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3,3′-Anisyl-Substituted BINOL, H_4BINOL, and H_8BINOL Ligands: Asymmetric Synthesis of Diverse Propargylic Alcohols and Their Ring-Closing Metathesis to Chiral Cycloalkenes

Yang Yue,[†,‡] Mark Turlington,[†] Xiao-Qi Yu,*[,‡] and Lin Pu*[,†]

[†]*Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904, and* [‡]*Department of Chemistry, Key Laboratory of Green Chemistry and Technology (Ministry of Education), Sichuan University, Chengdu, China 610064*

lp6n@virginia.edu

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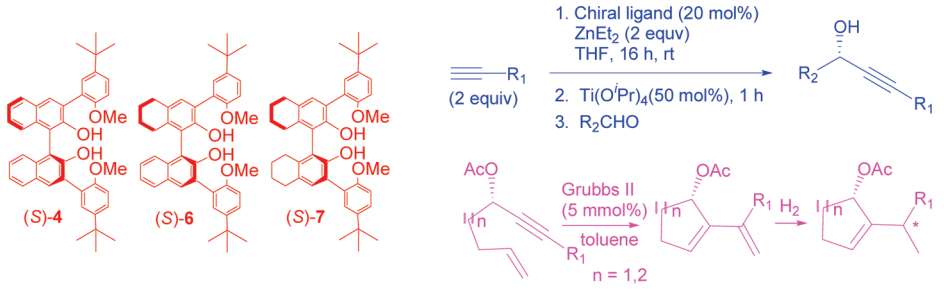

A series of optically active BINOL, H_4BINOL, and H_8BINOL derivatives were prepared. These compounds in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ were used to catalyze the asymmetric reaction of alkynes with aldehydes to generate chiral propargylic alcohols at room temperature. Through this comparative study, a 3,3′-bisanisyl-substituted H_8BINOL (*S*)-**7** was found to be a generally enantioselective catalyst for the reaction of structurally diverse terminal alkynes with a variety of aldehydes. It catalyzed the reactions of alkyl propiolates with 88−99% ee; the reactions of phenylacetylene with 81−87% ee; the reactions of 4-phenyl-1-butyne, an alkyl alkyne, with 77−89% ee; and the reactions of trimethylsilylacetylene with 92−97% ee. The optically active propargylic alcohols generated from this catalytic asymmetric alkyne addition were observed to undergo efficient ring-closing-metathesis (RCM) reaction in the presence of the Grubbs II catalyst to produce chiral cycloalkenes. It was further found that some of the chiral propargylic alcohols underwent a highly chemoselective tandem RCM hydrogenation reaction with retention of the enantiomeric purity.

Introduction

1,1′-Bi-2-naphthol (BINOL) and its substituted derivatives have found extensive applications in the development of chiral catalysts for asymmetric synthesis.[1] In recent years, the partially hydrogenated BINOLs including the derivatives of H_4BINOL (**1**)[2] and H_8BINOL (**2**)[3] have also been studied. The partially hydrogenated naphthalene rings in H_4BINOL and H_8BINOL contain sp^3 hybridized carbons that can

(1) For reviews on using BINOL-based compounds in asymmetric catalysis, see: (a) Chen, Y.; Yekta, S.; Yudin, A. *Chem. Rev.* **2003**, *103*, 3155–3211. (b) Kocovsky, P.; Vyskocil, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213–3245. (c) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–897. (d) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269–279. (e) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494.

(2) (a) Shen, X.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4321–4327. (b) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10–11. (c) Lu, Y.-N.; Guo, Q.-S.; Jiang, F.-Y.; Li, J.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 1842–1845. (d) Heumann, L. V.; Keck, G. E. *J. Org. Chem.* **2008**, *73*, 4725–4727.

