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

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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.

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

Introduction

Cyclic and bicyclic alcohols are present in a large number of natural products and pharmaceuticals (Figure 1).[1] For instance, these structural features are often found in the sesquiterpenoid family, which possess important biological activities, such as antitumor and antimicrobial properties.[2] 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 synthons, 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.[3] 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[4] of stereochemically complex structures.

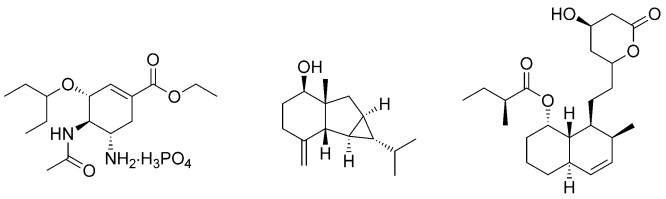
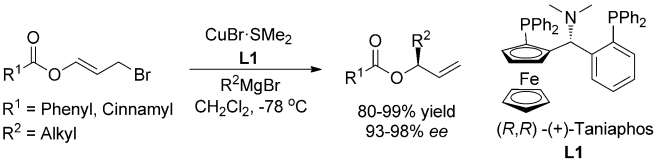


Figure 1. Bioactive compounds that contain various cyclic and bicyclic alcohol groups.

The copper-catalyzed asymmetric allylic alkylation (AAA) reaction represents a very powerful tool for the enantioselective construction of optically active molecules.[5] 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]



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

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[8] 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.

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Owing to the high affinity of copper for triple bonds,[11] the presence of an alkyne moiety could present a problem for the regio- or stereocontrol of the Cu-catalyzed AAA reaction. However, a successful Cu-catalyzed *h*-AAA[6] with these particular Grignard reagents would give rise to various enynes that contain a protected chiral alcohol motif, which could be further transformed into a wide range of highly functionalized ring systems (Scheme 2). Herein, we report a procedure for *h*-AAA reactions with this type of Grignard reagent.

Starting from vinyl ester **1**, efficient Cu-catalyzed *h*-AAA with alkene-containing Grignard reagents, followed by ring-closing olefin metathesis,[12] would provide cyclic benzoate esters,[13] including the formation of five-, six-, and seven-membered-ring structures. Relying on the Cu-catalyzed *h*-AAA with alkyne-containing Grignard reagents, the resulted enynes could be transformed into optically active 2,4-dienol esters[14] with different ring sizes through enyne metathesis.[15] In addition, the highly stereoselective synthesis of different fused-ring-functionalized carbobicycles from their corresponding 2,4-dienol esters or internal enyne esters is feasible through Diels–Alder[16] or Pauson–Khand[17] reactions. The distinctive features of this convergent strategy are the highly regio- and enantioselective synthesis of allylic esters and the potential for stereocontrol in later transformations to afford a variety of cyclic and bicyclic alcohols.

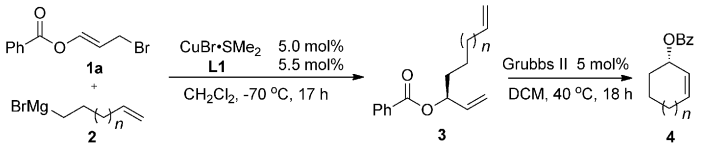
Results and Discussion

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 reagents,[6] with $CuBr{\cdot}SMe_2$ and (*R,R*)-(+)-Taniaphos (**L1**) as the catalytic system, 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*).[6a] 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 not successful with Grubbs second-generation catalyst, thus leading to recovery of the starting material.[18]

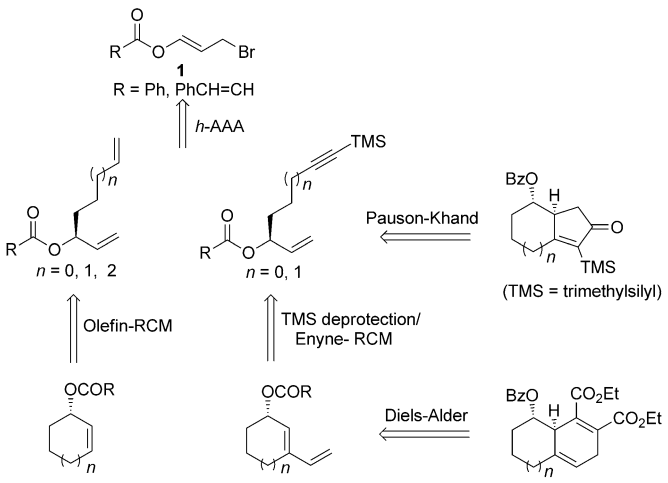
Next, we turned our attention to the use of challenging Grignard reagents that contained an alkyne functional group in the Cu-catalyzed *hetero*-allylic asymmetric alkylation (*h*-AAA) reaction (Table 2). To prevent competitive coordination between the terminal alkyne and the copper(I) species,[11] trimethylsilyl-protected alkynes were employed. Under the same conditions as for the Cu-catalyzed *h*-AAA discussed above, product **6b** was obtained with only modest

Table 1. *h*-AAA/RCM of cinnamyl substrates.[a]



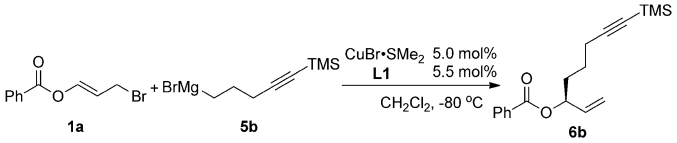
$n=0$	**3a**	γ/α > 99:1[b] 96% yield[c] 97% *ee*[d]	**(*S*)-4a**[e]	85% yield[c] 97% *ee*[d]
$n=1$	**3b**	γ/α > 99:1[b] 95% yield[c] 97% *ee*[d]	**4b**	89% yield[c] 95% *ee*[d]
$n=2$	**3c**	γ/α > 99:1[b] 83% yield[c] 96% *ee*[d]	**4c**	85% yield[c] 95% *ee*[d]

[a] General conditions for the *h*-AAA reaction: $CuBr{\cdot}SMe_2$ (5 mol%), (*R,R*)-(+)-Taniaphos (5.5 mol%), Grignard reagent **2** (2 equiv), CH_2Cl_2, −70 °C. [b] Regioselectivity was determined by ^1H NMR spectroscopy of the crude mixture. [c] Yield of isolated product. [d] Enantiomeric excess was determined by chiral HPLC analysis. [e] The absolute configuration was assigned by comparison of optical rotation with known compounds.[6a]



Scheme 2. Proposed routes to cyclic and bicyclic esters, with the *h*-AAA of functionalized Grignard reagents as the key step.

