provide easy access to highly functionalized cyclic or bicyclic protected alcohols in a concise and enantioselective manner. Although alkyl-Grignard reagents that contain alkene moieties have already been applied in Cu-catalyzed AAA/RCM reactions[9] to the best of our knowledge, there are no examples of the use of alkyl-Grignard reagents that contain alkyne moieties[10] in this transformation.

Figure 1. Bioactive compounds that contain various cyclic and bicyclic alcohol groups.

Scheme 1. Cu-catalyzed hetero-allylic asymmetric alkylation.

[a] B. Mao, Dr. M. Fañanás-Mastral, Prof. Dr. B. L. Feringa
Stratingh Institute for Chemistry
University of Groningen
Nijenborgh 4, 9747 AG Groningen (The Netherlands)
Fax: (+31)50-363-4296
E-mail: b.l.feringa@rug.nl
[b] Dr. M. Lutz
Bijvoet Center for Biomolecular Research
Utrecht University
Padualaan 8, 3584 CH Utrecht (The Netherlands)
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201202859.
Our initial studies were focused on the copper-catalyzed $h$-AAA reactions of substrates 1 with Grignard reagents that contain a terminal alkene moiety. Under the optimized conditions for the addition of simple alkyl-Grignard agents that contain a terminal alkene moiety, the desired alkylation products 3 were obtained in high yields (up to 96%) with excellent regio- (>99:1) and enantioselectivities (96–97% ee; Table 1).

With the isolated products 3 in hand, we attempted the synthesis of cyclic benzoate esters[13] through ring-closing olefin metathesis. When compound 3a was treated with Grubbs 2nd-generation catalyst (5 mol%), five-membered carbocycle (S)-4a was obtained in 85% yield and excellent enantioselectivity (97% ee).[60] The use of longer alkyl chains on the Grignard reagent did not affect the outcome of the reaction and allowed us to access the optically active six- and seven-membered ring structures 4b and 4c in high yields (85–89%) with excellent enantioselectivity (95% ee; Table 1). It should be emphasized that high yields and excellent enantioselectivities were found in all cases under the optimized conditions. No significant loss of enantioselectivity took place during the ring-closing step. Unfortunately, efforts to cyclize 1,8-diene esters to make their corresponding eight-membered carbocycles were unsuccessful with Grubbs second-generation catalyst, thus leading to recovery of the starting material.[18]

Next, we turned our attention to the use of challenging Grignard reagents that contained an alkene functional group in the Cu-catalyzed hetero-allylic asymmetric alkylation ($h$-AAA) reaction (Table 2). To prevent competitive coordination between the terminal alkene and the copper(I) species,[13] trimethylsilyl-protected alkynes were employed. Under the same conditions as for the Cu-catalyzed $h$-AAA discussed above, product 6b was obtained with only modest olefin metathesis.
enantioselectivity (36% ee; Table 2, entry 1). Screening of different reaction parameters indicated that lower amounts (1.5 equiv) and slower addition (4 h) of the Grignard reagent were essential for obtaining compound 6b in a fully enantioselective manner. \[19\] It was particularly rewarding to find that the treatment of 3-bromopropenyl ester 1a with Grignard reagent 5a under the optimized conditions (Table 2, entry 5) provided the desired S N2' product (6a) with excellent regio-(>99:1) and enantioselectivity (98% ee; Scheme 3). Grignard reagent 5b, in combination with cinnamyl ester 1b, readily provided alkylation products 6c in good yields with excellent regio- and enantioselectivity (>99:1, 96% ee; Scheme 3). Because ferrocenyl ligand L1 turned out not to be an effective ligand for the h-AAA reaction of β-substituted substrate 1c \[6a\] we turned our attention to phosphoramidites \[5g\] as potential chiral ligands. When the reaction was carried out with ligand L2, which has been described as an optimal ligand for related transformations, \[6a,20\] product 6d was obtained with high enantiocntrol (94% ee) but poor regioselectivity (γ/α 1:2; Scheme 3). However, ligand L3 afforded the desired product 6d with better regioselectivity (6:1) and similar enantioselectivity (92% ee).

