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Catalytic Asymmetric Enyne Addition to Aldehdyes and Rh(I)-Catalyzed Stereoselective Domino Pauson–Khand/[4 + 2] Cycloaddition

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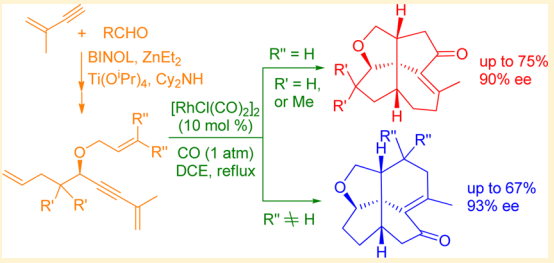
Supporting Information

ABSTRACT: The 1,1′-bi-2-naphthol–$ZnEt_2$–$Ti(O^iPr)_4$–Cy_2NH system is found to catalyze the 1,3-enyne addition to aliphatic aldehydes as well as other aldehydes at room temperature with 75–96% yield and 82–97% ee. This system is also broadly applicable for the highly enantioselective reaction of other alkyl-, aryl-, and silylalkynes with structurally diverse aldehydes. The propargylic alcohols prepared from the catalytic asymmetric enyne addition to aliphatic aldehydes are used to prepare a series of optically active trienynes. In the presence of a catalytic amount of $[RhCl(CO)_2]_2$ and 1 atm of CO, the optically active trienynes undergo highly stereoselective domino Pauson–Khand/[4 + 2] cycloaddition to generate optically active multicyclic products. The Rh(I) catalyst is also found to catalyze the coupling of a diyne with CO followed by [4 + 2] cycloaddition to generate an optically active multicyclic product. These transformations are potentially useful for the asymmetric synthesis of polyquinanes containing a quaternary chiral carbon center.



INTRODUCTION

Terpenoid natural products have been extensively investigated in both biology and organic synthesis. Polyquinanes represent a class of terpenoids containing multiple fused five-membered rings and some further fused with six-membered or other types of rings.[1−4] Figure 1 gives a few examples of the naturally occurring polyquinanes that contain a quaternary chiral carbon center shared by multiple rings. Efficient construction of these interesting molecular structures has continuously challenged the imagination of synthetic organic chemists.[1−4]

Chiral propargylic alcohols have found extensive applications in organic synthesis.[5−10] In the past few years, our laboratory has worked on the development of chiral catalysts for the asymmetric alkyne addition to aldehydes as well as the application of the chiral propargylic alcohols in the synthesis of cyclic organic compounds.[11−13] In this paper, we report our work on the first highly enantioselective addition of a conjugated enyne to linear aliphatic aldehydes in the presence of a chiral catalyst. The resulting chiral propargylic alcohols have been converted to chiral trienyne ethers. In the presence of a Rh(I) catalyst and CO, the chiral trienynes are discovered to undergo highly stereoselective domino Pauson–Khand (PK) and [4 + 2] cycloaddition to generate multicyclic organic compounds with a quaternary chiral carbon core.[14] These products resemble the polyquinanes shown in Figure 1 and are potentially useful for their synthesis.

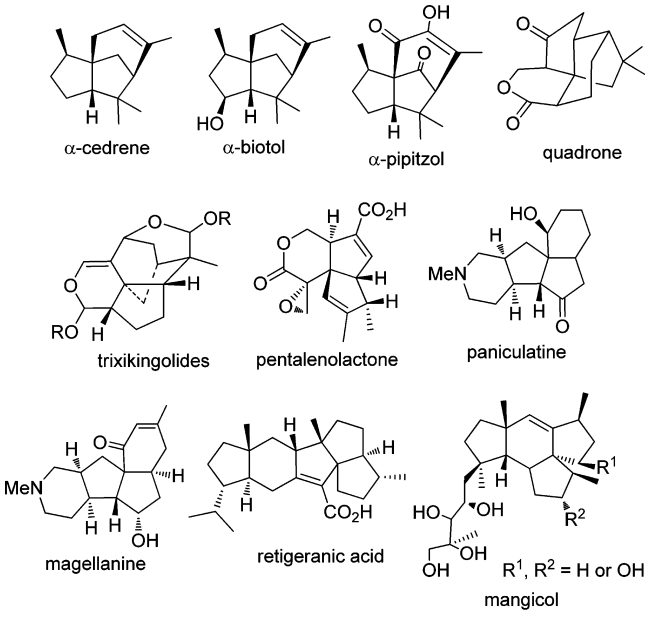


Figure 1. Examples of polyquinanes containing rings jointed by a quaternary chiral carbon.

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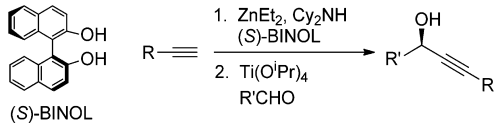
Table 1. Catalytic Enantioselective Reactions of Structurally Diverse Aldehydes with 3-Methyl-3-buten-1-yne and Other Alkynes



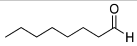
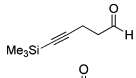
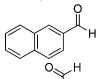
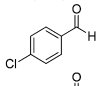
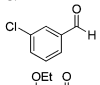
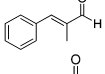
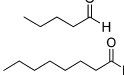
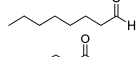
Entry	Alkyne	Aldehyde	Yield (%)	ee (%)
1[a]			85	90
2[a]			~75	82-90
3[a]			81	89
4[a]			85	89
5[a]			83	88
6[a]			84	96
7[a]			92	97
8[a]			96	98
9[a]			78	97
10[a]			93	91
11[a]			83	97
12[a]			94	92
13[a]			81	90
14[a]			85	98
15[b]			64	83
16[c]			81	91
17[c]			92	88
18[c]			88	90
19[b]			92	96
20[b]			94	98
21[b]			81	97
22[b]			87	99
23[b]			83	96
24[b]			74	95
25[b]			71	90
26[b]			94	91
27[b]			77	98
28[d]			99	84
29[d]			70	91
30[d]			68	90
31[d]			79	92
32[d]			61	93
33[d]			89	99
34[d]			80	99
35[d]			82	>99
36[d]			83	>99
37[d]			90	88
38[d]			96	93
39[d]			75	94
40[d]			99	99
41[d]			90	97
42[d]			70	97
43[a]			75	99
44[d]			93	97
45[d]			61	98
46[d]			68	94
47[d]			70	96
48[d]			68	97
49[d]			81	95
50[d]			84	88
51[d]			94	92
52[d]			68	92
53[d]			61	98

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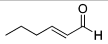
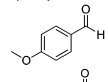
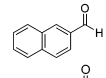
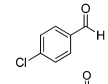
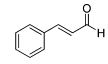
Table 1. continued

Entry	Alkyne	Aldehyde	Yield (%)	ee (%)
54[d]			56	93
55[d]			65	87
56[d]	TMS—		29	98
57[e]	TMS—		47	98
58[f]	TMS—		55	98
59[d,g]	TMS—		73	98
60[e,g]	TMS—		86	98
61[e,g]	TMS—		81	97
62[e,g]	TMS—		72	97
63[e,g]	TMS—		79	97
64[e,g]	TMS—		92	94
65[e,g]	TMS—		86	91

[a]Aldehyde/alkyne/(*S*)-BINOL/$ZnEt_2$/$Ti(O^iPr)_4$/Cy_2NH = 1:3:0.4:3:1:0.05. [b]Aldehyde/alkyne/(*S*)-BINOL/$ZnEt_2$/$Ti(O^iPr)_4$/Cy_2NH = 1:2.2:0.2:2:0.5:0.05. [c]Aldehyde/alkyne/(*S*)-BINOL/$ZnEt_2$/$Ti(O^iPr)_4$/Cy_2NH = 1:2.2:0.4:2:1:0.05. [d]Aldehyde/alkyne/(*S*)-BINOL/$ZnEt_2$/$Ti(O^iPr)_4$/Cy_2NH = 1:3:0.2:3:0.5:0.05. [e]Aldehyde/alkyne/(*S*)-BINOL/$ZnEt_2$/$Ti(O^iPr)_4$/Cy_2NH = 1:3:0.2:3:0.5:0.2. [f]Aldehyde/alkyne/(*S*)-BINOL/$ZnEt_2$/$Ti(O^iPr)_4$/Cy_2NH = 1:3:0.2:3:0.5:1. [g]48 h for the first step.