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

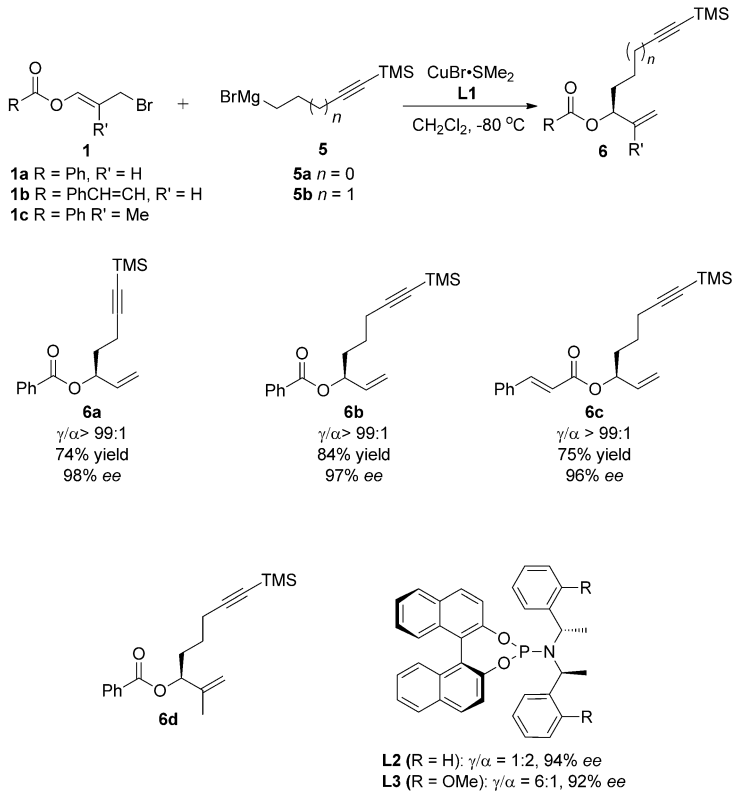


Entry	**1a**/**5b**	Addition time [h]	γ/α[b]	*ee* of **6b**[c] [%]
1	1:2	0.1	>99:1	36
2	1:2	0.5	>99:1	88
3	1:2	2	>99:1	92
4	1:1.5	2	>99:1	94
5	1:1.5	4	>99:1	97

[a] Reactions performed on a 0.32 mmol scale. Compound **5b** (1.5 M in Et_2O) was diluted with CH_2Cl_2 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.

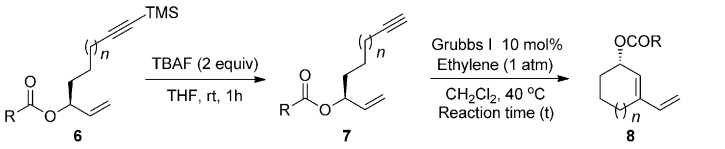
enantioselectivity (36% *ee*; Table 2, entry 1). Screening of different reaction parameters indicated that lower amounts (1.5 equiv) and slower addition (4 h) of the Grignard reagent were essential for obtaining compound **6b** in a fully enantioselective manner.[19] It was particularly rewarding to 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 enantiocontrol (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*).

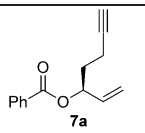
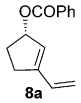
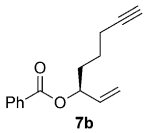
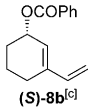
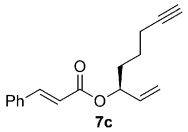
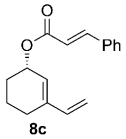
Optically enriched 2,4-dienols are key structural motifs in a variety of natural products.[14] Despite the importance and versatility of these compounds, approaches for their enantioselective synthesis have thus far been limited to the lipase-catalyzed kinetic resolution of racemic dienols.[14b–d] To 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



Scheme 3. Cu-catalyzed *h*-AAA of Grignard reagents that contain an alkyne moiety.

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



6a $n=0$, R = Ph	 **7a**	74% yield[a] 98% *ee*[b]	 **8a** $t=24$ h 43% yield[a] 98% *ee*[b]
6b $n=1$, R = Ph	 **7b**	85% yield[a] 97% *ee*[b]	 **(*S*)-8b**[c] $t=24$ h 87% yield[a] 96% *ee*[b]
6c $n=1$, R = PhCH=CH	 **7c**	83% yield[a] 96% *ee*[b]	 **8c** $t=48$ h 85% yield[a] 96% *ee*[b]

[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]

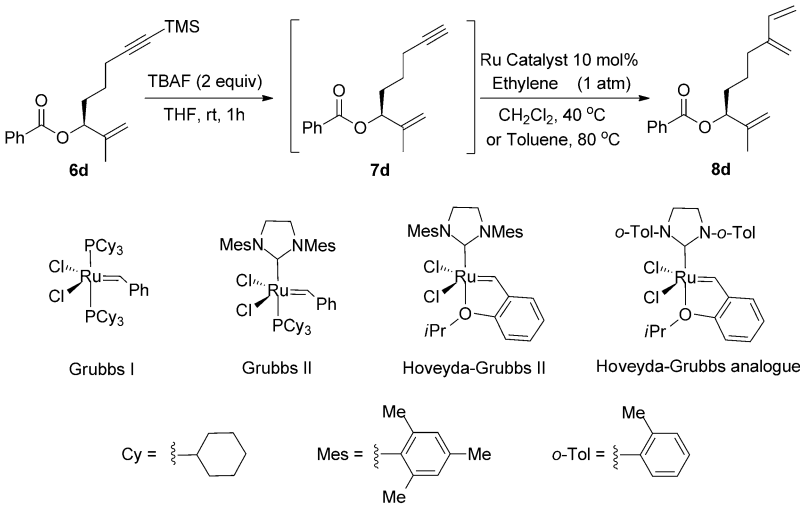
method for the enantioselective synthesis of cyclic 2,4-dienol esters.

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.