Optically enriched 2,4-dienols are key structural motifs in a variety of natural products. \[14\] Despite the importance and versatility of these compounds, approaches for their enantioselective synthesis have thus far been limited to the lipase-catalyzed kinetic resolution of racemic dienols. \[14b–d\] To obtain their chiral dienol derivatives, trimethylsilyl-protected allylic ester 6a was subjected to enyne metathesis \[15\] with Grubbs 1st-generation catalyst. No reaction was observed during this process, presumably owing to the steric effects of the trimethylsilyl group. \[15a\] Because it is known that enyne metathesis proceeds better with terminal alkynes, \[15a\] allylic products 6 were transformed into their corresponding terminal enynes 7, without compromising their stereochemical integrity, by treatment with 2 equivalents of tetra-n-butylammonium fluoride (TBAF) in THF. Then, we investigated the ring-closing metathesis of enynes 7 in the presence of catalytic amounts of Grubbs 1st-generation catalyst under an ethylene atmosphere (Table 3). The presence of ethylene was found to be essential for accelerating the reaction to access diene ester 8. \[21\] The reaction of enyne 7a to form five-membered cyclic 2,4-dienol ester 8a proceeded smoothly and, again, no erosion of the enantioselectivity was observed during this transformation. \[22\] Homologous six-membered dienol ester 8b was prepared in 87% yield and 96% ee under the same conditions (Table 3). Although enyne 7c, which contained a cinnamyl-ester moiety, showed slightly lower reactivity, thus requiring a longer reaction time, the desired diene product 8c was obtained in 85% yield and 96% ee. These results indicate that this strategy of combining hetero-allylic asymmetric alkylation with ring-closing enyne metathesis is a highly versatile.

### Table 2. Screening of the reaction condition for the copper-catalyzed h-AAA reaction with Grignard reagents that contain an alkyne moiety. \[a\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>1a/5b</th>
<th>Addition time [h]</th>
<th>γ/α [b]</th>
<th>ee of 6b [c] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:2</td>
<td>0.1</td>
<td>&gt;99:1</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>1:2</td>
<td>0.5</td>
<td>&gt;99:1</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>2</td>
<td>&gt;99:1</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>1:1.5</td>
<td>2</td>
<td>&gt;99:1</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>1:1.5</td>
<td>4</td>
<td>&gt;99:1</td>
<td>97</td>
</tr>
</tbody>
</table>

[a] Reactions performed on a 0.32 mmol scale. Compound 5b (1.5 mmol in Et2O) was diluted with CH2Cl2 and added dropwise. Complete conversion was achieved in all cases. \[b\] Regioselectivity was determined by 1H NMR spectroscopy of the crude mixture. \[c\] Enantiomeric excess was determined by chiral HPLC analysis.

![Scheme 3. Cu-catalyzed h-AAA of Grignard reagents that contain an alkyne moiety.](image-url)
The relative configuration of the products was assigned on the basis of $^1$H NMR and NOESY analysis of the products (9a and 9b; Figure 2). In each case, NOE correlations between the H$_a$–H$_b$ and H$_c$–H$_d$ protons indicated an *anti* stereochemical relationship for H$_a$–H$_b$. This exclusive stereochemical outcome was attributed to the stereogenic center that was established in the Cu-catalyzed h-AAA reaction and the facial selectivity of the Diels–Alder reaction.[24] It should be pointed out that the enantiomeric excess of the cycloaddition product was also not compromised during these reactions. This sequential stereoselective approach offers rapid access to enantiomerically pure complex bicyclic molecules.