RESULTS AND DISCUSSION

1. Catalytic Asymmetric Reactions of Aldehydes with 1,3-Enynes and Other Alkynes. In recent years, great progress has been made in the development of chiral catalysts for asymmetric alkyne addition to aldehydes and a number of highly enantioselective catalysts have been obtained.[5−10] Among these studies, several catalysts have shown high enantioselectivity for the asymmetric 1,3-enyne addition to aromatic aldehydes[15−17] and an α-branched aliphatic aldehyde.[17] The use of a stoichiometric amount of *N*-methylephedrine was reported to show high enantioselectivity for the reaction of a 1,3-enyne with an α-branched aliphatic aldehyde,[18] but the addition to a linear aliphatic aldehyde without an α-substituent gave much lower enantioselectivity and low yield.[19] There is no report on highly enantioselective catalysts for the reaction of 1,3-enynes with linear aliphatic aldehydes.

Recently, we reported that 1,1′-bi-2-naphthol (BINOL) in combination with $ZnEt_2$, $Ti(O^iPr)_4$ and dicyclohexylamine (Cy_2NH) catalyzed the reaction of linear alkynes with linear aliphatic aldehydes at room temperature with high enantioselectivity.[20] We further studied the use of this catalyst system for the asymmetric reaction of structurally diverse aldehydes with 1,3-enynes as well as other alkynes, and the results are summarized in Table 1. All these reactions were conducted in diethyl ether at room temperature under nitrogen in a two-step, one-pot process. In the first step, a terminal alkyne was treated with $ZnEt_2$ and Cy_2NH, which presumably generated a nucleophilic alkynylzinc reagent. In this step, it is proposed that coordination of Cy_2NH with $ZnEt_2$ could increase the basicity of the Et group on Zn to facilitate the deprotonation of the terminal alkyne. (*S*)-BINOL (20−40 mol %) was also added in the first step, which should be deprotonated by $ZnEt_2$. In the second step, $Ti(O^iPr)_4$ and an aldehyde were added. In this step, the combination of the deprotonated (*S*)-BINOL with $Ti(O^iPr)_4$ could generate a chiral Lewis acid complex to catalyze the addition of the alkynylzinc reagent to the aldehyde. After aqueous workup, a chiral propargylic alcohol product was obtained.

As shown in entries 1 and 2 of Table 1, the catalytic asymmetric enyne additions to linear aliphatic aldehydes were accomplished with high enantioselectivity. These were the first examples for the enyne addition to this type of aldehydes in the presence of a chiral catalyst. Entries 3−14 show that high enantioselectivities were also obtained for the enyne addition to other aliphatic, aromatic, and α,β-unsaturated aldehydes. Entries 15−65 show that besides the highly enantioselective enyne additions, the reactions of other aryl-, alkyl-, and silylalkynes with aromatic and aliphatic aldehydes can also be conducted with high enantioselectivity. Entries 56−60 show that increasing the amount of Cy_2NH can increase the yield for the reaction of trimethylsilylacetylene but has no influence on the enantioselectivity. For the reactions shown in Table 1, various stoichiometric amounts of the reagents were used as indicated in the footnotes, in which the higher amount of (*S*)-BINOL for certain substrates was used to improve the enantioselectivity and the higher amounts of the alkyne and $ZnEt_2$ were used to improve the yield. The results of Table 1 together with our previously reported linear alkyl alkyne[20] and diyne additions[13a] demonstrate that the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−Cy_2NH catalyst system has high generality in the asymmetric alkyne addition to aldehydes for the synthesis of structurally diverse propargylic alcohols under very mild conditions.

2. Preparation of the Optically Active Trienynes. The optically active propargylic alcohols (*R*)-**1** were prepared according to entries 2 and 4 of Table 1. As shown in Scheme 1, the optically active trienynes (*R*)-**2a**,**b**[14] were obtained by treatment of (*R*)-**1** with KOH and then allyl bromide at room temperature. The optically active compounds (*R*)-**2c**−**f** were prepared by treatment of (*R*)-**1** with NaH followed by reaction with the corresponding allylic bromides. In the second step, the preparation of (*R*)-**2c** required heating at 70 °C, but that of (*R*)-**2d**−**f** proceeded at room temperature. Compound (*R*)-**2d** contains one additional alkene unit in comparison with the other trienynes.

3. Catalytic Conversions of (*R*)-2a−f in the Presence of $[RhCl(CO)_2]_2$. The catalytic PK cycloaddition of an alkene and an alkyne with CO has been extensively investigated, and a number of catalysts have been developed.[21−29] Previously, we have studied the use of Rh(I) complexes to catalyze the intramolecular PK reaction of the optically active propargylic alcohol-based enynes to synthesize chiral bicyclic cyclopentenones.[13] We have also tested the PK reaction of (*R*)-**2b** in the presence of a Rh(I) complex. When (*R*)-**2b** was treated with $[RhCl(CO)_2]_2$ (10 mol %) under 1 atm of CO in refluxing 1,2-dichloroethane (DCE), a tetracyclic product **3b** was

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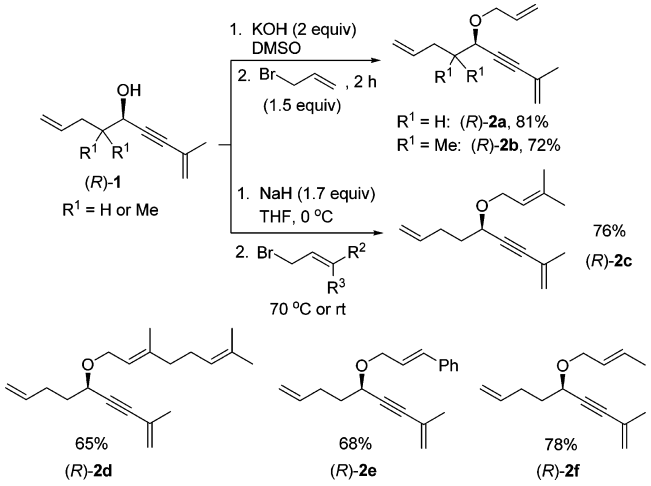
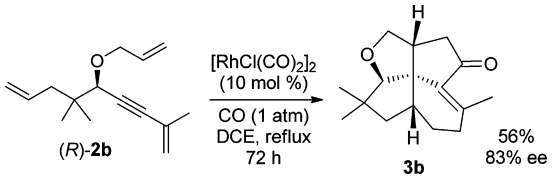
Scheme 1. Preparation of the Optically Active Trienynes (*R*)-2a–f



obtained in 56% yield and 83% ee (Scheme 2).[14] That is, an apparent domino intramolecular PK and [4 + 2] cyclization

Scheme 2. Catalytic Conversion of (*R*)-2b To Generate 3b



took place chemoselectively and stereoselectively to give **3b**. In **3b**, three new chiral carbon centers are generated whose formation is controlled by the original chiral propargylic center of (*R*)-**2b**. The two newly formed bridgehead hydrogens of **3b** have the *syn* configuration as shown (vide infra).

The structure of **3b** was established by high-resolution mass spectroscopic analysis and various ^{1}H and ^{13}C NMR spectroscopic analyses including COSY, NOESY, HSQC 2D NMR, and DEPT 135°. As shown in Figure 2, the observed NOE effects between the proton signals have allowed the determination of its structure. For detailed signal assignments, see the Supporting Information.

When the conversion of (*R*)-**2b** to **3b** was stopped early (in 5 h), the PK cyclization product **4b** was isolated and its steric structure was established by 2D COSY and NOESY NMR analyses. When **4b** was heated in DCE under reflux, no thermal intramolecular Diels–Alder reaction was observed. However, when $[RhCl(CO)_2]_2$ was added as the catalyst, **4b** was converted to **3b** smoothly in refluxing DCE.[30] This demonstrates that both the PK cycloaddition and the [4 + 2] cyclization steps require the Rh catalyst.

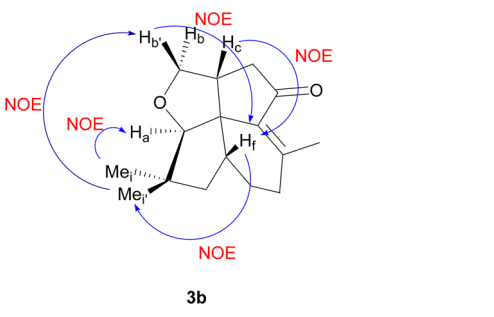
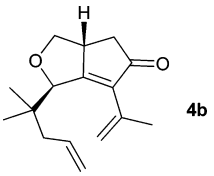
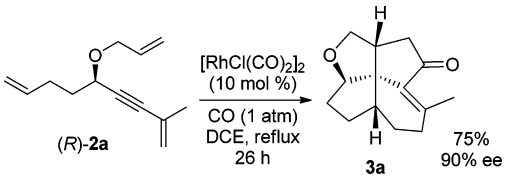


Figure 2. Observed NOE effects of **3b**.