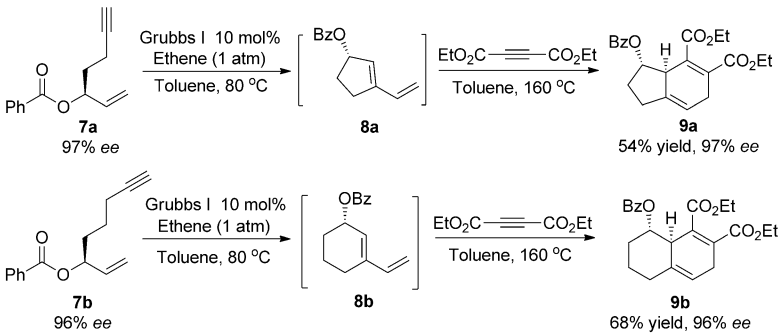
Dienols **8** are suitable substrates for Diels–Alder reactions that would give rise to important bicyclic scaffolds **9** in a diastereoselective fashion.[23] As outlined in Scheme 5, we have developed a one-pot consecutive enyne-metathesis/Diels–Alder reaction in the presence of diethyl acetylenedicarboxylate. Optically enriched terminal enynes **7a** and **7b** were subjected to the enyne-metathesis conditions described above; then, the dienophile was added after the complete formation of diene ester **8**. To our delight, chiral intermediate **8** underwent cycloaddition with dienophile at 160 °C in each case to yield the corresponding cycloadduct **9** as a single diastereomer (Scheme 5).

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_c and H_b–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



Scheme 4. Further elaboration of enyne **6d**.



Scheme 5. One-pot consecutive sequence of enyne metathesis and Diels–Alder reactions.

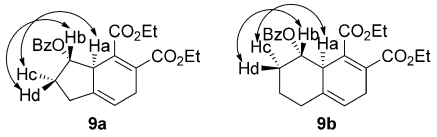
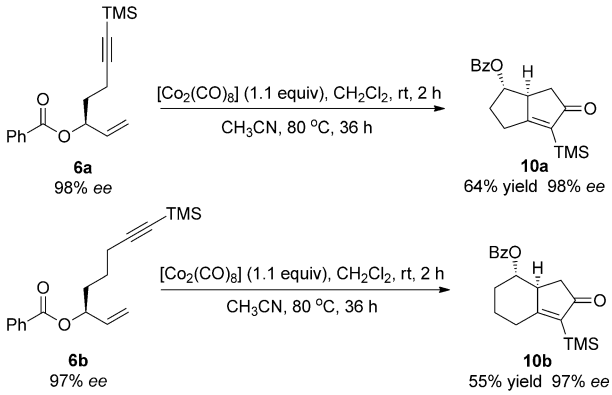


Figure 2. Relevant NOESY correlations in products **9a** and **9b**.

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 $[Co_2(CO)_8]$ in CH_2Cl_2 at room temperature, generated the corresponding hexacarbonyldicobalt 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*).



Scheme 6. Intramolecular Pauson–Khand reaction of enynes **6a** and **6b**.

The relative stereochemistry of the two adjacent stereogenic centers in compounds **10a** and **10b** was determined by ^{1}H NMR and NOESY analysis. The observed *exo* configuration was expected for an intramolecular PK reaction.[25] 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,β-unsaturated ketone. The synthetic diversity of this strategy was illustrated by the facile installation of an all-carbon quaternary stereogenic center[27] on the bridgehead carbon atom (Scheme 7). Bicyclic pentanone **10a** was treated with lithium dimethylcuprate in Et_2O at −20 °C. After deprotection of the TMS group, the final product **11** was obtained as a single isomer in 62% yield.

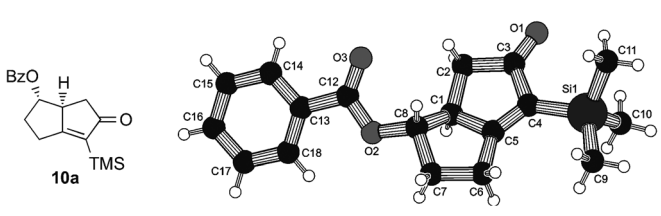
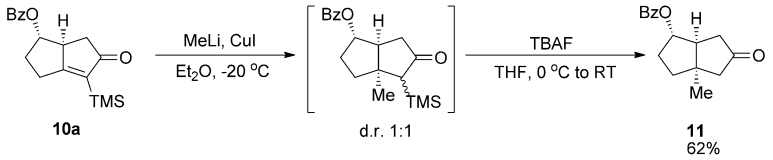


Figure 3. Molecular structure of compound **10a** in the crystal.[26]

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.



Scheme 7. Synthesis of an all-carbon quaternary stereogenic center at the bridgehead carbon atom in compound **11**.

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 $KMnO_4$ (10 g) and K_2CO_3 (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. ^{1}H and ^{13}C 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 $CDCl_3$ as the solvent. Chemical shifts are reported in

ppm by using the solvent resonance as an internal standard (^{1}H: δ = 7.26 ppm, ^{13}C: 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 rotations were measured in $CHCl_3$ on a Schmidt+Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c*, given in g/100 mL). Conversion of the reactants was determined by GC (GC, HP6890: MS HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). The regioselectivity of the reaction was determined by ^{1}H NMR spectroscopy of the crude mixture. Enantioselectivities were determined by HPLC analysis on a Shimadzu LC-10ADVP HPLC that was equipped with a Shimadzu SPD-M10AVP diode-array detector. All of the reactions were carried out under a nitrogen atmosphere by using oven-dried glassware and standard Schlenk techniques. All solvents were of reagent grade and were dried and distilled prior to use (if necessary). THF and Et_2O were distilled over Na/benzophenone. Toluene and CH_2Cl_2 were distilled over calcium hydride. All of the ligands and CuBr·SMe_2 were purchased from Aldrich and used without further purification. Alkyl bromides, except for 4-bromo-1-trimethylsilyl-1-butyne[28] and 5-bromo-1-trimethylsilyl-1-pentyne,[28] which were synthesized according to literature procedures, were purchased from Aldrich. All other commercially available reagents were used as received. Starting materials **1a**, **1b**, and **1c** were synthesized according to the procedure reported by Trombini, Lombardo, and co-workers.[29] Grignard reagents were prepared from their corresponding alkyl bromides and magnesium turnings in Et_2O by following standard procedures. Grignard reagents were titrated by using *sec*-BuOH and catalytic amounts of 1,10-phenanthroline. Compounds **3a** and **4a** have been reported in our previous paper.[6a]