(3) (a) A review: Au-Yeung, T. L.-L.; Chan, S.-S.; Chan, A. S. C. *Adv. Synth. Catal.* **2003**, *345*, 537–555. (b) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559–7570. (c) Kumaraswamy, G.; Jena, N.; Sastry, M. N. V.; Padmaja, M.; Markondaiah, B. *Adv. Synth. Catal.* **2005**, *347*, 867–871. (d) Huang, H.; Liu, X.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 693–697. (e) Kim, J. G.; Camp, E. H.; Walsh, P. J. *Org. Lett.* **2006**, *8*, 4413–4416. (f) Wu, K.-H.; Gau, H.-M. *J. Am. Chem. Soc.* **2006**, *128*, 14808–14809. (g) Muramatsu, Y.; Harada, T. *Chem.—Eur. J.* **2008**, *14*, 10560–10563. (h) Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 2458–2462. (i) Zhou, S.; Wu, K.-H.; Chen, C.-A.; Gau, H.-M. *J. Org. Chem.* **2009**, *74*, 3500–3505.

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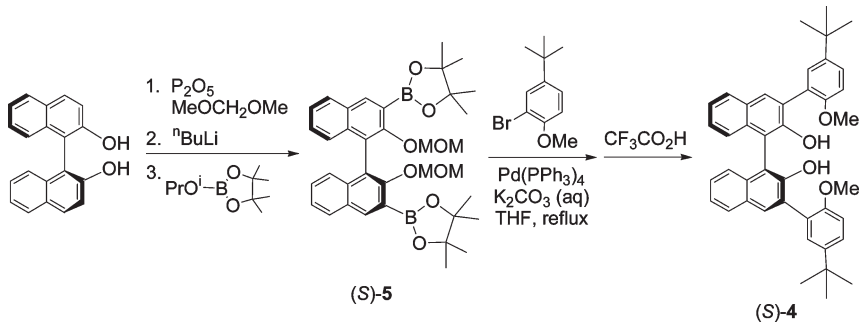
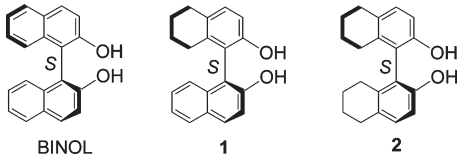
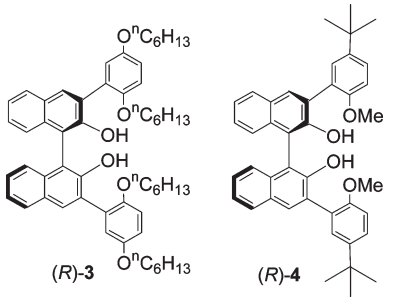
SCHEME 1. Synthesis of the BINOL Derivative (*S*)-4



increase the steric bulkiness of these ligands and change the biaryl dihedral angle. In a number of cases, these structurally modified BINOLs have led to improved enantioselectivity in asymmetric catalysis.



Previously, we found that the 3,3′-aryl ether-substituted BINOL (*R*)-**3** could catalyze the diethylzinc and diphenylzinc additions to aldehydes with high enantioselectivity.[4a,b] The 3,3′-aryl ether-substituted BINOLs were also used to catalyze the asymmetric alkyne addition to aldehydes,[4c,d,5] resulting in the synthetically useful chiral propargylic alcohols.[6] Although (*R*)-**3** was found to be a poor catalyst for the alkyne addition to aldehydes, through a systematic variation of the 3,3′-anisyl groups, compound (*R*)-**4**[4c] was obtained as a good catalyst for the enantioselective phenylacetylene addition to aromatic aldehydes in the presence of $ZnEt_2$ and $Ti(O^iPr)_4$.



To further develop the asymmetric reaction of the structurally diverse terminal alkynes with various aldehydes, we have synthesized the H_4BINOL and H_8BINOL derivatives of (*R*)-**4** and compared their catalytic properties. Through this study, a highly enantioselective catalyst that is generally applicable for the asymmetric reaction of various alkynes with aldehydes is discovered. We have also conducted the ring-closing metathesis (RCM) and tandem RCM hydrogenation of the chiral propargylic alcohol products generated from the asymmetric alkyne additions to synthesize a number of functional chiral cycloalkenes. Herein, these results are reported.[7]

Results and Discussion

1. Synthesis of the Anisyl-Substituted BINOL, H_4BINOL, and H_8BINOL Derivatives. Compound (*S*)-**4** was synthesized as shown in Scheme 1 by modifying the literature procedure.[4c] (*S*)-BINOL was protected with two MOM groups in 84% yield by reaction with dimethoxymethane in the presence of P_2O_5. Upon ortho-metalation[8] and treatment with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*S*)-**5** was obtained in 80% yield. The Suzuki coupling of (*S*)-**5** with 2-bromo-4-*tert*-butylanisole followed by treatment with trifluoroacetic acid gave (*S*)-**4** in 84% yield.