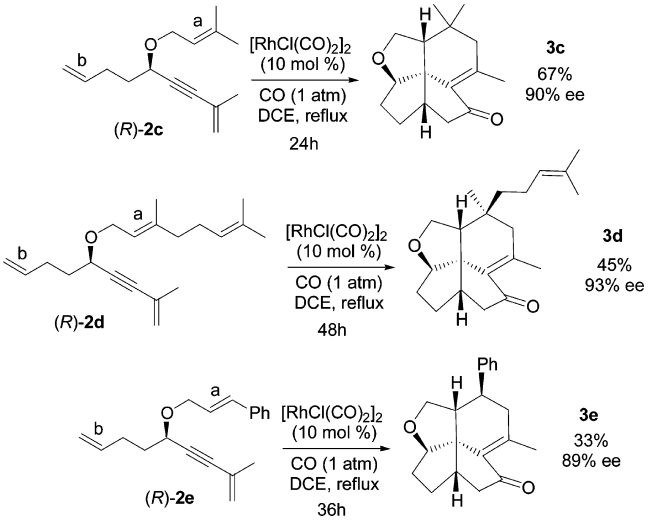
Similar to the conversion of (*R*)-**2b** to **3b**, when (*R*)-**2a** was treated with $[RhCl(CO)_2]_2$ and CO, compound **3a** was obtained as a single diastereomer in 75% yield and 90% ee (Scheme 3).[14] The stereochemistry of **3a** was assigned on the basis of the NMR analyses similar to those of **3b**.

Scheme 3. Catalytic Conversion of (*R*)-2a To Generate 3a



Compound (*R*)-**2c**, in which the allylic ether double bond was substituted with two additional methyl groups, was also subjected to the same reaction conditions catalyzed by $[RhCl(CO)_2]_2$ which generated **3c** as a single diastereomer in 67% yield and 90% ee (Scheme 4). The formation of **3c**

Scheme 4. Catalytic Conversions of (*R*)-2c–e



indicates that the PK reaction is sensitive to the substitution on the allylic ether double bond. The two methyl groups on the double bond *a* have inhibited its PK cycloaddition, which allows the PK reaction of the less substituted double bond *b* to take place first followed by the [4 + 2] cycloaddition of the resulting conjugated diene with the double bond *a* to give **3c**. Similarly, when compounds (*R*)-**2d** and (*R*)-**2e** were treated with $[RhCl(CO)_2]_2$ under CO, the corresponding products **3d** and **3e** were isolated in 45% (93% ee) and 33% (89% ee) yields, respectively.

The structure of **3e** was determined by high-resolution mass spectroscopic analysis and a variety of ^{1}H and ^{13}C NMR

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spectroscopic analyses including COSY, NOESY, HSQC 2D NMR, and DEPT 135°. As shown in Figure 3, the observed NOE effects between the proton signals have allowed the determination of its structure. For detailed signal assignments, see the Supporting Information.

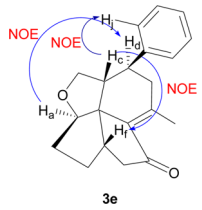
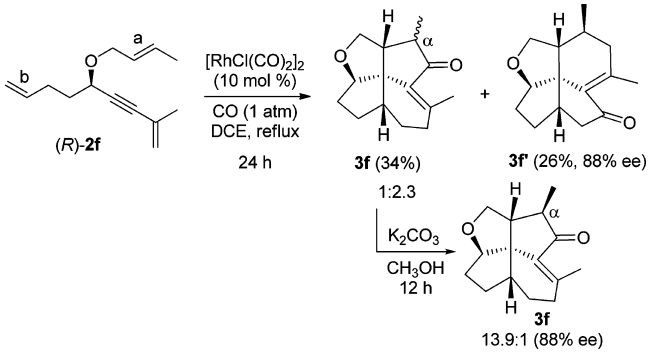


Figure 3. Observed NOE effects of **3e**.

We have also studied the reaction of (*R*)-**2f** that contains only one methyl group on the allylic ether double bond *a* (Scheme 5). The result shows that the mono methyl substitution led to the formation of both products **3f** and **3f′**. The product **3f** was found to contain a 1:2.3 mixture of two diastereomers attributed to the two epimers of the α methyl group. When a methanol solution of this 1:2.3 mixture of **3f** was stirred at room temperature with K_2CO_3, it was converted to a 13.9:1 mixture of **3f** with the α methyl group *up* as the major diastereomer. The stereochemistry of **3f** was determined by NMR analyses similar to those of **3b** and **3e**. The enantiomeric purities of both **3f** and **3f′** were found to be almost the same as that of the starting chiral propargylic alcohol.

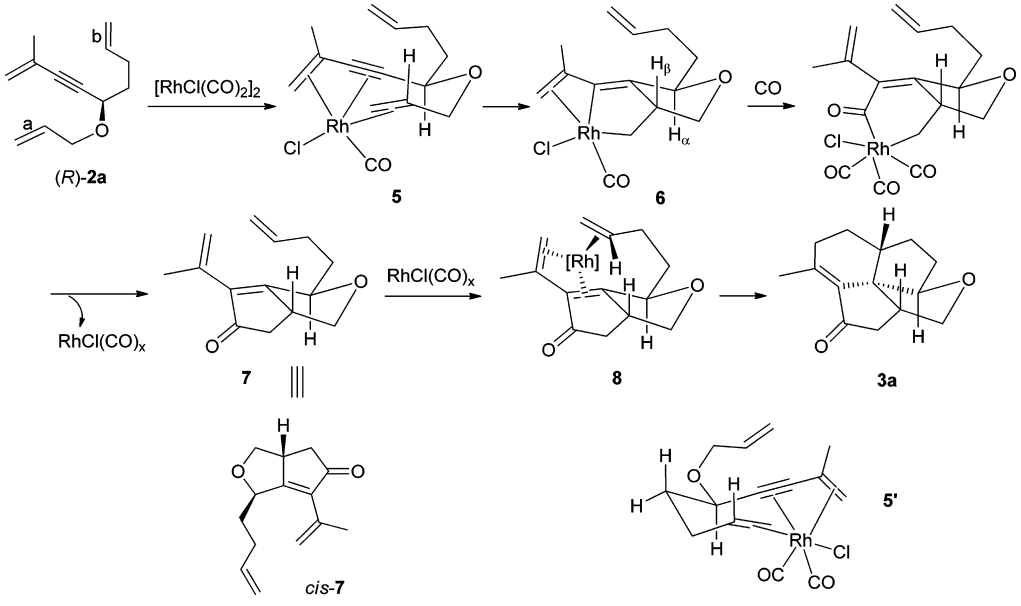
Scheme 5. Catalytic Conversion of (*R*)-2f



4. Proposed Mechanistic Explanation for the Chemoselectivity and Stereoselectivity of the Domino PK and [4 + 2] Cycloadditions. On the basis of the previous studies on the Rh-catalyzed PK reaction[13,27] and [4 + 2] cyclization,[30] mechanisms are proposed to illustrate the formation of the products **3a**–**e**. As shown in Scheme 6, coordination of (*R*)-**2a** with the metal center of the catalyst could generate a chairlike intermediate **5** in which the homoallylic substituent occupies a more favorable equatorial position. Oxidative coupling of the coordinated triple bond and double bond of **5** should give **6**. In this step, the *anti* configuration of H_α and H_β is produced. Migratory insertion of **6** with CO followed by reductive elimination should give the PK cycloaddition product *cis*-**7**. In the presence of the Rh catalyst, **7** could undergo a metal-catalyzed [4 + 2] cycloaddition via the intermediate **8** to give the product **3a** with the observed *exo*-Diels–Alder reaction stereochemistry.[30] In this reaction, when (*R*)-**2a** is treated with the Rh catalyst, **5′** is another possible chairlike intermediate in which the double bond *b* is coordinated instead of the double bond *a*. One of the possible factors that **5** is more favorable than **5′** might be the greater 1,3-diaxial interaction in **5′** than in **5**. The difference of the electronic effect in the formation of an ether ring verses a carbocycle should also be important for the observed chemoselectivity.