General procedure for the copper catalyzed *hetero*-allylic asymmetric alkylation[6] with Grignard reagents that contain terminal alkene groups: A solution of Grignard reagent **2** (0.64 mmol, 2 equiv) in Et_2O was added dropwise over 5 min to a homogeneous, stirring solution of the allylic bromide (0.32 mmol), CuBr·SMe_2 (5.0 mol %), and **L1** (5.5 mol %) in CH_2Cl_2 (3.5 mL) at −70 °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 quenched with MeOH (5 mL). The reaction mixture was allow to warm to RT and a saturated aqueous solution of NH_4Cl (5 mL) was added. The mixture was partitioned between CH_2Cl_2 (5 mL) and water. The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated under vacuum. Purification by flash column chromatography on silica gel (Et_2O/*n*-pentane, 1 % to 2 %) afforded pure product **3** as a colorless oil.

(+)-(*S*)-Octa-1,7-dien-3-yl benzoate (3b): According to the general procedure, compound **3b** was obtained as a colorless oil (95 % yield, 97 % *ee*). $[\alpha]_D^{20}$ = +33.2 (*c* = 3.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 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* = 7.0 Hz, 2H), 1.90–1.67 (m, 2H), 1.52 ppm (dd, *J* = 15.2, 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 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* calcd for $C_{15}H_{18}O_2Na$: 253.11990 $[M+Na]^+$; found: 253.12015; enantiomeric excess was determined by chiral HPLC (Chiralpak OB-H; *n*-heptane/2-propanol, 99:1; 0.5 mL min^{-1}; 224 nm; column temperature: 40 °C): t_R (major) = 9.94 min, t_R (minor) = 11.54 min.

(+)-(*S*)-Nona-1,8-dien-3-yl benzoate (3c): According to the general procedure, compound **3c** was obtained as a colorless oil (83 % yield, 96 % *ee*). $[\alpha]_D^{20}$ = +21.4 (*c* = 3.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.00 (m, 2H), 7.61–7.51 (m, 1H), 7.45 (m, 2H), 5.89 (ddd, *J* = 14.4, 10.3, 5.1 Hz, 1H), 5.84–5.69 (m, 1H), 5.49 (ddd, *J* = 12.2, 6.1, 1.1 Hz, 1H), 5.38–5.28 (m, 1H), 5.20 (dt, *J* = 10.5, 1.2 Hz, 1H), 5.07–4.87 (m, 2H), 2.10–2.03 (m, 2H), 1.88–1.66 (m, 2H), 1.52–1.34 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 138.9, 136.8, 133.1, 130.8, 129.8, 128.6, 116.9, 114.7, 75.5, 34.4, 33.8, 28.9, 24.8 ppm; HRMS (ESI+): *m/z* calcd for $C_{16}H_{20}O_2Na$: 267.13555 $[M+Na]^+$; found: 267.13507; enantiomeric excess was determined by chiral HPLC (Chiralpak OB-H; *n*-heptane/2-propanol, 98:2; 0.5 mL min^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 8.68 min, t_R (minor) = 10.00 min.

General procedure for the Ru-catalyzed ring-closing metathesis (RCM) reaction:[6] Allylic ester **3** (0.6 mmol) was dissolved in degassed CH_2Cl_2 (12 mL) under a N_2 atmosphere. Grubbs 2nd-generation catalyst (0.03 mmol) was tipped into the solution and the mixture was heated at reflux (40 °C) for 18 h. Then, the mixture was cooled to RT and the solvents were removed under reduced pressure. Purification by column chromatography on silica gel (Et_2O/*n*-pentane, 1 % to 2 %) afforded the desired product **4**.

(−)-(*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*). $[\alpha]_D^{20}$ = −187.3 (*c* = 3.7 in $CHCl_3$); [lit.[13e] (*S* isomer, 90 % *ee*): $[\alpha]_D^{20}$ = −164 (*c* = 0.96 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31–7.83 (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 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 133.1, 133.0, 131.0, 129.8, 128.5, 125.9, 68.8, 28.6, 25.2, 19.2 ppm; HRMS (ESI+): *m/z* calcd for $C_{13}H_{14}O_2Na$: 225.08860 $[M+Na]^+$; found: 225.04333; enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H; *n*-heptane/2-propanol, 99.9:0.1; 0.5 mL min^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 19.55 min, t_R (minor) = 18.66 min.

(−)-(*S*)-Cyclohept-2-en-1-yl benzoate (4c): According to the general procedure, compound **4c** was obtained as a colorless oil (85 % yield, 95 % *ee*). $[\alpha]_D^{20}$ = −37.4 (*c* = 2.3 in $CHCl_3$); [lit.,[13e] (*S* isomer, 97 % *ee*): $[\alpha]_D^{20}$ = −52 (*c* = 0.85 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.00 (m, 2H), 7.64–7.51 (m, 1H), 7.49–7.35 (m, 2H), 5.95–5.85 (m, 1H), 5.83–5.76 (m, 1H), 5.71–5.63 (m, 1H), 2.33–2.21 (m, 1H), 2.20–2.09 (m, 1H), 2.07–1.93 (m, 2H), 1.90–1.66 (m, 3H), 1.53–1.45 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 133.7, 133.0, 132.2, 130.9, 129.8, 128.5, 74.9, 33.1, 28.8, 26.9, 26.8 ppm; HRMS (ESI+): *m/z* calcd for $C_{14}H_{16}O_2Na$: 337.12304 $[M+Na]^+$; found: 337.12205; enantiomeric excess was determined by chiral HPLC (Chiralpak AS-H; *n*-heptane/2-propanol, 99.9:0.1; 0.5 mL min^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 11.60 min, t_R (minor) = 10.50 min.