(*S*)-BINOL was partially hydrogenated to a mixture of (*S*)-H_4BINOL and (*S*)-H_8BINOL by slightly modifying a literature procedure.[9] The isolated (*S*)-H_4BINOL and (*S*)-H_8BINOL were used to prepare the corresponding 3,3′-bisanisyl-substituted derivatives, respectively. The synthesis of the H_4BINOL derivative (*S*)-**6** parallels that of (*S*)-**4** (Scheme 2). The yield for each step is also very close to that in the preparation of the BINOL derivative.

(*S*)-H_8BINOL exhibits different reactivity from (*S*)-BINOL in the electrophilic aromatic substitution. When (*S*)-BINOL was treated with bromine, the substitution occurred first at the 6,6′-positions and then at the 4,4′-positions.[10]

(4) (a) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364–1365. (b) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222–4223. (c) Moore, D.; Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2002**, *43*, 8831–8834. (d) Xu, M.-H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555–4557.

(5) Examples of other BINOL-based catalysts used in the asymmetric alkyne addition to aldehydes: (a) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636–12637. (b) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143–4146. (c) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197–3199. (d) Liu, Q.-Z.; Xie, N.-S.; Luo, Z.-B.; Cui, X.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *J. Org. Chem.* **2003**, *68*, 7921–7924. (e) Ooi, T.; Miura, T.; Ohmatsu, K.; Saito, A.; Maruoka, K. *Org. Biomol. Chem.* **2004**, *2*, 3312–3319. (f) Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 5457–5460. (g) Zou, X.-W.; Zheng, L.-F.; Wu, L.-L.; Zong, L.-L.; Cheng, Y.-X. *Chin. J. Chem.* **2008**, *26*, 373–378.

(6) For reviews on the asymmetric alkyne addition to aldehydes, see: (a) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373–381. (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095–4105. (d) Lu, G.; Li, Y.-M.; Li, X.-S.; Chan, A. S. C. *Coord. Chem. Rev.* **2005**, *249*, 1736–1744.

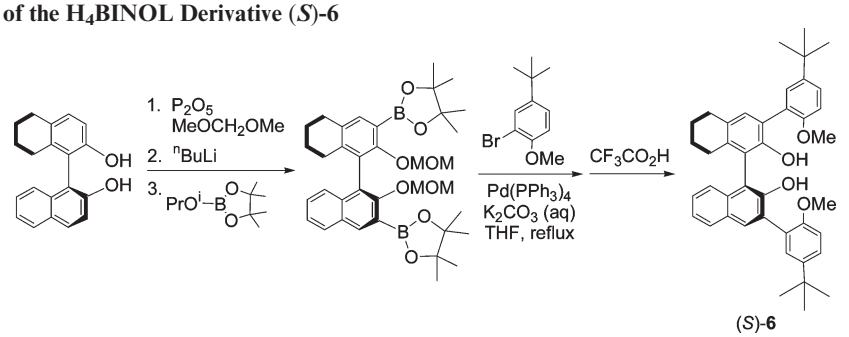
(7) Part of this work has been communicated: Turlington, M.; DeBerardinis, A. M.; Pu, L. *Org. Lett.* **2009**, *11*, 2441–2444.

(8) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253–2256.

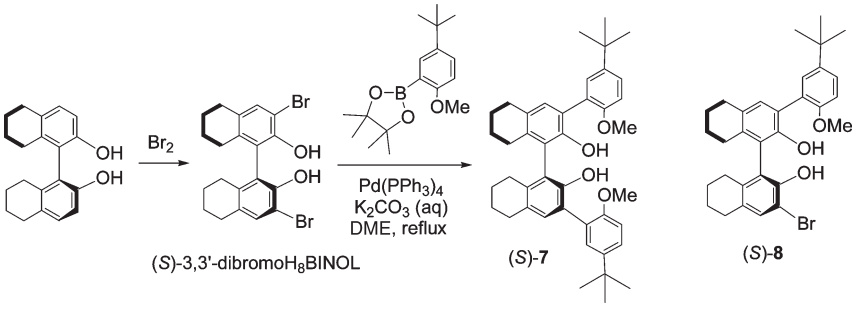
(9) Korostyleve, A.; Tararov, V. I.; Fischer, C.; Monsees, A.; Borner, A. *J. Org. Chem.* **2004**, *69*, 3220–3221.