To establish the synthetic compatibility of allylic esters 6 for the purposes of diversity-oriented synthesis,[4] we also explored the intramolecular Pauson–Khand (PK) reactions of 1,5-enyne 6a and the complete formation of diene ester 8. To our delight, chiral intermediate 8 underwent cycloaddition with diene at 160°C in each case to yield the corresponding cycloadduct 9 as a single diastereomer (Scheme 5).

Table 3. Deprotection of the TMS group, followed by enyne metathesis.

<table>
<thead>
<tr>
<th>Compound</th>
<th>n</th>
<th>R</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>0</td>
<td>Ph</td>
<td>74%</td>
<td>98%</td>
</tr>
<tr>
<td>6b</td>
<td>1</td>
<td>Ph</td>
<td>85%</td>
<td>97%</td>
</tr>
<tr>
<td>6c</td>
<td>1</td>
<td>PhCH=CH</td>
<td>83%</td>
<td>96%</td>
</tr>
</tbody>
</table>

[a] Yield of isolated product. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] The absolute configuration was assigned by comparison of optical rotation with known compounds.[14b]

method for the enantioselective synthesis of cyclic 2,4-dienol esters.

Unfortunately, when enyne 7d, which was obtained after the removal of the TMS group on compound 6d, was exposed to the same conditions as discussed above, an enyne-metathesis reaction with ethylene proceeded in an intermolecular fashion to afford the linear product (8d; Scheme 4). Although a variety of ruthenium catalysts and different reaction conditions[21b] were tested, the reaction did not result in the formation of the desired product.

Dienols 8 are suitable substrates for Diels–Alder reactions that would give rise to important bicyclic scaffolds 9 in a diastereoselective fashion.[23] As outlined in Scheme 5, we have developed a one-pot consecutive enyne-metathesis/Diels–Alder reaction in the presence of diethyl acetylenedicarboxylate. Optically enriched terminal enynes 7a and 7b were subjected to the enyne-metathesis conditions described above; then, the dienophile was added after
1,6-enyne 6b to afford functionalized bicyclo-[3.3.0]pentanones in a stereoselective manner (Scheme 6). The cobalt-promoted Pauson–Khand reactions of internal enynes 6, with 1.1 equivalents of [Co₂(CO)₈] in CH₂Cl₂ at room temperature, generated the corresponding hexacarboxylidicobalt complexes. Subsequently, the resulting complexes were transformed into their corresponding substituted cyclopentenones 10 in 55–64% yield with complete diastereoselectivity and almost-complete enantioselectivity (97–98% ee).

The relative stereochemistry of the two adjacent stereogenic centers in compounds 10a and 10b was determined by ¹H NMR and NOESY analysis. The observed exo configuration was expected for an intramolecular PK reaction. Single-crystal X-ray structure determination of compound 10a confirmed this relative configuration (Figure 3). The absolute stereochemistry was established unequivocally by the Flack parameters (see the Supporting Information).

The resulting bicyclic compounds 10 possess a high degree of functionalization, including an ester group and an α-TMS-substituted α,β-unsaturated ketone. The synthetic diversity of this strategy was illustrated by the facile installation of an all-carbon quaternary stereogenic center on the bridgehead carbon atom (Scheme 7). Bicyclic pentanone 10a was treated with lithium dimethylecuprate in Et₂O at −20°C. After deprotection of the TMS group, the final product 11 was obtained as a single isomer in 62% yield.

**Conclusion**

In summary, we have developed a highly regio- (>99:1) and enantioselective (up to 98% ee) Cu-catalyzed hetero-allylic asymmetric alkylation (h-AAA) reaction with functionalized Grignard reagents that contain alkene or alkyne moieties. A new strategy that was based on the h-AAA reaction, in combination with ring-closing metathesis (RCM), of dienes and enynes has been applied for the catalytic enantioselective synthesis of cyclic allylic esters. In addition, we have shown the diversity-oriented synthesis of four different ring-fused [5,6], [6,6], [5,5], and [6,5] bicyclic structures through Diels–Alder reactions on 2,4-dienol esters or Pauson–Khand reactions on enyne substrates. The synthetic versatility of this method was illustrated by the stereocontrolled installation of an all-carbon quaternary center on the bridgehead carbon atom of a carbon [5,5] bicyclic structure. The resulting compounds are suitable synthons for the synthesis of multiscaffold libraries.