General procedure for the copper-catalyzed *hetero*-allylic asymmetric alkylation[6] with Grignard reagents that contain alkyne groups: **Method A**. A solution of Grignard reagent **5** (0.48 mmol, 1.5 equiv) in Et_2O (1.5 M and 1.6 M for **5a** and **5b**, respectively) was diluted with CH_2Cl_2 (combined volume of 1 mL) and added dropwise over 4 h to a homogeneous, stirring solution of the allylic bromide (0.32 mmol), CuBr·SMe_2 (5.0 mol %), and **L1** (5.5 mol %) in CH_2Cl_2 (3.2 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 quenched with MeOH (5 mL). The mixture was allowed to warm to RT and a saturated aqueous solution of NH_4Cl (5 mL) was added. The mixture was partitioned between CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated under vacuum. Purification by flash column chromatography on silica gel (Et_2O/*n*-pentane, 1 % to 2 %) to afford the product (**6**) as a colorless oil.

Method B. A solution of Grignard reagent **5b** (0.38 mmol, 1.2 equiv) in Et_2O (1.6 M) was diluted with CH_2Cl_2 (combined volume of 1 mL) and added dropwise over 4 h to a homogeneous, stirring solution of allylic bromide **1c** (0.32 mmol), copper(I) thiophene-2-carboxylate (CuTC, 3.0 mol %), and **L2** (3.3 mol %) in CH_2Cl_2 (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*). $[\alpha]_D^{20}$ = +14.2 (*c* = 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 9.8, 1.6 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 135.7, 132.9, 130.3, 129.6, 129.6, 128.3, 117.2, 105.9, 85.3, 74.1, 33.3, 16.0, 0.0 ppm; HRMS (ESI+): *m/z* calcd for $C_{17}H_{22}O_2SiNa$: 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^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 11.60 min, t_R (minor) = 10.50 min.

(+)-(*S*)-8-(Trimethylsilyl)oct-1-en-7-yn-3-yl benzoate (6b): According to the general procedure Method A, compound **6b** was obtained as a colorless oil (84% yield, 97% *ee*). $[\alpha]_D^{20} = +10.1$ ($c = 5.7$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$–7.91 (m, 2H), 7.63–7.51 (m, 1H), 7.50–7.32 (m, 2H), 6.11–5.77 (m, 1H), 5.53 (dd, $J = 12.7$, 6.3 Hz, 1H), 5.34 (d, $J = 17.2$ Hz, 1H), 5.22 (d, $J = 10.6$ Hz, 1H), 2.28 (t, $J = 7.1$ Hz, 2H), 2.01–1.81 (m, 2H), 1.75–1.54 (m, 2H), 0.14 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.8$, 136.3, 132.9, 130.4, 129.6, 128.3, 116.8, 106.7, 85.0, 74.7, 33.3, 24.2, 19.7, 0.1 ppm; HRMS (ESI+): *m/z* calcd for $C_{18}H_{24}O_2SiNa$: 323.14378 $[M+Na]^+$; found: 323.14404; enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H; *n*-heptane/2-propanol, 99.9:0.1; 0.5 mL min^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 13.80 min, t_R (minor) = 12.98 min.

(+)-(*S*)-8-(Trimethylsilyl)oct-1-en-7-yn-3-yl cinnamate (6c): According to the general procedure Method A, compound **6c** was obtained as a colorless oil (75% yield, 96% *ee*). $[\alpha]_D^{20} = +16.0$ ($c = 0.4$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 16.0$ Hz, 1H), 7.60–7.47 (m, 2H), 7.44–7.29 (m, 3H), 6.46 (d, $J = 16.0$ Hz, 1H), 5.90–5.78 (m, 1H), 5.41 (d, $J = 5.9$ Hz, 1H), 5.31 (d, $J = 15.9$ Hz, 1H), 5.21 (d, $J = 10.5$ Hz, 1H), 2.30–2.24 (m, 2H), 1.80 (t, $J = 6.6$ Hz, 2H), 1.68–1.52 (m, 2H), 0.13 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.8$, 144.8, 136.3, 134.4, 130.3, 128.9, 128.1, 118.3, 116.8, 106.7, 85.0, 74.3, 33.3, 24.2, 19.6, 0.1 ppm; HRMS (ESI+): *m/z* calcd for $C_{20}H_{26}O_2SiNa$: 349.15943 $[M+Na]^+$; found: 349.15943; enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H; *n*-heptane/2-propanol, 99/1; 0.5 mL min^{-1}; 270 nm; column temperature: 40 °C): t_R (major) = 14.48 min, t_R (minor) = 12.64 min.

(+)-(*S*)-2-Methyl-8-(trimethylsilyl)oct-1-en-7-yn-3-yl benzoate (6d): According to the general procedure Method B, compound **6d** was obtained as a colorless oil (72% yield, 92% *ee*). $[\alpha]_D^{20} = +13.0$ ($c = 1.9$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.07$ (dd, $J = 8.1$, 1.0 Hz, 2H), 7.64–7.52 (m, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 5.44 (t, $J = 6.5$ Hz, 1H), 5.05 (s, 1H), 4.94 (s, 1H), 2.28 (t, $J = 6.9$ Hz, 2H), 1.91 (dt, $J = 14.4$, 4.7 Hz, 2H), 1.81 (s, 3H), 1.70–1.52 (m, 2H), 0.14 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.71$, 142.9, 132.9, 130.5, 129.6, 128.3, 112.8, 106.7, 85.1, 77.3, 31.7, 24.3, 19.6, 18.2, 0.1 ppm; HRMS (APCI+): *m/z* calcd for $C_{19}H_{27}O_2Si$: 315.17748 $[M+H]^+$; found: 315.17749; enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H; *n*-heptane/2-propanol, 99.9:0.1; 0.5 mL min^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 14.62 min, t_R (minor) = 12.83 min.

General procedure for the deprotection of the trimethylsilyl (TMS) alkynes: In a round-bottomed flask, TBAF (1.0 M in THF, 2.0 equiv) was added dropwise to a solution of allylic ester **6** (1.0 equiv) in dry THF (0.05 M) at 0 °C. The mixture was allowed to warm to RT over 1 h. The reaction was quenched with water and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by column chromatography on silica gel (Et_2O/*n*-pentane, 1% to 2%) to yield the desired product (**7**).

(+)-(*S*)-Hept-1-en-6-yn-3-yl benzoate (7a): According to the general procedure, compound **7a** was obtained as a colorless oil (74% yield, 98% *ee*). $[\alpha]_D^{20} = +15.6$ ($c = 0.8$ in $CHCl_3$); ^{1}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, $J = 17.2$ Hz, 1H), 5.25 (d, $J = 10.6$ Hz, 1H), 2.33 (td, $J = 7.3$, 2.6 Hz, 2H), 2.19–1.85 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.7$, 135.6, 133.0, 130.3, 129.6, 128.4, 117.3, 83.1, 73.9, 69.0, 33.1, 14.6 ppm; HRMS (ESI+): *m/z* calcd for $C_{14}H_{14}O_2Na$: 237.08860 $[M+Na]^+$; found: 237.08813; enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H; *n*-heptane/2-propanol, 99:1; 0.5 mL min^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 17.15 min, t_R (minor) = 14.71 min.