Previously, we reported that when a propargyl alcohol derived dienediyne compound **9** was treated with the Rh catalyst under CO, the PK cycloaddition product **10** was obtained as a 1:2 mixture of the *cis* and *trans* stereoisomers with the *trans* isomer being the major product (Scheme 7).[13b] This is in sharp contrast to that observed for (*R*)-**2a** which should only form the *cis* intermediate **7** in the production of **3a** as observed for the steric structure of **4b**. The formation of the *trans* product **10** from **9** was explained by proposing an

Scheme 6. Proposed Mechanism for the Rh(I)-Catalyzed Domino Cycloaddition of (*R*)-2a



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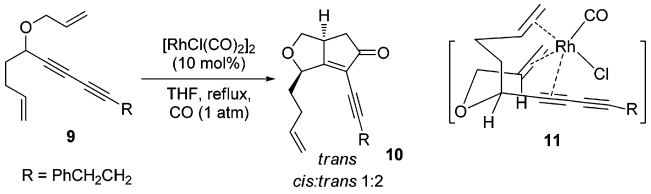
Scheme 7. Catalytic PK Reaction of the Dienediyne 9



intermediate **11** in which the homoallyl group occupies the axial position encouraged by its coordination to the Rh center. In order to explain the high *cis* selectivity in the PK reaction of (*R*)-**2a**, we propose that in the intermediate **5**, besides the coordination of the triple bond and the allyl ether double bond to the Rh center, the double bond of the conjugated enyne unit can also coordinate to the Rh metal center. This coordination discourages the coordination of the homoallyl double bond to the Rh center and encourages it to occupy the equatorial position as shown in **5**, leading to the predominate formation of *cis*-**7** rather than its *trans* stereoisomer like **10**.

When the substrate (*R*)-**2c** was used, because of the much greater steric hindrance for the double bond *a* to coordinate to the metal center, coordination of the less sterically hindered double bond *b* to the Rh center becomes more favorable to generate the chairlike intermediate **12** (Scheme 8). In **12**, the allyloxide group is placed at the equatorial position. The intermediate **12** can then undergo oxidative coupling to give **13**. In this step, the *anti* configuration of H_α and H_γ is produced. Migratory insertion of **13** with CO followed by reductive elimination should give the PK cycloaddition product **14**. In the presence of the Rh catalyst, **14** could undergo a metal-catalyzed [4 + 2] cycloaddition via the intermediate **15** to give the product **3c** with the observed *exo*-Diels–Alder reaction stereochemistry.

For compound (*R*)-**2f**, its two double bonds *a* and *b* should have similar activity with respect to the intramolecular PK cycloaddition. Thus, in the catalytic conversion of (*R*)-**2f** shown in Scheme 5, both mechanisms depicted in Schemes 6 and 8 might have been involved to give a mixture of products **3f** and **3f′**.

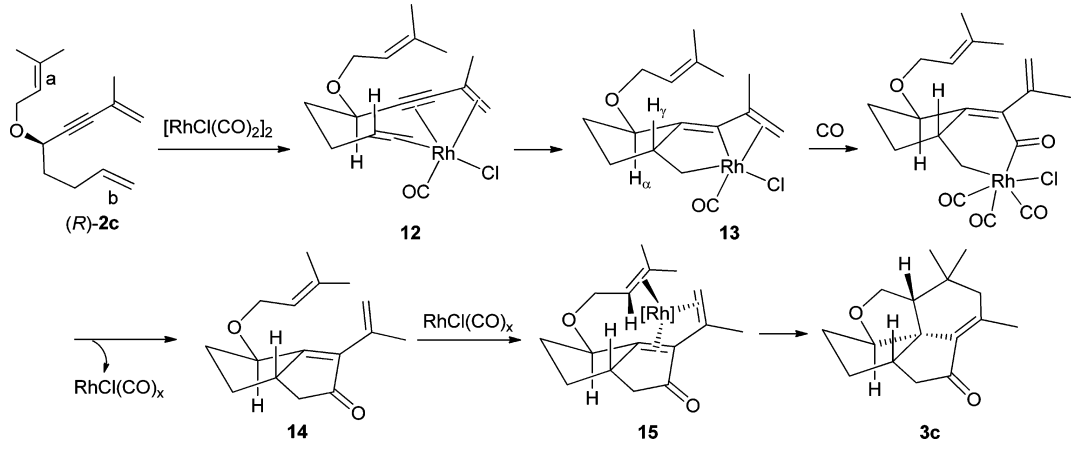
5. Catalytic Conversions of a Chiral Dienediyne (*R*)-17 in the Presence of $[RhCl(CO)_2]_2$. As shown in the above Rh-catalyzed reactions, the PK cycloaddition normally involves the coupling of one alkyne unit, one alkene unit, and CO to form a cyclopentenone. The coupling of two alkyne units with CO would generate a cyclopentadienone. Because of the anti-aromatic character of a cyclopentadienone structure, it has greatly reduced stability without metal coordination and its catalytic formation was much more difficult. Pd complexes were found to catalyze the diyne coupling with CO to generate cyclopentadienones either as nonisolated intermediates[31a,b] or double bond migrated products.[31c] Although Rh(I) catalysts were developed by Ojima in 1996 to catalyze the intramolecular coupling of diynes with CO, the reaction required the addition of a silane molecule which probably reduced one of the alkyne unit to an alkene to promote the coupling.[32] Ir(I) complexes were found to catalyze the intramolecular coupling of diynes with CO to generate either the bistriarylsilyl stabilized cyclopentadienones or the double bond migrated products, but poor efficiency was observed when $[Rh(COD)Cl]_2$ was used.[33] Since 1999, Chung has conducted an extensive study on the Co-catalyzed diyne coupling with CO to generate multicyclic products which might involve the formation of the reactive cyclopentadienone intermediates.[34]

We have prepared the optically active diyne (*R*)-**16** according to entry 5 of Table 1 by using the catalytic asymmetric alkyne addition to aldehyde. Treatment of (*R*)-**16** with ^{n}BuLi at −78 °C followed by reaction with allyl bromide gave the chiral dienediyne (*R*)-**17** (Scheme 9). When (*R*)-**17** was treated with $[RhCl(CO)_2]_2$ under CO, the tetracyclic product **18** was obtained in 36% yield as a single diastereomer.[14] A single crystal X-ray analysis of **18** has established its structure which is consistent with the NMR analysis data.[14] Formation of **18** demonstrates that in the first step the two alkyne units of (*R*)-**17** can couple with CO to presumably generate a cyclopentadienone intermediate prior to the subsequent [4 + 2] cyclization. Previously, Chung also reported that under 30 atm of CO at 130 °C $Co_2(CO)_8$ catalyzed the domino cyclization of racemic dienediynes to generate racemic multicyclic products similar to **18**.[34g,h]

SUMMARY

We have found that the highly enantioselective enyne addition to linear aliphatic aldehydes as well as other aldehydes can be achieved at room temperature by using the BINOL–$ZnEt_2$–$Ti(O^iPr)_4$–Cy_2NH catalyst system. We have further shown that this system is broadly applicable for the asymmetric reaction of other alkyl-, aryl-, and silylalkynes with structurally diverse

Scheme 8. Proposed Mechanism for the Rh(I)-Catalyzed Domino Cycloaddition of (*R*)-2c



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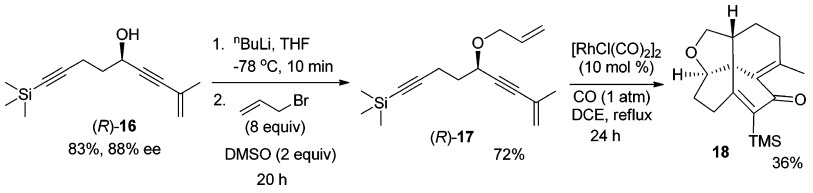
Scheme 9. Preparation of a Chiral Dienediyne and Its Catalytic Conversion



aldehydes. Using the propargylic alcohols prepared from the asymmetric enyne addition to linear aliphatic aldehydes we have prepared a series of optically active trienynes. These optically active trienynes are discovered to undergo highly chemoselective and stereoselective domino PK and [4 + 2] cycloaddition in the presence of a Rh catalyst to generate optically active multicyclic products. The Rh(I) catalyst is also found to catalyze the coupling of a diyne with CO followed by [4 + 2] cycloaddition. This study could potentially provide an efficient method for the asymmetric synthesis of polyquinanes with a quaternary chiral carbon center.