**Experimental Section**

**General:** All of the experiments were carried out in flame-dried or oven-dried glassware under an atmosphere of nitrogen (unless otherwise specified) by using standard Schlenk techniques. Schlenk tubes with screw caps were equipped with a Teflon-coated magnetic stirrer bar, flame dried under vacuum, and allowed to return to RT prior to being charged with the reactants. A manifold that permitted alternation between a nitrogen atmosphere and a vacuum was used to control the atmosphere in the reaction vessel. Column chromatography was performed on silica gel (Silica-P flash silica gel from Silicycle, size 40–63 μm). TLC was performed on silica gel 60/Kieselguhr F254; the components were visualized by using UV light and by staining with a solution of KMnO₄ (10 g) and K₂CO₃ (10 g) in water (500 mL). Mass spectra were recorded on a LTQ Orbitrap XL mass spectrometer (ESI+/APCI+/APPI+) or a Xevo® G2 QTof mass spectrometer with DART ionization. ¹H and ¹³C NMR spectra were recorded on Varian AMX400 (400 and 100.59 MHz, respectively) or Varian Unity Plus Varian-500 spectrometers (500 and 125 MHz, respectively) by using CDCl₃ as the solvent. Chemical shifts are reported in...
ppm by using the solvent resonance as an internal standard (1H: δ = 7.26 ppm, 13C: δ = 77.0 ppm); the data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant(s) [Hz], and integration. Optical rotation was determined with a CHIRALPAK OJ-H column (10 μm) under a nitrogen atmosphere.

(→)–(S)-Cyclohex-2-en-1-yl benzoate (4b). According to the general procedure, compound 4b was obtained as a colorless oil (89% yield, 95% ee). [α](D) = −187.3 (c = 3.7 in CHCl3); [lit.14] (S isomer, 90% ee): [α](D) = −164 (c = 0.86 in CHCl3); 1HNMR (400 MHz, CDCl3); δ = 8.3–7.83 (m, 2H), 7.61–7.50 (m, 1H), 7.48–7.34 (m, 2H), 6.11–5.94 (m, 1H), 5.90–5.80 (m, 1H), 5.51 (dd, J = 3.4, 1.6 Hz, 1H), 2.15–2.04 (m, 2H), 2.03–1.94 (m, 1H), 1.93–1.77 (m, 2H), 1.77–1.65 ppm (1H), 13C NMR (100 MHz, CDCl3); δ = 166.4, 133.1, 133.0, 131.0, 129.8, 128.5, 65.8, 28.6, 25.2, 19.2 ppm; HRMS (ESI+): m/z: calculated for C16H15O2Na: 225.0886 [M+Na]+; found: 225.0433; enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H; n-heptane/2-propanol, 99.9:0.1; 0.5 mL/min; 226 nm; column temperature: 40°C): tk (major) = 19.55 min, tk (minor) = 18.66 min.

General procedure for the copper-catalyzed hetero-allylic asymmetric alkylation20 with Grignard reagents that contain alkylene groups: Method A. A solution of Grignard reagent 5 (0.48 mmol, 1.5 equiv) in CH2Cl2 (1.5 mL) under a nitrogen atmosphere was added dropwise over 5 min to a homogeneous, stirring solution of the allylic bromide (0.32 mmol), CuBr (0.64 mmol, 2 equiv) in CH2Cl2 (3 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred at the indicated temperature until it had gone to completion (typically overnight) and was then washed with MeOH (5 mL). The reaction mixture was allowed to warm to RT and a saturated aqueous solution of NH4Cl (5 mL) was added. The mixture was partitioned between CH2Cl2 (5 mL) and water. The organic layer was dried (MgSO4), filtered, and the solvent was evaporated under vacuum. Purification by flash column chromatography on silica gel (EtOAc/pentane, 1% to 2%) afforded pure product 3a as a colorless oil.