(10) Hu, Q.-S.; Pugh, V.; Sabat, M.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7528–7536.

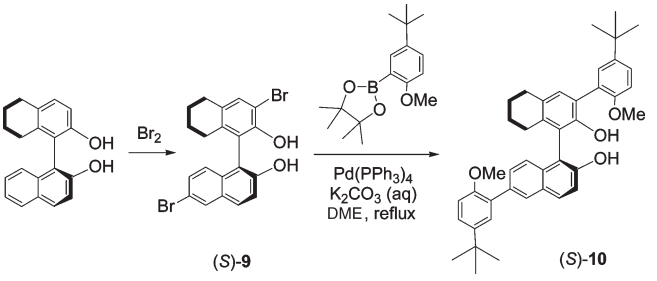
SCHEME 2. Synthesis of the H_4BINOL Derivative (*S*)-6



SCHEME 3. Synthesis of the H_8BINOL Derivatives (*S*)-7 and (*S*)-8



SCHEME 4. Synthesis of the H_4BINOL Derivative (*S*)-10

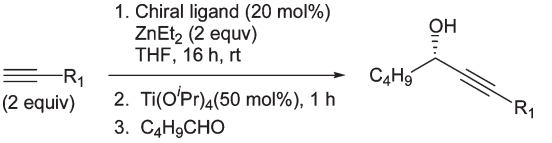


The 3,3′-positions of (*S*)-BINOL cannot be directly brominated and the ortho-metalation of its MOM-protected derivative followed by treatment with bromine is needed.[8] However, the ortho-positions of (*S*)-H_8BINOL can be directly brominated by the reaction with bromine to generate (*S*)-3,3′-dibromoH_8BINOL in 92% yield (Scheme 3). This allows a significantly more efficient synthesis of the H_8BINOL derivative (*S*)-**7** than (*S*)-**4** and (*S*)-**6**. As shown in Scheme 3, the two-step reaction from (*S*)-H_8BINOL led to the formation of (*S*)-**7** in overall yields of 86−94%.[11] Different from the transformations in Schemes 1 and 2, no protection and deprotection steps were needed for those in Scheme 3. This sequence also gave a small amount of the monocoupling product (*S*)-**8** (< 10%).

When (*S*)-H_4BINOL was treated with bromine directly, the unsymmetric 3,6′-dibromide (*S*)-**9** was obtained in 91% yield. The Suzuki coupling of (*S*)-**9** with an anisyl boronate gave the 3,6′-bisanisyl-substituted H_4BINOL (*S*)-**10** in 89% yield (Scheme 4).

2. Asymmetric Alkyne Addition to Aldehydes Catalyzed by the BINOL, H_4BINOL, and H_8BINOL Derivatives. The catalytic properties of the BINOL, H_4BINOL, and H_8BINOL derivatives for the asymmetric alkyne addition to an aliphatic aldehyde, pentyl aldehyde, are compared (Scheme 5). The results are summarized in Table 1. As shown in Table 1, the H_8BINOL derivative (*S*)-**7** is generally more enantioselective than the other chiral compounds except in the trimethylsilylacetylene addition where the BINOL derivative (*S*)-**4** is slightly more enantioselective. The BINOL derivative (*S*)-**4** and the H_8BINOL derivative (*S*)-**7** are both C_2 symmetric and they provide much greater enantioselectivity than the C_1 symmetric H_4BINOL derivative (*S*)-**6**. The monoanisyl-substituted H_8BINOL (*S*)-**8** also showed quite high enantioselectivity in the asymmetric alkyne additions, but the H_4BINOL derivative (*S*)-**10** gave very low and opposite enantioselectivity. This indicates that the bromine atom in (*S*)-**8** could also contribute to the enantioselectivity. Compound (*S*)-**10** has one less substituent adjacent to the central hydroxyl groups than (*S*)-**7** and (*S*)-**8**, leading to a dramatically different stereocontrol in the catalysis. We also examined the use of (*S*)-3,3′-dibromoH_8BINOL to catalyze the reaction of methyl propiolate with pentyl aldehyde, but only a trace amount of the product was generated. This demonstrates that the methoxy group in (*S*)-**7** and (*S*)-**8** is important for the catalysis.