(+)-(*S*)-Oct-1-en-7-yn-3-yl benzoate (7b): According to the general procedure, compound **7b** was obtained as a colorless oil (85% yield, 97% *ee*). $[\alpha]_D^{20} = +18.7$ ($c = 3.7$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.15$–7.97 (m, 2H), 7.63–7.51 (m, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 5.90 (ddd, $J = 16.9$, 10.5, 6.2 Hz, 1H), 5.55 (d, $J = 6.2$ Hz, 1H), 5.34 (d, $J = 17.2$ Hz, 1H), 5.22 (d, $J = 10.5$ Hz, 1H), 2.25 (m, 2H), 1.97 (s, 1H), 1.89 (m, 2H), 1.78–1.52 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.7$, 136.2, 132.9, 130.4, 129.6, 128.3, 116.9, 83.8, 74.7, 68.8, 33.3, 24.0, 18.2 ppm; HRMS (ESI+): *m/z* calcd for $C_{15}H_{16}O_2Na$: 251.10425 $[M+Na]^+$; found: 251.10459; enantiomeric excess was determined by chiral HPLC (Chiralpak OB-H; *n*-heptane/2-propanol, 98:2; 0.5 mL min^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 13.95 min, t_R (minor) = 16.48 min.

(+)-(*S*)-Oct-1-en-7-yn-3-yl cinnamate (7c): According to the general procedure, compound **7c** was obtained as a colorless oil (83% yield, 96% *ee*). $[\alpha]_D^{20} = +33$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 16.0$ Hz, 1H), 7.60–7.48 (m, 2H), 7.45–7.36 (m, 3H), 6.46 (d, $J = 16.0$ Hz, 1H), 5.85 (ddd, $J = 17.0$, 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, $J = 10.5$, 1.2 Hz, 1H), 2.25 (td, $J = 7.0$, 2.6 Hz, 2H), 1.97 (s, 1H), 1.88–1.78 (m, 2H), 1.70–1.57 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.2$, 144.9, 136.3, 134.4, 130.3, 128.9, 128.1, 118.2, 116.9, 83.9, 74.3, 68.7, 33.2, 24.0, 18.2 ppm; HRMS (ESI+): *m/z* calcd for $C_{17}H_{18}O_2Na$: 277.11990 $[M+Na]^+$; found: 277.12027; enantiomeric excess was determined by chiral HPLC (Chiralpak OJ-H; *n*-heptane/2-propanol, 99:1; 0.5 mL min^{-1}; 270 nm; column temperature: 40 °C): t_R (major) = 31.19 min, t_R (minor) = 35.12 min.

General procedure for the Ru-catalyzed eneyne-metathesis reaction:[7a] Compound **7** was dissolved in degassed CH_2Cl_2 (0.05 M) 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 (24–48 h), as indicated by GCMS. The mixture was filtered through a pad of silica, concentrated under vacuum, and purified by column chromatography on silica gel (Et_2O/*n*-pentane, 1% to 2%) to yield the desired product (**8**) as a colorless oil.

(−)-(*S*)-3-Vinylcyclopent-2-en-1-yl benzoate (8a): According to the general procedure, compound **8a** was obtained as a colorless oil (43% yield, 98% *ee*). $[\alpha]_D^{20} = -145.4$ ($c = 3.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.06$–7.95 (m, 2H), 7.53 (dd, $J = 10.5$, 4.3 Hz, 1H), 7.39–7.46 (m, 2H), 6.62 (dd, $J = 17.5$, 10.6 Hz, 1H), 6.04–5.93 (m, 1H), 5.88 (s, 1H), 5.29 (d, $J = 17.5$ Hz, 1H), 5.25 (d, $J = 10.7$ Hz, 1H), 2.76–2.65 (m, 1H), 2.41–2.55 (m, 2H), 2.07 ppm (ddd, $J = 8.7$, 6.4, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.4$, 148.2, 132.8, 132.7, 130.7, 129.6, 128.2, 127.8, 117.5, 81.0, 30.1, 29.2 ppm; MS (TOF, DART): *m/z* calcd for $C_{14}H_{14}O_2$: 215.1028 $[M+H]^+$; found: 215.0989; enantiomeric excess was determined by chiral HPLC (Chiralpak OB-H; *n*-heptane/2-propanol, 99:1; 0.5 mL min^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 17.73 min, t_R (minor) = 11.67 min.

(−)-(*S*)-3-Vinylcyclohex-2-en-1-yl benzoate (8b): According to the general procedure, compound **8b** was obtained as a colorless oil (87% yield, 96% *ee*). $[\alpha]_D^{20} = -204$ ($c = 5.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$–8.02 (m, 2H), 7.64–7.50 (m, 1H), 7.49–7.28 (m, 2H), 6.38 (dd, $J = 17.5$, 10.7 Hz, 1H), 5.86 (d, $J = 3.5$ Hz, 1H), 5.62 (d, $J = 4.3$ Hz, 1H), 5.27 (d, $J = 17.5$ Hz, 1H), 5.09 (d, $J = 10.8$ Hz, 1H), 2.30 (dt, $J = 17.3$, 5.7 Hz, 1H), 2.23–2.09 (m, 1H), 2.06–1.83 (m, 3H), 1.83–1.70 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.2$, 140.7, 139.0, 132.8, 130.7, 130.5, 129.6, 128.3, 126.4, 113.5, 69.5, 28.4, 23.6, 19.1 ppm; HRMS (ESI+): *m/z* calcd for $C_{15}H_{16}O_2Na$: 251.10425 $[M+Na]^+$; found: 251.10461; enantiomeric excess was determined by chiral HPLC (Chiralpak OB-H; *n*-heptane/2-propanol, 99:1; 0.5 mL min^{-1}; 226 nm; column temperature: 40 °C): t_R (major) = 15.08 min, t_R (minor) = 10.45 min.