(→)–(S)-Octa-1,7,12-trien-3-yl benzoate (3b). According to the general procedure, compound 3b was obtained as a colorless oil (95% yield, 97% ee). [α](D) = +33.2 (c = 3.6 in CHCl3); 1HNMR (400 MHz, CDCl3); δ = 8.07 (d, J = 7.9 Hz, 2H), 7.56 (t, J = 6.9 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 5.99–5.68 (m, 2H), 5.62–5.44 (m, 1H), 5.33 (d, J = 17.2 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 5.04 (s, 1H), 5.00–4.88 (m, 1H), 2.11 (q, J = 7.5 Hz, 2H), 1.90–1.67 (m, 2H), 1.52 (1H), 1.32 (m, 1H), 1.23 ppm (m, 1H); 13C NMR (100 MHz, CDCl3); δ = 166.1, 138.5, 136.7, 133.1, 130.0, 129.8 (2 × C), 128.6 (2 × C), 116.9, 115.1, 75.4, 34.0, 33.7, 24.6 ppm; HRMS (ESI+): m/z: calculated for C17H22O2SiNa: 309.12813 [M+Na]+; found: 323.12015; enantiomeric excess was determined by chiral HPLC (Chiralpak AS-H; n-heptane/2-propanol, 99.9:0.1; 0.5 mL/min; 226 nm; column temperature: 40°C): tk (major) = 16.10 min, tk (minor) = 10.50 min.

General procedure for the copper-catalyzed hetero-allylic asymmetric alkylation with Grignard reagents that contain alkylene groups: Method A. A solution of Grignard reagent 5 (0.48 mmol, 1.5 equiv) in CH2Cl2 (1.5 mL) under a nitrogen atmosphere was added dropwise over 4 h to a homogenous, stirring solution of the allylic bromide (0.32 mmol), CuBr2-SiMe2 (5.0 mol%), and Li (5.5 mol%) in CH2Cl2 (3 mL) at −80°C under a nitrogen atmosphere. The reaction mixture was stirred at the indicated temperature until it had gone to completion (typically overnight) and was then washed with MeOH (5 mL). The reaction mixture was allowed to warm to RT and a saturated aqueous solution of NH4Cl (5 mL) was added. The mixture was partitioned between CH2Cl2 (5 mL) and water. The organic layer was dried (MgSO4), filtered, and the solvent was evaporated under vacuum. Purification by flash column chromatography on silica gel (EtOAc/ pentane, 1% to 2%) afforded pure product 6 as a colorless oil.

Method B. A solution of Grignard reagent 5b (0.38 mmol, 1.2 equiv) in EtO2 (1.6 mL) was diluted with CH2Cl2 (combined volume of 1 mL) and added dropwise over 4 h to a homogenous, stirring solution of allylic bromide 1c (0.32 mmol), copper(I) thiophene-2-carboxylate (CuTC, 3.0 mol %), and L2 (3.3 mol %) in CH2Cl2 (3.2 mL) at −80°C under a nitrogen atmosphere. The remaining steps were the same as those described in Method A.