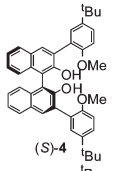
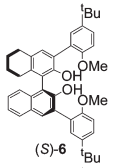
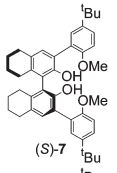
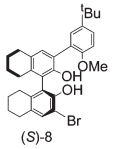
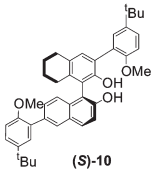
SCHEME 5. Reactions of Various Alkynes with Pentyl Aldehyde Catalyzed by the BINOL, H_4BINOL, and H_8BINOL Derivatives



Because of the generally high enantioselectivity of the C_2 symmetric H_8BINOL derivative (*S*)-**7** as shown in Table 1, we have explored the use of this compound to catalyze the reaction of various alkynes with a few representative aliphatic and aromatic aldehydes. As the results summarized in Table 2 show, (*S*)-**7** in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ catalyzed

(11) Bartoszek, M.; Beller, M.; Deutsch, J.; Klawonn, M.; Kockritz, A.; Nemati, N.; Pews-Davtyan, A. *Tetrahedron* **2008**, *64*, 1316–1322.

TABLE 1. Comparison of the BINOL, H_4BINOL, and H_8BINOL Derivatives in the Asymmetric Alkyne Addition to Pentyl Aldehyde

Chiral Ligand	Alkyne: —CO$_2$Me Yield (%)	ee (%)	—Ph Yield (%)	ee (%)	—CH$_2$CH$_2$Ph Yield (%)	ee (%)	—TMS Yield (%)	ee (%)
 (*S*)-**4**	62	85	83	81	89	81	65	97
 (*S*)-**6**	94	77	89	50	89	61	48	78
 (*S*)-**7**	76	95	88	81	78	84	56	93
 (*S*)-**8**	83	89	85	73	80	81	60	89
 (*S*)-**10**	45	-50	82	-34	86	-65	43	-69

diverse alkyne additions to aldehydes at room temperature with high enantioselectivity. These results demonstrate that (*S*)-**7** is generally useful for the asymmetric alkyne addition to aldehydes. The absolute configuration of the propargylic alcohol product generated in entry 7 is determined to be *S* by comparing its optical rotation with the literature data.[12] The absolute configurations of all other propargylic alcohol products generated by (*S*)-**7** were assigned by analogy.

3. Ring-Closing Metathesis of the Optically Active Propargylic Alcohols. To demonstrate the utility of the chiral propargylic alcohols, we have explored the ruthenium carbene-catalyzed ring-closing metathesis reaction (RCM)[13] of the optically active enynes[14] generated from the asymmetric alkyne additions catalyzed by (*S*)-**7**. We found that the propargylic alcohols need to be protected with an acyl group for the RCM reaction.[15] The RCM of the propargylic alcohol **11**, prepared from the reaction of phenylacetylene with 5-hexenal in the presence of (*S*)-**7** (87% ee, entry 13 in Table 2) was first investigated. To determine the enantiomeric purity of the RCM product with ^{1}H NMR spectroscopy, we have prepared (*R*)-(−)-acetylmandelic ester **12** from **11** (Scheme 6). When **12** was treated with the second generation Grubbs carbene catalyst (Grubbs II),[16] it underwent RCM reaction to generate the cyclohexene product **13** in 85% yield. The ^{1}H NMR spectrum of **13** showed that this compound had essentially the same enantiomeric purity (86% ee) as the starting propargylic alcohol **11**.

A few optically active propargylic alcohols were converted to their acetates (Scheme 7). The RCM reactions of these acetates in the presence of Grubbs II were conducted to produce various chiral cycloalkene products. These results are summarized in Table 3. Excellent yields were obtained for the substrates derived from both aromatic and aliphatic alkynes (entries 1−4). In entry 5, the substrate derived from allyl propiolate led to the formation of a bicyclic diene product.