EXPERIMENTAL SECTION

General Procedure for Preparation of Racemic Propargylic Alcohols from Alkyne Addition to Aldehydes. The racemic propargylic alcohols are prepared according to the reported procedure.[13a] An alkyne (1 mmol, 2 equiv) was weighed into a tared flask and placed under nitrogen atmosphere. The alkyne was dissolved in THF (5 mL) and cooled to −78 °C. ^{n}BuLi (2.5 M in hexane, 1.4 equiv) was added, and the reaction mixture was stirred for 30 min. An aldehyde (1 mmol) was then added. After 1 h, the reaction was quenched with saturated aqueous ammonium chloride solution (5 mL) and extracted three times with CH_2Cl_2. The organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel.

General Procedure for the (*S*)-BINOL-Catalyzed Enantioselective Alkyne Additions. The catalytic alkyne additions were conducted according to the reported procedure.[13a] Under nitrogen atmosphere, (*S*)-BINOL was weighed into a tared flask and dissolved in Et_2O (3 mL). An alkyne, Cy_2NH, and Et_2Zn were added, and the mixture was stirred for 16 h (or 48 h). Then, $Ti(O^iPr)_4$ was added, followed by an aldehyde (0.25 mmol), and the mixture was stirred for another 4 h (for the stoichiometry of the catalyst and metal reagents in the reactions of various alkynes, see Table 1). The reaction was quenched with saturated aqueous ammonium chloride and extracted three times with CH_2Cl_2. The organic layer was dried with anhydrous sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel eluted with hexanes/ethyl acetate to give the product in 56−99% yield and 81 to >99% ee.

Characterizations of the New Optical Active Propargylic Alcohol Products Generated from the Alkyne Additions to Aldehydes in Table 1. *2-Methyldodec-1-en-3-yn-5-ol (Entry 1).* Colorless oil, 41 mg, 85% yield. 90% ee determined by HPLC analysis: Chiralpak AD-H column, 98:2 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 12.9, t_{minor} = 11.9. $[\alpha]^{22}_D$ = −4.5 (*c* = 1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.27 (m, 1H), 5.21 (m, 1H), 4.46 (t, 1H, *J* = 6.6 Hz), 2.02 (s, 1H), 1.87 (dd, 3H, *J* = 1.1 Hz), 1.74−1.66 (m, 2H), 1.48−1.40 (m, 2H), 1.34−1.22 (m, 8H), 0.87 (t, 3H, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 126.5, 122.3, 89.5, 86.2, 63.1, 38.1, 32.0, 29.4, 25.4, 23.7, 22.9, 14.3. HRMS (ESI) for $C_{13}H_{23}O$ (MH^+): calcd 195.1749, found 195.1744.

1-Cyclohexyl-4-methylpent-4-en-2-yn-1-ol (Entry 3). Colorless oil, 36 mg, 81% yield. 89% ee determined by HPLC analysis: Chiralpak AD-H column, 98:2 hexanes/ ^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 16.0, t_{minor} = 14.3. $[\alpha]^{23}_D$ = −11.4 (*c* = 1.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.29−5.26 (m, 1H), 5.23−5.19 (m, 1H), 4.24 (d, 1H, *J* = 6.0 Hz), 1.95 (s, 1H), 1.88−1.74 (m, 7H), 1.65−1.51 (m, 2H), 1.27−1.03 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 126.6, 122.2, 88.5, 87.0, 67.7, 44.4, 28.8, 28.4, 26.6, 26.1, 23.7. HRMS (ESI) for $C_{12}H_{19}O$ (MH^+): calcd 179.1436, found 179.1431.

4-Methyl-1-phenylpent-4-en-2-yn-1-ol (Entry 6). Colorless oil, 36 mg, 84% yield. 96% ee determined by HPLC analysis: Chiralcel OD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 7.7 t_{minor}= 6.0. $[\alpha]^{24}_D$ = 6.3 (*c* = 1.80, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57−7.54 (m, 2H), 7.42−7.34 (m, 3H), 5.57 (d, 1H, *J* = 6.0 Hz), 5.39−5.35 (m, 1H), 5.30−5.27 (m, 1H), 2.44 (d, 1H, *J* = 6.3 Hz), 1.95−1.92 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 128.9, 128.6, 126.9, 126.4, 122.9, 88.0, 87.9, 65.2, 23.6. HRMS (ESI) for $C_{12}H_{13}O$ (MH^+): calcd 137.0966, found 137.0968.

4-Methyl-1-(p-tolyl)pent-4-en-2-yn-1-ol (Entry 7). Colorless oil, 43 mg, 92% yield. 97% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} =10.3, t_{minor} = 8.4. $[\alpha]^{22}_D$ = 9.9 (c = 1.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, 2H, *J* = 8.1 Hz), 7.19 (d, 2H, *J* = 8.1 Hz), 5.54 (d, 1H, *J* = 5.1 Hz), 5.36 (s, 1H) 5.27 (s, 1H), 2.37 (s, 3H), 2.30 (d, 1H, *J* = 5.7 Hz), 1.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 138.0, 129.5, 126.9, 126.4, 122.8, 88.1, 87.8, 65.0, 23.6, 21.4. HRMS (ESI): for $C_{13}H_{15}O$ (MH^+) calcd 187.1123, found 187.1120.

4-Methyl-1-(naphthalen-2-yl)pent-4-en-2-yn-1-ol (Entry 8). White solid, 53 mg, 96% yield. 98% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 16.8, t_{minor} = 12.1. Mp = 45−46 °C. $[\alpha]^{22}_D$ = −2.5 (*c* = 2.20, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.90−7.82 (m, 3H), 7.67 (dd, 1H, *J* = 7.8, 1.8 Hz), 7.54−7.46 (m, 2H), 5.74 (d, 1H, *J* = 4.5 Hz), 5.39 (d, 1H, *J* = 0.9 Hz), 5.32 −5.27 (m, 1H), 2.39 (d, 1H, *J* = 8.1 Hz), 1.95 (t, 3H, *J* = 2.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 133.5, 133.4, 128.8, 128.4, 127.9, 126.5, 126.4, 125.7, 124.9, 123.0, 88.3, 87.9, 23.6. HRMS (ESI) for $C_{16}H_{15}O$ (MH^+) calcd 223.1123, found 223.1126.

4-Methyl-1-(naphthalen-1-yl)pent-4-en-2-yn-1-ol (Entry 9). Colorless oil, 43 mg, 78% yield. 97% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 18.1, t_{minor} = 11.0. $[\alpha]^{23}_D$ = −7.4 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31(d, 1H, *J* = 8.7 Hz), 7.93−7.85 (m, 1H), 7.85 (d, 2H, *J* = 7.5 Hz), 7.61−7.46 (m, 3H), 6.22 (d, 1H, *J* = 4.8 Hz), 5.40 (s, 1H), 5.33−5.29 (m, 2H), 2.71 (d, 1H, *J* = 5.1 Hz), 1.96 (t, 3H, *J* = 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.3, 130.8, 129.6, 129.0, 126.7, 126.5, 126.1, 125.5, 124.9, 124.2, 122.9, 88.7, 87.9, 63.4, 23.6. HRMS (ESI): for $C_{16}H_{15}O$ (MH^+) calcd 223.1123, found 223.1125.

1-(4-Chlorophenyl)-4-methylpent-4-en-2-yn-1-ol (Entry 10). Colorless oil, 48 mg, 93% yield. 91% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 9.8, t_{minor} = 8.2. $[\alpha]^{23}_D$ = 12.5 (*c* = 1.84, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, 2H, *J* = 8.7 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 5.55 (d, 1H, *J* = 6.0 Hz), 5.35 (s, 1H), 5.31−5.27 (m, 1H), 2.36 (d, 1H, *J* = 6.0 Hz), 1.91 (t, 3H, *J* = 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 134.4, 129.0, 128.3, 126.2, 123.2, 88.3, 87.4, 64.5 23.5. HRMS (ESI): for $C_{12}H_{12}ClO$ (MH^+) calcd 207.0577, found 207.0572.

1-(3-Chlorophenyl)-4-methylpent-4-en-2-yn-1-ol (Entry 11). Colorless oil, 43 mg, 83% yield. 97% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 8.6, t_{minor} = 7.5. $[\alpha]^{23}_D$ = 16.4 (*c* = 1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, 1H, *J* = 0.6

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Hz), 7.45−7.37 (m, 1H), 7.33−7.27(m, 2H), 5.54 (s, 1H), 5.36 (s, 1H), 5.31−5.27 (m, 2H), 2.66 (s, 1H), 1.94−1.89 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 134.7, 130.1, 128.7, 127.1, 126.1, 125.0, 123.3, 88.4, 87.2, 64.4, 23.5. HRMS (ESI) for $C_{12}H_{12}ClO$ (MH^+): calcd 207.0577, found 207.0574.