(−)-(*S*)-3-Vinylcyclohex-2-en-1-yl benzoate (8c): According to the general procedure, compound **8c** was obtained as a colorless oil (85% yield, 96% *ee*). $[\alpha]_D^{20} = -197$ ($c = 3.1$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.72$ (d, $J = 16.0$ Hz, 1H), 7.55 (dd, $J = 6.7$, 2.8 Hz, 2H), 7.44–7.37 (m, 3H), 6.47 (d, $J = 16.0$ Hz, 1H), 6.41 (dd, $J = 17.5$, 10.8 Hz, 1H), 5.83 (d, $J = 3.3$ Hz, 1H), 5.54 (d, $J = 4.0$ Hz, 1H), 5.29 (d, $J = 17.4$ Hz, 1H), 5.12 (d, $J = 10.8$ Hz, 1H), 2.31 (dt, $J = 17.2$, 5.6 Hz, 1H), 2.23–2.14 (m, 1H), 2.03–1.70 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.3$, 147.3, 143.4, 141.7, 137.2, 132.9, 131.6, 130.7, 129.1, 121.2, 116.2, 71.6, 31.2, 26.4, 21.5 ppm; HRMS (ESI+): *m/z* calcd for $C_{17}H_{18}O_2Na$: 277.11990 $[M+Na]^+$; found: 277.12029; enantiomeric excess was determined by chiral HPLC (Chiralpak AS-H; *n*-heptane/2-propanol, 99:1;

0.5 mL min^{-1}; 221 nm; column temperature: 40 °C): t_R (major) = 10.54 min, t_R (minor) = 14.00 min.

(+)-(*S*)-2-Methyl-7-methylenenona-1,8-dien-3-yl benzoate (8d): In a round-bottomed flask, TBAF (1.0 M in THF, 2.0 equiv) was added dropwise to a 0.05 M 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 Et_2O (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. Then, the corresponding intermediate (**7d**) was dissolved in degassed CH_2Cl_2 (0.05 M) and Grubbs 1st-generation catalyst (10 mol %) was added to the solution in two portions. The reaction mixture was heated at refluxed under an ethylene atmosphere (1 atm, balloon) until it had gone to completion (20 h), as indicated by GCMS. The mixture was filtered through a pad of silica, concentrated under vacuum, and purified by column chromatography on silica gel (Et_2O/*n*-pentane, 1% to 2%) to yield the desired product (**8d**) as a colorless oil (66% yield). $[\alpha]_D^{20} = +11$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.59–7.88 (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), 4.81 (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); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.8$, 152.9, 151.2, 143.2, 132.8, 130.6, 129.6, 128.3, 125.3, 112.7, 111.5, 77.8, 35.2, 32.3, 23.6, 18.2 ppm; HRMS (APCI+): *m/z* calcd for $C_{18}H_{23}O_2$: 271.16926 $[M+H]^+$; found: 271.16884.

General procedure for one-pot consecutive enyne-metathesis/Diels–Alder reactions: The substrate (**7a**/**7b**) was dissolved in dry toluene (0.05 M) and Grubbs 1st-generation catalyst (10 mol %) was added to the solution 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/*n*-pentane, 10% to 20%) to yield the desired product (**9a**/**9b**). The stereochemistry of the product was determined by ^{1}H NMR and NOESY analysis.

(+)-(3*S*,3a*R*)-Diethyl-3-(benzoyloxy)-2,3,3a,6-tetrahydro-1*H*-indene-4,5-dicarboxylate (9a): According to the general procedure, compound **9a** was obtained as a colorless oil (54% yield, 97% *ee*). $[\alpha]_D^{20} = +70.2$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.08$ (d, $J = 7.4$ Hz, 1H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 5.62 (s, 1H), 5.22 (dd, $J =$ 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); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.4$, 168.5, 168.4, 141.8, 138.1, 135.8, 132.6, 132.3, 131.1, 130.5, 119.1, 64.0, 63.8, 48.9, 32.4, 32.3, 30.6, 29.5, 16.7, 16.3 ppm; HRMS (ESI+): *m/z* calcd for $C_{22}H_{25}O_6$: 385.16456 $[M+H]^+$; found: 385.16560; enantiomeric excess was determined by chiral HPLC (Chiralpak OJ-H; *n*-heptane/2-propanol, 97:3; 0.5 mL min^{-1}; 232 nm; column temperature: 40 °C): t_R (major) = 10.54 min, t_R (minor) = 14.00 min.

(+)-(8*S*,8a*R*)-Diethyl-8-(benzoyloxy)-3,5,6,7,8,8a-hexahydronaphthalene-1,2 dicarboxylate (9b): According to the general procedure, compound **9a** was obtained as a colorless oil (68% yield, 96% *ee*). $[\alpha]_D^{20} = +87$ ($c =$ 2.4 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.05$ (dd, $J = 8.2$, 1.2 Hz, 2H), 7.57 (dd, $J = 10.6$, 4.3 Hz, 1H), 7.46 (t, $J = 7.7$ Hz, 2H), 5.58 (s, 1H), 4.90 (td, $J = 10.7$, 4.4 Hz, 1H), 4.20 (dq, $J = 10.9$, 7.1 Hz, 1H), 4.11 (dq, $J = 10.9$, 7.1 Hz, 1H), 3.80 (dq, $J = 10.7$, 7.2 Hz, 1H), 3.64 (dt, $J = 11.2$, 6.7 Hz, 1H), 3.45 (dq, $J = 10.7$, 7.2 Hz, 1H), 3.18 (dd, $J = 23.2$, 7.3 Hz, 1H), 2.85 (dddd, $J = 23.2$, 6.1, 3.9, 2.3 Hz, 1H), 2.34 (d, $J = 13.0$ Hz, 1H), 2.27 (dd, $J = 12.5$, 3.4 Hz, 1H), 2.02 (t, $J = 13.0$ Hz, 1H), 1.91 (d, $J =$ 13.1 Hz, 1H), 1.71–1.59 (m, 1H), 1.54–1.42 (m, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 0.78 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 169.4, 167.3, 165.5, 135.0, 134.6, 133.2, 131.7, 130.2, 129.9, 128.4, 117.5, 77.1, 61.3, 61.2, 45.0, 34.7, 32.9, 28.0, 25.1, 14.2, 13.2 ppm; HRMS (ESI+): *m/z* calcd for $C_{23}H_{29}O_6Na$: 421.16216 $[M+Na]^+$; found: 421.16245; enantiomeric excess was determined by chiral HPLC (Chiralpak OJ-H; *n*-heptane/2-propanol, 99:1; 0.5 mL min^{-1}; 233 nm; column temperature: 40 °C): t_R (major) = 32.440 min, t_R (minor) = 28.68 min.