4. Highly Chemoselective Tandem Ring-Closing Metathesis and Hydrogenation of the γ-Hydroxy-α,β-acetylenic Esters. The ruthenium complex used in the RCM reaction can be converted to a hydrogenation catalyst in the presence of hydrogen.[17] This makes it possible to conduct a tandem RCM and hydrogenation reaction. We have investigated the

(12) Johansson, M.; Kopcke, B.; Anke, H.; Sterner, O. *Tetrahedron* **2002**, *58*, 2523–2528.

(13) Selected reviews on the RCM reactions: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (b) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251.

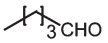
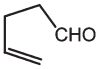
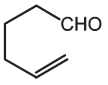
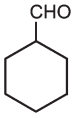
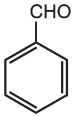
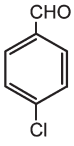
(14) Selected reviews on the enyne metathesis: (a) Diver, S. T.; Giessert, A. *J. Chem. Rev.* **2004**, *104*, 1317–1382. (b) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55–66.

(15) A report on the RCM of propargylic acetates: Yoshida, K.; Shishikura, Y.; Takahashi, H.; Imamoto, T. *Org. Lett.* **2008**, *10*, 2777–2780.

(16) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558.

(17) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312–11313.

TABLE 2. Reactions of Various Alkynes with Aliphatic and Aromatic Aldehydes Catalyzed by (*S*)-7[a]

Entry	Aldehyde	Alkyne	Yield (%)	ee (%)[b]
1		—CO_2Me	76	95
2		—CO_2Et	60	94
3		—Ph	88	81
4		—$(CH_2)_2Ph$	78	84
5		—TMS	65	97
6		—CO_2Me	76	95
7		—CO_2Et	71	92
8		—Ph	97	81
9		—$(CH_2)_2Ph$	67	81
10		—TMS	68	95
11		—CO_2Me	67	95
12		—CO_2Et	63	94
13		—Ph	84	87
14		—$(CH_2)_2Ph$	74	81
15		—TMS	68	94
6		—CO_2Me	84	95
17		—CO_2Et	84	99
18		—Ph	94	80
19		—$(CH_2)_2Ph$	83	77
20		—TMS	81	92
21		—CO_2Me	64	90
22		—CO_2Et	52	88
23		—Ph	91	83
24		—$(CH_2)_2Ph$	61	89
25		—TMS	50	95
26		—CO_2Me	83	92
27		—Ph	87	84
28		—$(CH_2)_2Ph$	72	80
29		—TMS	68	94

[a](*S*)-**7**:$ZnEt_2$:$Ti(O^iPr)_4$:alkyne:aldehyde = 0.2:2:0.5:2:1. THF was used as the solvent for the addition to the aliphatic aldehydes, and a THF/Et_2O (1:4) mixed solvent was used for the addition to the aromatic aldehydes. [b]The ee values of the products of entries 5, 10, 13, 14, 15, 19, 20, and 28 were determined by using the ^1H NMR spectra of their esters prepared with (*R*)-PhCH(OAc)CO_2H; that of entry 1 by HPLC-Chiralcel OD column (2% isopropanol in hexane, 0.5 mL/min); those of entries 2, 6, 7, 11, and 12 by HPLC-Chiralcel OD column (2% isopropanol in hexane, 1.0 mL/min); those of entries 3, 8, 18, 22, 23, 24, 27, and 29 by HPLC-OD column (10% isopropanol in hexane, 1.0 mL/min); those of entries 4, 9, 16, and 17 by HPLC-Chiralpak AD-H column (1% isopropanol in hexane, 0.3 mL/min); and those of entries 21, 25, and 26 by HPLC-Chiralcel OD column (5% isopropanol in hexane, 1.0 mL/min).

tandem RCM hydrogenation of the optically active propargylic alcohols, particularly the γ-hydroxy-α,β-acetylenic esters.