1-(2-Ethoxyphenyl)-4-methylpent-4-en-2-yn-1-ol (Entry 12). Colorless oil, 51 mg, 94% yield. 92% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} =12.5, t_{minor} = 11.7. $[\alpha]^{23}_D$ = 10.8 (*c* = 2.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57−7.51 (m, 1H), 7.32−7.25 (m, 1H), 6.97 (td, 1H, *J* = 1.5, 0.9 Hz), 6.90 (d, 2H, *J* = 8.4 Hz), 5.80 (d, 1H, *J* = 6.0 Hz), 5.34 (s, 1H), 5.25 (t, 1H, *J* = 1.8 Hz), 4.18−4.06 (m, 2H), 3.24 (d, 1H, *J* = 6.3 Hz), 1.92 (t, 3H, *J* = 1.2 Hz), 1.45 (t, 3H, J=7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 129.8, 129.2, 128.2, 126.7, 122.4, 121.0, 112.0, 87.7, 87.3, 64.2, 62.0, 23.6, 15.1. HRMS (ESI) for $C_{14}H_{17}O_2$ (MH^+): calcd 217.1299, found 217.1298.

(E)-6-Methyl-1-phenylhepta-1,6-dien-4-yn-3-ol (Entry 13). White solid, 40 mg, 81% yield. 90% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min. λ = 254 nm, retention time: t_{major} = 15.0, t_{minor} = 12.6. Mp = 48−49 °C. $[\alpha]^{24}_D$ = 1.4 (*c* = 1.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.40 (m, 2H), 7.36−7.25 (m, 3H), 6.77 (d, 1H, *J* = 15.9 Hz), 6.32 (dd, 1H, *J* = 12.6, 6.0 Hz), 5.37 (d, 1H, *J* = 0.3 Hz), 5.31−5.26 (m, 1H), 5.18 (t, 1H, *J* = 5.0 Hz), 2.35 (d, 1H, *J* = 4.8 Hz), 1.95−1.91 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.3, 132.1, 128.8, 128.4, 128.3, 127.1, 126.4, 123.0, 87.8, 87.2, 53.5, 23.6. HRMS (ESI) for $C_{14}H_{15}O$ (MH^+): calcd 119.1123, found 223.1124.

(E)-2,6-Dimethyl-1-phenylhepta-1,6-dien-4-yn-3-ol (Entry 14). Colorless oil, 45 mg, 85% yield. 98% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} =11.3, t_{minor} = 8.9. $[\alpha]^{23}_D$ = −36.00 (*c* = 1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.30 (m, 4H), 7.28−7.22 (m, 1H), 6.71 (s, 1H), 5.36 (s, 1H), 5.31−5.26 (m, 1H), 5.05 (d, 1H, *J* = 5.1 Hz), 2.30 (d, 1H, *J* = 5.7 Hz), 2.02 (d, 3H, *J* = 1.5 Hz), 1.93 (t, 3H, *J* = 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.3, 137.0, 129.3, 128.4, 127.4, 127.0, 126.4, 122.8, 87.7, 87.3, 68.9, 23.6, 14.4. HRMS (ESI) for $C_{15}H_{17}O$ (MH^+): calcd 213.1279, found 213.1281.

7-Phenylhept-4-yn-3-ol (Entry 28). Colorless oil, 47 mg, 99% yield. 84% ee determined by HPLC analysis: Chiralcel OD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 220 nm, retention time: t_{major} = 7.5, t_{minor} = 13.3. $[\alpha]^{22}_D$ = 6.2 (*c* = 1.55, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−7.28 (m, 2H), 7.23−7.21 (m, 3H), 4.29 (s, 1H), 2.83 (t, 2H, *J* = 7.5 Hz), 2.51 (td, 2H, *J* = 7.5, 1.5 Hz), 1.80 (d, 1H, *J* = 3.6 Hz), 1.75−1.60 (m, 2H), 0.96 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 128.7, 128.6, 126.5, 85.0, 82.1, 64.2, 35.3, 31.3, 21.1, 9.7. HRMS (ESI) for $C_{13}H_{17}O$ (MH^+): calcd 189.1279, found 189.1280.

1-(2-Chlorophenyl)-5-phenylpent-2-yn-1-ol (Entry 37). Colorless oil, 61 mg, 90% yield. 88% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 225 nm, retention time: t_{major} = 14.1, t_{minor} = 11.7. $[\alpha]^{23}_D$ = −16.5 (*c* = 2.72, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67−7.63 (m, 1H), 7.39−7.36 (m, 1H), 7.33−7.20 (m, 7H), 5.82−5.77 (m, 1H), 2.87 (t, 2H, *J* = 7.5 Hz), 2.58 (td, 2H, *J* = 7.5, 2.1 Hz), 2.46 (d, 1H, *J* = 5.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 138.5, 133.0, 129.9, 129.7, 128.8, 128.6, 127.4, 126.6, 87.2, 79.9, 62.3, 35.0, 21.2. HRMS (ESI) for $C_{17}H_{16}ClO$ (MH^+): calcd 271.0890, found 271.0894.

1-(2-Ethoxyphenyl)-5-phenylpent-2-yn-1-ol (Entry 38). Colorless oil, 67 mg, 96% yield. 93% ee determined by HPLC analysis: Chiralcel OD column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 11.0, t_{minor} = 16.9. $[\alpha]^{23}_D$ = 14.7 (*c* = 1.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (dd, 1H, *J* = 7.5, 1.2 Hz), 7.33−7.21 (m, 6H), 6.95 (t, 1H, *J* = 7.5 Hz), 6.89 (d, 1H, *J* = 8.1 Hz), 4.19−4.02 (m, 2H), 3.12 (d, 1H, *J* = 5.4 Hz), 2.89 (t, 3H, *J* = 7.5 Hz), 2.60 (td, 2H, *J* = 7.5, 1.5 Hz), 1.45 (t, 3H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 140.9, 129.7, 129.5, 128.8, 128.6, 128.2, 126.5, 120.9, 111.8, 86.4, 80.2, 64.1, 61.8, 35.2, 21.4, 15.2. HRMS (ESI) for $C_{19}H_{21}O_2$ (MH^+): calcd 281.1542, found 281.1540.

(E)-2-Methyl-1,7-diphenylhept-1-en-4-yn-3-ol (Entry 40). Colorless oil, 68 mg, 99% yield. 99% ee determined by HPLC analysis: Chiralcel OD-H column, 90:10 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 12.0, t_{minor} = 31.9. $[\alpha]^{23}_D$ = −15.5 (*c* = 1.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.23 (m, 10H), 6.66 (s, 1H), 4.91 (s, 1H), 2.87 (t, 2H, *J* = 7.5 Hz), 2.58 (td, 2H, *J* = 7.5, 1.5 Hz), 2.03 (s, 1H), 1.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 137.5, 129.3, 128.72, 128.66, 128.4, 127.0, 126.6, 86.6, 80.3, 68.8, 35.2, 21.3, 14.3. HRMS (ESI) for $C_{20}H_{21}O$ (MH^+): calcd 277.1592, found 277.1589.

1-(m-Tolyl)hept-2-yn-1-ol (Entry 45). Colorless oil, 31 mg, 61% yield. 98% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate =1.0 mL/min, λ = 254 nm, retention time: t_{major} = 9.7, t_{minor} = 8.6. $[\alpha]^{22}_D$ = 18.1 (*c* = 0.93, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.32 (m, 2H), 7.27 (t, 1H, *J* = 7.5 Hz), 7.14 (d, 1H, *J* = 7.2 Hz), 5.41 (s, 1H), 2.38 (s, 3H), 2.35 (br, 1H), 2.29 (td, 2H, *J* = 6.9, 1.8 Hz), 1.57−1.41 (m, 4H), 0.94 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5, 138.4, 129.2, 128.7, 127.6, 123.9, 87.7, 80.3, 65.0, 30.9, 22.2, 21.7, 18.8, 13.9.

1-(4-Chlorophenyl)hept-2-yn-1-ol (Entry 48). Colorless oil, 38 mg, 68% yield. 97% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate =1.0 mL/min, λ = 254 nm, retention time: t_{major} = 11.0, t_{minor} = 9.3. $[\alpha]^{22}_D$ = 19.4 (*c* = 1.54, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, 2H, *J* = 8.4 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 5.41 (s, 1H), 2.34−2.20 (m, 3H), 1.57−1.35 (m, 4H), 0.91 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0, 134.2, 128.9, 128.3, 88.3, 79.8, 64.3, 30.8, 22.22, 18.7, 13.8.