(→)–(S)-7-(Trimethylsilyl)hept-1-en-6-yn-3-yl benzoate (6a). According to the general procedure Method A, compound 6a was obtained as a colorless oil (74% yield, 98% ee). [α](D) = +41.2 (c = 1.1 in CHCl3); 1HNMR (400 MHz, CDCl3); δ = 8.06 (dd, J = 9.8, 1.8 Hz, 1H), 7.61–7.51 (m, 1H), 7.44 (t, J = 6.8 Hz, 1H), 5.98–5.79 (m, 1H), 5.57 (dd, J = 12.4, 6.6 Hz, 1H), 5.35 (d, J = 16.0 Hz, 1H), 5.24 (d, J = 10.6 Hz, 1H), 2.36 (t, J = 7.5 Hz, 1H), 2.14–1.87 (m, 1H), 0.13 ppm (s, 4H); 13C NMR (100 MHz, CDCl3); δ = 165.6, 135.7, 132.9, 130.3, 129.6, 128.7, 112.7, 105.9, 85.3, 74.1, 33.3, 16.0, 0.0 ppm; HRMS (ESI+): m/z: calculated for C16H16SiNa: 309.12813 [M+Na]+; found: 309.12846; enantiomeric excess was determined by chiral HPLC (Chiralpak AS-H; n-heptane/2-propanol, 99.9:0.1; 0.5 mL/min; 226 nm; column temperature: 40°C): tk (major) = 16.10 min, tk (minor) = 10.50 min.
propanol, 99.9:0.1; 0.5 mL/min; 226 mm; column temperature: 40°C); \( t_R \) (major) = 11.60 min, \( t_R \) (minor) = 10.50 min.

\((\pm)-3\)-(Triethylsilyl)oct-1-en-7-yn-3-yl benzoate (6b): According to the general procedure Method A, compound 6b was obtained as a colorless oil (88% yield, 97% ee). \([\alpha]_D^{20} = +41.56 (c = 0.08 in CHCl_3); \) \( \text{H} \) NMR (400 MHz, CDCl_3): \( \delta = 8.16-7.99 \) (m, 2H), 7.59-7.54 (m, 1H), 7.46-7.43 (m, 2H), 6.01-5.80 (m, 1H), 5.61 (dd, \( J = 12.9, 6.3 \) Hz, 1H), 5.37 (d, \( J = 17.2, 6.9 \) Hz, 1H, 5.32 (d, \( J = 10.6, 1H \)). 2.33 (td, \( J = 7.3, 2.6 \) Hz, 2H), 2.18-1.85 ppm (m, 3H). \( \text{C} \) NMR (100 MHz, CDCl_3): \( \delta = 165.7, 153.6, 133.0, 129.3, 126.9, 128.4, 117.3, 83.1, 73.9, 69.0, 33.1, 14.6 ppm; \) \text{HRMS (ESI+):} \( m/z \) calcd for \( \text{C}_{17}\text{H}_{18}\text{O}_2\text{Na}: 277.11990 [M+Na]^+; \) found: 277.1207; enantiomeric excess was determined by chiral HPLC (Chiralpak OB-H; \( 0.5 \) mL/min; 226 mm; column temperature: 40°C); \( t_R \) (major) = 16.98 min, \( t_R \) (minor) = 16.38 min.

\((\pm)-3\)-(Octafluorophenyl)oct-1-en-7-yn-3-yl benzoate (7c): According to the general procedure, compound 7c was obtained as a colorless oil (83% yield, 96% ee). \([\alpha]_D^{20} = +43.3 (c = 1.1 in CHCl_3); \) \( \text{H} \) NMR (400 MHz, CDCl_3): \( \delta = 7.70 \) (d, \( J = 16.0, 1H \)), 7.60-7.48 (m, 2H), 7.45-7.36 (m, 3H), 6.46 (d, \( J = 16.0, 1H \)), 5.85 (dd, \( J = 17.0, 10.5, 6.3 \) Hz, 1H), 5.41 (dd, \( J = 13.0, 6.2 \) Hz, 1H), 5.31 (dt, \( J = 17.2, 1.3 \) Hz, 1H), 5.21 (dt, \( J = 10.5, 1H \)), 2.25 (td, \( J = 7.0, 2.6 \) Hz, 1H), 1.97 (s, 1H), 1.88-1.78 (m, 2H), 1.70-1.57 ppm (m, 2H). \( \text{C} \) NMR (100 MHz, CDCl_3): \( \delta = 166.2, 144.9, 136.3, 134.4, 130.3, 128.9, 128.5, 118.5, 116.7, 80.5, 74.7, 33.3, 24.2, 19.7, 0.1 ppm; \) \text{HRMS (ESI+):} \( m/z \) calcd for \( \text{C}_{17}\text{H}_{18}\text{O}_2\text{Na}: 277.11990 [M+Na]^+; \) found: 277.1207; enantiomeric excess was obtained from chiral HPLC (Chiralpak OJ-H; \( 2.5 \) mL/min; 226 mm; column temperature: 40°C); \( t_R \) (major) = 16.98 min, \( t_R \) (minor) = 16.38 min.