First, the optically active (*S*)-γ-hydroxy-α,β-acetylenic ester **14** (95% ee, entry 6 in Table 2) was converted to ester **15a** (Scheme 8). This compound was then subjected to the tandem RCM hydrogenation conditions. It was first treated with the Grubbs II catalyst (5 mol %) in toluene at room temperature for 1 h. Then, H_2 (100 psi) was introduced and

SCHEME 6. RCM of the Mandelate of the Propargylic Alcohol 11

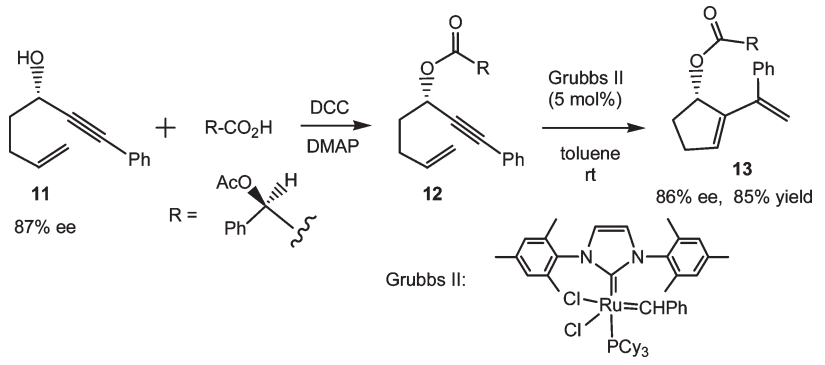
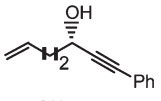
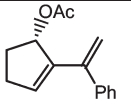
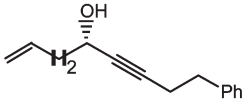
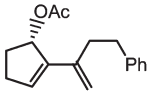
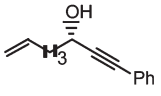
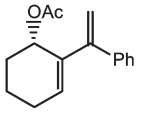
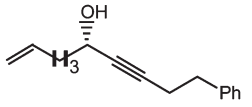
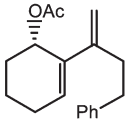
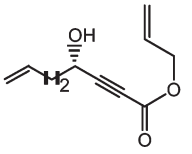
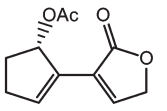
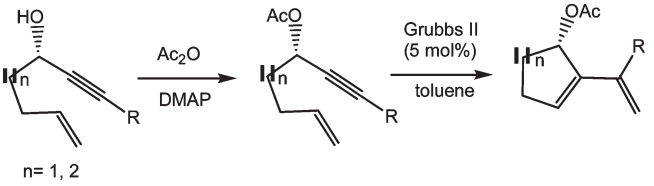


TABLE 3. Results for the RCM of the Acetates of Various Propargylic Alcohols

Entry	Propargylic Alcohol	Product	Yield (%)
1			94
2			85
3			97
4			87
5			61

SCHEME 7. RCM of the Acetates of Various Propargylic Alcohols



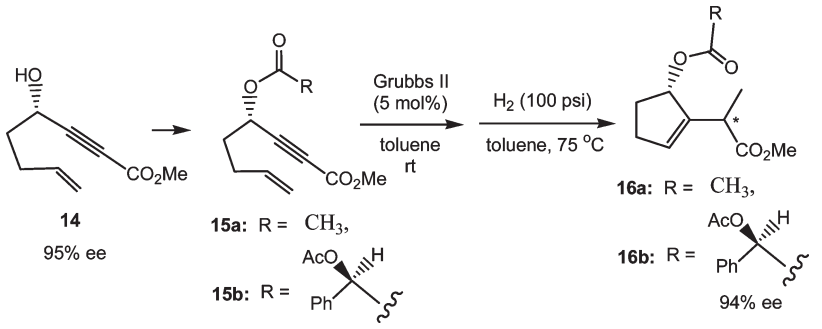
the mixture was heated at 75 °C. After 10 h, product **16a** was obtained in 88% yield from the propargylic alcohol. It was found that hydrogenation occurred with high chemoselectivity, hydrogenating only the terminal alkene with the internal alkene untouched. The product from the tandem RCM hydrogenation contained two diastereomers with a 2:1 ratio.

To determine the enantiomeric purity of the tandem RCM hydrogenation product with NMR spectroscopy, compound **14** was reacted with (*R*)-(−)-α-acetylmandelic acid to prepare the chiral acetyl group protected **15b**. The tandem RCM hydrogenation of this compound was found to proceed with the same chemoselectivity and diastereoselectivity as the Ac-protected **15a**. This implies that a bulkier chiral acyl group has no influence on the RCM hydrogenation process. The enantiomeric purity of the product **16b** was 94% for both diastereomers by using ^{1}H NMR spectroscopy. This demonstrates that the tandem RCM hydrogenation maintains the enantiomeric purity of the starting γ-hydroxy-α,β-acetylenic ester.