General procedure for the Pauson–Khand reaction:[25] A solution of enyne **6** (1.0 equiv) in dry CH_2Cl_2 (0.05 M) was added to a flask that contained $[Co_2(CO)_8]$ (1.1 equiv) under a N_2 atmosphere. The resulting solution was stirred at RT for 2 h until the formation of the cobalt complex was complete (TLC). The solvent was removed under vacuum, the residue was diluted with MeCN (0.025 M), and the resulting solution was heated at 80 °C until complete consumption of the cobalt complex (purple color) was observed. The reaction mixture was filtered through a plug of silica and washed with Et_2O. The combined organic solvents were evaporated and the residue was purified by column chromatography on silica gel (EtOAc/*n*-pentane, 5% to 20%) to yield the desired product (**10**).

(−)-(1*S*,6a*S*)-5-Oxo-4-(trimethylsilyl)-1,2,3,5,6,6a-hexahydropentalen-1-yl benzoate (10a): According to the general procedure, compound **10a** was obtained as colorless crystals (64% yield, 98% *ee*). M.p. 85–91 °C; $[\alpha]_D^{20} =$ −19 ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.08$ (d, $J =$ 7.4 Hz, 2H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 2H), 4.99 (dd, $J =$ 17.3, 8.9 Hz, 1H), 3.32–3.18 (m, 1H), 2.94 (ddd, $J = 18.4$, 11.7, 2.5 Hz, 1H), 2.82–2.71 (m, 1H), 2.67 (dd, $J = 17.9$, 6.6 Hz, 1H), 2.64–2.57 (m, 1H), 2.42 (dd, $J = 17.8$, 3.9 Hz, 1H), 2.21 (tt, $J = 12.7$, 8.4 Hz, 1H), 0.24 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 215.9$, 193.9, 169.1, 141.2, 135.8, 132.6, 132.3, 131.1, 55.3, 44.7, 34.3, 29.3, 1.5 ppm; HRMS (ESI+): *m/z* calcd for $C_{18}H_{22}O_3SiNa$: 337.12304 $[M+Na]^+$; found: 337.12205; enantiomeric excess was determined by chiral HPLC (Chiralpak AS-H; *n*-heptane/2-propanol, 99:1; 0.5 mL min^{-1}; 229 nm; column temperature: 40 °C): t_R (major) = 12.56 min, t_R (minor) = 11.75 min.

(+)-(7*S*,7a*S*)-2-Oxo-3-(trimethylsilyl)-2,4,5,6,7,7a-hexahydro-1*H*-inden-7-yl benzoate (10b): According to the general procedure, compound **10b** was obtained as colorless crystals (55% yield, 97% *ee*). M.p. 79–82 °C; $[\alpha]_D^{20} = +166.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.06$ (dd, $J = 8.0$, 0.9 Hz, 2H), 7.60 (dd, $J = 10.5$, 4.3 Hz, 1H), 7.48 (t, $J =$ 7.7 Hz, 2H), 4.78 (td, $J = 10.9$, 4.3 Hz, 1H), 3.06 (d, $J = 13.8$ Hz, 1H), 3.02–2.93 (m, 1H), 2.54 (dd, $J = 18.7$, 6.9 Hz, 1H), 2.37–2.30 (m, 1H), 2.30–2.17 (m, 1H), 2.16–2.07 (m, 1H), 1.85–1.64 (m, 1H), 1.65–1.47 (m, 1H), 0.34–0.02 ppm (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 211.7$, 185.5, 165.9, 139.5, 133.1, 130.2, 129.6, 128.4, 78.5, 49.0, 40.1, 31.2, 30.3, 23.8, −0.4 ppm; HRMS (ESI+): *m/z* calcd for $C_{19}H_{24}O_3SiNa$: 351.13869 $[M+Na]^+$; found: 351.13911; enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H; *n*-heptane/2-propanol, 95:5; 0.5 mL min^{-1}; 228 nm; column temperature: 40 °C): t_R (major) = 14.14 min, t_R (minor) = 11.34 min.

(+)-(1*S*,3a*R*,6a*S*)-3a-Methyl-5-oxooctahydropentalen-1-yl benzoate (11): A solution of methyl lithium (1.6 M) in dry Et_2O (0.62 mL, 1 mmol) was slowly added to a suspension of CuI (95.2 mg, 0.5 mmol) in Et_2O (1 mL) at 0 °C under a N_2 atmosphere. The resulting mixture was cooled to −20 °C and a solution of substrate **10a** (15.7 mg, 0.05 mmol) in Et_2O (1 mL) was added dropwise. After stirring at −20 °C for 4 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (4 mL). Then, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were concentrated under vacuum. The crude mixture was dissolved in dry THF, TBAF (1 M in THF, 0.1 mL, 0.1 mmol) was added dropwise to the solution at 0 °C, and the mixture was allowed to warm to RT over 1 h. The organic solvent was removed under vacuum. The crude material was purified by column chromatography on silica gel (Et_2O/*n*-pentane, 10% to 20%) to afford the desired product (**11**) as a colorless oil (62% yield). $[\alpha]_D^{20} = +23.8$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.06$ (d, $J = 7.9$ Hz, 2H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 2H), 5.19 (dt, $J = 6.2$, 3.1 Hz, 1H), 2.75 (ddd, $J = 11.4$, 10.4, 1.6 Hz, 1H), 2.56–2.46 (m, 1H), 2.42–2.21 (m, 4H), 2.13–2.03 (m, 1H), 1.97 (dt, $J = 13.3$, 8.0 Hz, 1H), 1.80 (ddd, $J = 13.5$, 8.0, 5.7 Hz, 1H), 1.39 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 220.9$, 168.8, 135.5, 133.0, 132.0, 131.0, 85.6, 55.8, 54.8, 48.7, 45.2, 40.9, 34.1, 31.1 ppm; HRMS (APPI+): *m/z* calcd for $C_{16}H_{18}O_3$: 259.13287 $[M+H]^+$; found: 259.13288.

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