0.5 mL min−1; 221 nm; column temperature: 40°C); tR (major) = 10.54 min, tR (minor) = 14.00 min.

(+)-(S)-2-Methyl-7-methylenon-1,8-dien-3-yl benzoate (8d): In a round-bottomed flask, TBAF (1.0 mol in THF, 2.0 equiv) was added dropwise to a 0.05 mol solution of allylic ester 6d (1.0 equiv) in dry THF at 0°C. The mixture was allowed to warm to RT over 1 h. The reaction was quenched with water and extracted with EtO 2 (5 × 10 mL). The combined organic extracts were dried over MgSO4, filtered, and concentrated under vacuum. Then, the corresponding intermediate (7d) was dissolved in degassed CH2Cl2 (0.05 equiv) and Grubbs 1st-generation catalyst (10 mol%) was added to the solution in two portions. The reaction mixture was heated at reflux under an ethylene atmosphere (1 atm, balloon) until it had gone to completion (20 h), as indicated by GCMS. The reaction mixture was filtered through a plug of silica, concentrated under vacuum, and purified by column chromatography on silica gel (EtOAc/pentane, 1% to 2%) to yield the desired product (8d) as a colorless oil (66% yield). [α]D22.5 = +11 (c = 1.0 in CHCl3); 1H NMR (400 MHz, CDCl3): δ = 8.59–7.97 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 5.68 (d, J = 2.9 Hz, 1H), 5.42 (d, J = 6.5 Hz, 1H), 5.39 (d, J = 3.0 Hz, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 4.83 (s, 1H), 4.31 (s, 1H), 2.24 (t, J = 7.4 Hz, 2H), 1.79 (s, 3H), 1.77–1.66 (m, 2H), 1.57–1.40 ppm (m, 2H); 13C NMR (100 MHz, CDCl3): δ = 165.12, 158.26, 151.12, 143.32, 130.86, 132.09, 129.68, 128.73, 125.33, 112.75, 111.5, 77.38, 35.3, 32.3, 23.6, 18.2 ppm; HRMS (APCI+): m/z calcd for C22H20O6: 350.1577 [M+H]+; found: 350.1588.

General procedure for one-pot consecutive enyne-metathesis/Diels-Alder reactions: The substrate (7a/b) was dissolved in dry toluene (0.05 mol) to get a reaction solution (0.05 mol) as indicated by GCMS. The solution was added in two portions (5 mol% at the start and 5 mol% after 6 h). The mixture was heated at reflux in toluene (80°C) under an ethylene atmosphere (1 atm, balloon) until complete conversion into dienol ester (8a/8b) had been achieved, as indicated by TLC. Then, diethyl acetylenedicarboxylate (10 equiv) was added dropwise and the resulting solution was heated at 160°C in a sealed tube until TLC analysis indicated the complete consumption of the diene. Then, the reaction mixture was filtered through a plug of silica and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/pentane, 10% to 20%) to yield the desired product (9a/b). The stereochemistry of the product was determined by 1H NMR and NOESY analysis.