1-(3-Chlorophenyl)hept-2-yn-1-ol (Entry 49). Colorless oil, 45 mg, 81% yield. 95% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate =1.0 mL/min, λ = 254 nm, retention time: t_{major} = 9.6, t_{minor} = 8.7. $[\alpha]^{22}_D$ = 20.1 (*c* = 1.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56−7.52 (m, 1H), 7.43−7.36 (m, 1H), 7.32−7.26 (m, 2H), 5.41 (s, 1H), 2.39 (br, 1H), 2.27 (td, 2H, *J* = 6.9, 2.1 Hz), 1.58−1.38 (m, 4H), 0.92 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 134.6, 130.0, 128.5, 127.1, 125.0, 88.4, 79.6, 64.3, 30.8, 22.2, 18.7, 13.8. HRMS (ESI) for $C_{13}H_{16}ClO$ (MH^+): calcd 223.0890, found 223.0888.

1-(2-Ethoxyphenyl)hept-2-yn-1-ol (Entry 51). Colorless oil, 55 mg, 94% yield. 92% ee determined by HPLC analysis: Chiralpak AD-H column, 90:10 hexanes/^{i}PrOH, flow rate =1.0 mL/min, λ = 254 nm, retention time: t_{major} = 12.3, t_{minor} = 10.3. $[\alpha]^{22}_D$ = 7.48 (*c* = 1.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (dd, 1H, *J* = 7.5, 1.5 Hz), 7.26 (td, 1H, *J* = 7.8, 1.5 Hz), 6.96 (td, 1H, *J* = 7.5, 0.9 Hz), 6.87 (d, 1H, *J* = 8.4 Hz), 5.71 (dt, 1H, *J* = 6.0, 1.8 Hz), 4.18−4.02 (m, 2H), 3.13 (d, 1H, *J* = 6.0 Hz), 2.28 (td, 2H, *J* = 6.9, 1.8 Hz), 1.59−1.37 (m, 7H), 0.92 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 129.7, 129.6, 128.1, 120.9, 111.8, 87.2, 79.5, 64.1, 61.7, 30.9, 22.2, 18.8, 15.1, 13.9. HRMS (ESI) for $C_{15}H_{20}O_2$ (MH^+): calcd 232.1463, found 232.1460.

2-Methyldec-2-en-5-yn-4-ol (Entry 55). Colorless oil, 27 mg, 65% yield. 87% ee determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes/^{i}PrOH, flow rate =0.5 mL/min, λ = 254 nm, retention time: t_{major} = 20.2, t_{minor} = 18.6. $[\alpha]^{23}_D$ = −121.9 (*c* = 0.61, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.65 (qd, 1H, *J* = 6.0, 0.9 Hz), 4.72 (s, 1H), 2.22 (t, 2H, *J* = 6.6 Hz), 1.90 (s, 1H), 1.72 (d, 3H, *J* = 0.9 Hz), 1.62 (d, 3H, *J* = 6.9 Hz), 1.51−1.35 (m, 4H), 0.89 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 122.3, 86.9, 79.7, 68.5, 30.9, 22.2, 18.7, 13.8, 13.5, 12.0. HRMS (ESI) for $C_{11}H_{19}O$ (MH^+): calcd 167.1436, found 167.1433.

Preparation and Characterization of the Optically Active Trienynes (*R*)-2c−f. *(R)-2-Methyl-5-((3-methylbut-2-en-1-yl)oxy)-nona-1,8-dien-3-yne, (R)-**2c**.* Under nitrogen, NaH (60% w/w) (102 mg, 2.55 mmol, 1.7 equiv) was weighed and dissolved in dry THF (5 mL) in a flame-dried, two-necked, round-bottom flask and cooled in an ice bath. Then a dry THF solution (5 mL) of the optical active propargylic alcohol 2-methylnona-1,8-dien-3-yn-5-ol (entry 2 in Table 1) (225 mg, 1.5 mmol) was injected into the flask, followed by 3,3-dimethylallyl bromide (0.21 mL, 1.8 mmol, 1.2 equiv). The mixture was heated at 70 °C for ∼12 h. After the reaction was complete, it was quenched with ammonium chloride (10 mL saturated water) and

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extracted three times with CH_2Cl_2 (3 × 10 mL). The organic layer was dried with sodium sulfate, concentrated with rotary evaporation and purified by using column chromatography to give (*R*)-**2c** as a colorless liquid in 76% yield (248 mg). $[\alpha]^{25}_D$ = 89.8 (*c* = 0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89−5.75 (m, 1H), 5.37−5.33 (m, 1H), 5.30−5.26 (m, 1H), 5.23−5.19 (m, 1H), 5.08−4.95 (m, 2H), 4.26−4.12 (m, 2H), 4.03−3.91 (m, 1H), 2.22 (q, 2H, *J* = 7.5 Hz), 1.89 (s, 3H), 1.84−1.80 (m, 2H), 1.75 (s, 3H), 1.72−1.68 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 137.9, 126.7, 122.0, 121.0, 115.2, 87.7, 87.2, 68.4, 65.3, 35.1, 29.8, 26.1, 23.7, 18.2. HRMS (ESI) for $C_{15}H_{23}O$ (MH^+): calcd 219.1749, found 219.1752.

*(R,E)-5-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-2-methylnona-1,8-dien-3-yne, (R)-**2d***. By following the procedure used to synthesize (*R*)-**2c**, compound (*R*)-**2d** was prepared from the optical active propargylic alcohol 2-methylnona-1,8-dien-3-yn-5-ol (entry 2 in Table 1) (165 mg, 1.1 mmol), NaH (60% w/w) (75 mg, 1.87 mmol, 1.7 equiv), and geranyl bromide (0.19 mL, 0.94 mmol, 0.85 equiv). The reaction mixture was stirred at room temperature instead of heating to give (*R*)-**2d** as a colorless liquid in 65% yield (204 mg). $[\alpha]^{24}_D$ = 83.1 (*c* = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87−3.71 (m, 1H), 5.36−5.30 (m, 1H), 5.29−5.25 (m, 1H), 5.22−5.18 (m,1H), 5.08−4.94 (m, 3H), 4.24−4.15 (m, 2H), 4.05−3.97 (m, 1H), 2.21 (q, 2H, *J* = 7.2 Hz), 2.10−2.05 (m, 4H), 1.90−1.86 (m, 3H), 1.85−1.81 (m, 2H), 1.69 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 138.0, 131.7, 126.7, 124.2, 121.9, 120.1, 115.2, 87.7, 87.1, 68.2, 65.2, 39.9, 35.1, 29.8, 26.6, 25.9, 23.7, 17.9, 16.6. HRMS (ESI) for $C_{20}H_{31}O$ (MH^+): calcd 287.2375, found 287.2384.

*(R,E)-(3-((2-Methylnona-1,8-dien-3-yn-5-yl)oxy)prop-1-en-1-yl)-benzene, (R)-**2e***. By following the procedure used to synthesize (*R*)-**2d**, compound (*R*)-**2e** was obtained from the optical active propargylic alcohol 2-methylnona-1,8-dien-3-yn-5-ol (entry 2 in Table 1) (195 mg, 1.3 mmol), NaH (60% w/w) (88 mg, 2.21 mmol, 1.7 equiv), and cinnamyl bromide (205 mg, 1.04 mmol, 0.8 equiv) to give (*R*)-**2e** as a light yellow oil in 68% yield (235 mg). $[\alpha]^{23}_D$ = 87.2 (*c* = 1.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46−7.42 (m, 2H), 7.38−7.34 (m. 2H), 7.30−7.26 (m, 1H), 6.69 (d, 1H, *J* = 15.9 Hz), 6.39−6.31 (m, 1H), 5.92−5.86 (m, 1H), 5.84 (s, 1H), 5.30 (q, 1H, *J* = 1.5 Hz), 5.07−5.03 (m, 2H), 4.47 (ddt, 1H, *J* = 12.6, 5.7, 1.5 Hz), 4.32 (t, 1H, *J* = 6.6 Hz), 4.19 (ddt, 1H, *J* = 12.6, 6.6, 1.2 Hz), 2.34−2.29 (m, 2H), 2.03−1.89(m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 137.0, 132.9, 128.8, 127.4, 126.8, 126.7, 126.1, 122.3, 115.4, 87.6, 87.5, 69.6, 68.8, 35.2, 29.9, 23.8. HRMS (ESI) for $C_{19}H_{23}O$ (MH^+): calcd 267.1749, found 267.1748.

*(R,E)-5-(But-2-en-1-yloxy)-2-methylnona-1,8-dien-3-yne, (R)-**2f***. By following the procedure used to synthesize (*R*)-**2d**, compound (*R*)-**2f** was prepared from the optical active propargylic alcohol, entry 2 (150 mg, 1 mmol), NaH 60% w/w (68 mg, 1. Seven mmol, 1.7 equiv) and crotyl bromide (0.15 mL, 1.5 mmol, 1.5 equiv) to give (*R*)-**2f** as a colorless oil in 78% yield (159 mg). $[\alpha]^{24}_D$ = 81.1 (*c* = 0.57, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89−5.54 (m, 3H), 5.28 (s, 1H), 5.24−5.20 (m, 1H), 5.07−4.95 (m, 2H), 4.20−4.14 (m, 2H), 3.41−3.85 (m, 1H), 2.22 (q, 2H, *J* = 7.2 Hz), 1.89 (d, 3H, *J* = 0.6 Hz), 1.85−1.77 (m, 2H), 1.71 (d, 3H, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 130.1, 127.5, 126.6, 122.1, 115.2, 87.5, 87.2, 69.6, 68.4, 35.1, 29.7, 23.7, 18.0. HRMS (EI) for $C_{14}H_{20}O$ (M): calcd 204.1514, found 204.1511.

General Procedure for the Rh(I)-Catalyzed Domino Pauson−Khand/[4 + 2] Cycloaddition. Under nitrogen, a trienyne or diendiyne (0.25 mmol) and $[Rh(CO)_2Cl]_2$ (9.8 mg, 0.10 equiv) were weighed into a tared two-necked round-bottom flask and dissolved in DCE (5 mL). The flask was fitted with reflux condenser fit with a septum, and the side arm of the flask was also fitted with a septum. The solution was bubbled with CO gas for 2 min through the side arm fitted with septum and a vent needle in the septum of the reflux condenser. Then, the solution was placed under CO atmosphere by using a balloon. After the reaction mixture was heated at 65 °C to reflux temperature for 26−72 h, it was cooled to room temperature and the CO was released cautiously in the hood. The reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel.

Characterizations of the Pauson−Khand/[4 + 2] Cycloaddition Products 3c−f′. *3c*. Colorless oil, 41 mg, 67% yield. 90% ee determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 10.4, t_{minor} = 8.3. $[\alpha]^{24}_D$ = 95.9 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.99 (dd, 1H, *J* = 9.0, 7.2 Hz), 3.77 (d, 1H, *J* = 4.8 Hz), 3.78 (dd, 1H, *J* = 10.8, 9.0 Hz,), 2.58 (dd, 1H, *J* = 19.8, 11.4 Hz), 2.42−2.37 (m, 1H), 2.27 (d, 1H, *J* = 16.8 Hz), 2.17 (d, 3H, *J* = 0.6 Hz), 2.11−2.05 (m, 1H), 1.99 (dd, 1H, *J* = 7.2, 1.8 Hz), 1.95 (dd, 1H, *J* = 19.8, 5.4 Hz), 1.88−1.85 (m, 1H), 1.68−1.59 (m, 3H), 0.93 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.6, 145.9, 134.9, 93.2, 70.3, 62.5, 55.7, 44.3, 43.3, 42.8, 33.0, 30.7, 30.5, 27.0, 26.9, 20.7. HRMS (ESI) for $C_{16}H_{23}O_2$ (MH^+): calcd 247.1698, found 247.1690.

3d. Colorless oil, 35 mg, 45% yield. 93% ee determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 9.1, t_{minor} = 7.1. $[\alpha]^{24}_D$ = 63.1 (*c* = 0.60, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.00−4.96 (m, 1H), 3.98 (dd, 1H, *J* = 9.0, 7.8 Hz), 3.76 (d, 1H, *J* = 4.2 Hz), 3.87 (dd, 1H, *J* = 10.5, 9.3 Hz), 2.59 (dd, 1H, *J* = 19.8, 11.4 Hz), 2.42−2.37 (m, 1H), 2.21−2.16 (m, 4H), 2.12−2.06 (m, 2H), 1.95 (dd, 1H, *J* = 19.8, 6.0 Hz), 1.91−1.81 (m, 3H), 1.77−1.71 (m, 1H), 1.66 (s, 3H), 1.62−1.58 (m, 2H), 1.55 (s, 3H), 1.20−1.15 (m, 1H), 1.07−1.02 (m, 1H), 0.91 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.5, 145.3, 135.4, 131.7, 124.2, 93.3, 70.0, 62.5, 54.3, 44.4, 43.4, 40.6, 38.3, 35.9, 30.8, 30.4, 25.7, 23.3, 22.2, 20.6, 17.5. HRMS (ESI) for $C_{21}H_{31}O_2$ (MH^+): calcd 315.2324, found 315.2325.

3e. White solid, 24 mg, 33% yield. 89% ee determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 13.1, t_{minor} = 14.6. $[\alpha]^{24}_D$ = 32.6 (*c* = 0.40, $CHCl_3$). Mp: 151−152 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (t, 2H, *J* = 7.5 Hz), 7.23 (t, 1H, *J* = 7.2 Hz), 7.18 (d, 2H, *J* = 7.2 Hz), 4.99 (d, 1H, *J* = 3.0 Hz), 3.81 (dd, 1H, *J* = 8.7, 4.5 Hz), 3.62 (d, 1H, *J* = 8.4 Hz), 2.98 (td, 1H, *J* = 10.2, 6.0 Hz), 2.78 (dd, 1H, *J* = 19.8, 11.4 Hz), 2.63 (dd, 1H, *J* = 19.8, 6.0 Hz), 2.52−2.49 (m, 1H), 2.37 (dd,1H, *J* = 19.5, 10.5 Hz), 2.32 (dd, 1H, *J* = 10.8, 4.2 Hz), 2.08 (s, 3H), 2.05−1.97 (m, 3H), 1.72−1.68 (m, 1H), 1.64−1.61 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.5, 146.5, 144.0, 133.4, 128.7, 127.9, 126.7, 89.9, 72.6, 61.9, 50.3, 45.4, 42.6, 42.1, 41.6, 34.0, 32.6, 19.2. HRMS (ESI) for $C_{20}H_{23}O_2$ (MH^+): calcd 295.1698, found 295.1695.

3f. Colorless oil, 20 mg, 34% yield. 88% ee determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 15.9, t_{minor} = 12.1. $[\alpha]^{24}_D$ = −39.5 (*c* = 0.65, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.15 (dd, 1H, *J* = 4.8 Hz), 4.05 (dd, 1H, *J* = 9.0, 4.8 Hz), 3.88 (d, 1H, *J* = 9.0 Hz), 2.22 (s, 3H), 2.20−2.03 (m, 6H), 1.86−1.82 (m, 1H), 1.79−1.72 (m, 1H), 1.63−1.58 (m, 2H), 1.53−1.47 (m, 1H), 1.13 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 207.9, 150.6, 133.6, 90.9, 72.7, 61.0, 56.2, 48.4, 41.7, 34.2, 33.3, 31.5, 28.8, 20.1, 14.9. HRMS (ESI) for $C_{15}H_{21}O_2$ (MH^+): calcd 233.1542, found 233.1537.

3f′. Colorless oil, 15 mg, 26% yield. 88% ee determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes/^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 11.8, t_{minor} = 10.2. $[\alpha]^{24}_D$ = 36.9 (*c* = 0.44, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.98 (dd, 1H, *J* = 8.4, 4.8 Hz), 3.91 (d, 1H, *J* = 4.8 Hz), 3.76 (dd, 1H, *J* = 9.0, 3.6 Hz), 2.66 (dd, 1H, J =19.8, 11.4 Hz), 2.43−2.37 (m, 2H), 2.14 (s, 3H), 2.07−2.01 (m, 1H), 1.96−1.92 (m, 2H), 1.91−1.85 (m, 3H), 1.63−1.57 (m, 2H), 0.92 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.8, 146.7, 133.5, 90.8, 72.4, 61.5, 52.1, 44.7, 43.6, 39.4, 32.8, 31.8, 29.5, 20.0, 19.5. HRMS (ESI) for $C_{15}H_{21}O_2$ (MH^+): calcd 233.1542, found 233.1542.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional data for synthesis and characterization of the compounds, HPLC plots, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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