(+)-(35,3R)-Diethyl-3-(benzoxyl)-2,3,3a,6-tetrahydro-1H-indene-4,5-dicarboxylate (9a): According to the general procedure, compound 9a was obtained as a colorless oil (54% yield, 97% ee). [α]D22.5 = +70.2 (c = 0.2 in CHCl3); 1H NMR (500 MHz, CDCl3): δ = 8.05 (m, 1H), 8.50–7.99 (m, 3H), 7.95 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 5.62 (s, 1H), 5.22 (d, J = 16.5, 7.5 Hz, 1H), 4.19–4.24 (m, 4H), 3.96–4.01 (m, 1H), 3.83–3.89 (m, 1H), 3.62 (d, J = 9.2 Hz, 1H), 3.19 (dt, J = 22.6, 6.0 Hz, 1H), 2.99 (dd, J = 22.5, 11.9 Hz, 1H), 2.58 (d, J = 11.8 Hz, 1H), 2.39–2.48 (m, 2H), 1.85–1.74 (m, 1H), 1.29 (t, J = 7.3 Hz, 3H), 1.10 ppm (t, J = 7.2 Hz, 3H); 13C NMR (125 MHz, CDCl3): δ = 171.41, 160.5, 160.4, 141.8, 138.1, 135.8, 132.6, 132.1, 132.0, 129.6, 128.3, 124.9, 123.0, 121.3, 120.6, 115.6, 18.1 ppm; HRMS (ESI+): m/z calcd for C23H21O8: 385.16546 [M+H]+; found: 385.16560; enantiomeric excess was determined by chiral HPLC (Chiralpak OD-H; n-heptane/2-propanol, 97:3; 0.5 mL min−1; 229 nm; column temperature: 40°C); tR (major) = 11.51 min, tR (minor) = 14.41 min.

(+)-(35,3R,6aR)-3-Methyl-5-oxo-2-hexanoylhydroptentalen-1-yl benzoate (11): A solution of methyl lithium (1.6 mol) in dry EtO 2 (0.62 mmol) in EtO 2 (1 mL) was added dropwise to a suspension of Cu (95.2 mg, 0.5 mol%) in EtO 2 (1 mL) at 0°C under a N2 atmosphere. The resulting mixture was cooled to −20°C and a solution of substrate 10a (15.7 mg, 0.05 mmol) in EtO 2 (1 mL) was added dropwise. After stirring at −20°C for 4 h, the reaction mixture was quenched with a saturated aqueous solution of NH4Cl (4 mL). Then, the organic layer was separated and the aqueous layer was extracted with EtO 2 (3×5 mL). The combined organic layers were concentrated under vacuum. The crude mixture was dissolved in dry THF, TBAF (1.0 mol in THF, 1 mL, 0.1 mol%) was added dropwise to the solution at 0°C, and the mixture was heated at room temperature for 1 h. The organic solvent was removed under vacuum. The crude material was purified by column chromatography on silica gel (EtOAc/pentane, 10% to 20%) to afford the desired product (11) as a colorless oil (62% yield). [α]D22.5 = +43.8 (c = 0.7 in CHCl3); 1H NMR (500 MHz, CDCl3): δ = 8.06 (d, J = 7.9 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.48 (s, J = 7.7 Hz, 2H), 5.19 (s, J = 6.2, 3.1 Hz, 1H), 2.75 (dd, J = 11.4, 10.4, 1.6 Hz, 1H), 2.56–2.46 (m, 1H), 2.42–2.21 (m, 1H), 1.73–1.59 (m, 1H), 1.13 (dd, J = 13.5, 8.0, 5.7 Hz, 1H), 1.39 ppm (s, 1H); 13C NMR (125 MHz, CDCl3): δ = 209.28, 168.71, 133.0, 132.0, 131.0, 85.5, 55.8, 54.8, 48.7, 45.2, 40.9, 34.1, 31.1 ppm; HRMS (APCI+): m/z calcd for C13H12O3: 209.1323 [M+Na]+; found: 259.13288.
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[4] For selected reviews on metal-mediated or -catalyzed cyclization re


[8] For selected examples of the enantioselective synthesis of cyclic benzo


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