To determine the configuration of the newly formed stereogenic center (α) after hydrogenation, compound **16a** was reduced to the diol **17** by using $LiAlH_4$, which was then converted to the Mosher' esters **18** and **19**, respectively (Scheme 9). The ^{1}H NMR signals of the two diastereotopic protons H_a and H_b in compounds **18** and **19** are analyzed. The chemical shift difference of H_a and H_b is $\Delta\delta$. According to that established previously by Kobayashi, the $\Delta\delta$ of the compound whose configuration at α is the same as its Mosher's ester fragment should be greater than the one whose configuration at α is different from its Mosher's ester.[18] The chemical shifts of the H_a and H_b of **19** from the major diastereomer of **16a** are at δ = 4.250 (dd) and 4.192 (dd) ($\Delta\delta$ = 0.058), and those of **18** are at δ = 4.114 (dd) and 4.078 (dd) ($\Delta\delta$ = 0.036). Since the $\Delta\delta$ of **19** is greater than that of **18**, the configuration at α could be assigned to *S*. Thus, the major diastereomer of **16a** could be assigned to

(18) Tsuda, M.; Toriyabe, Y.; Endo, T.; Kobayashi, J. *Chem. Pharm. Bull.* **2003**, *51*, 448–451.

SCHEME 8. The Tandem RCM Hydrogenation of γ-Hydroxy-α,β-acetylenic Esters



SCHEME 9. Synthesis of Compounds 18 and 19 for Configuration Assignment

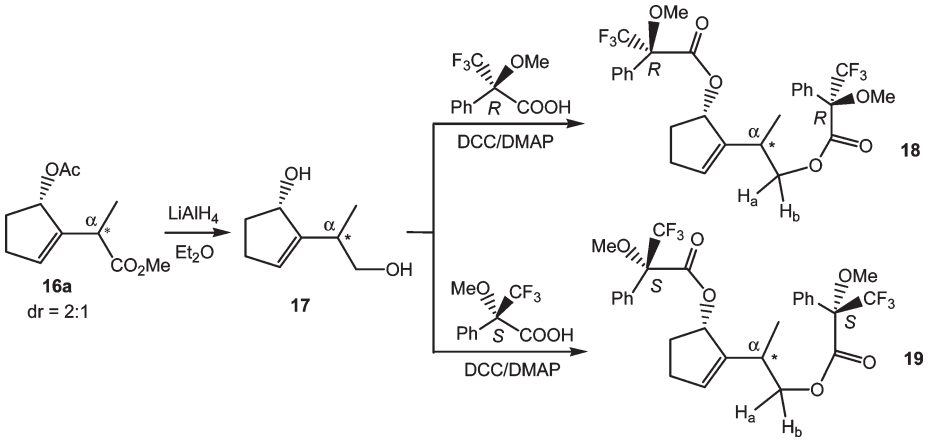
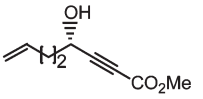
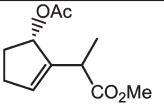
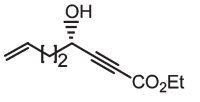
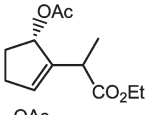
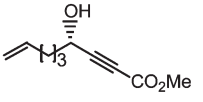
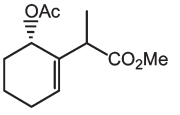
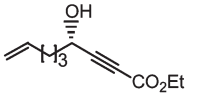
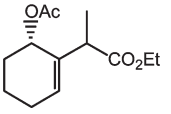


TABLE 4. The Chemoselective Tandem RCM Hydrogenation of γ-Hydroxy-α,β-acetylenic Esters

Entry	γ-Hydroxy-α,β-acetylenic Ester	Product	Yield (%)	dr
1			88	2:1
2			89	3:1
3			90	2:1
4			91	3:1

have *S* and the minor diastereomer *R* configuration at the α position.

Other optically active γ-hydroxy-α,β-acetylenic esters were also subjected to the tandem RCM hydrogenation and the results are summarized in Table 4. As shown in the table, both chiral cyclopentene and cyclohexene products were generated efficiently with high chemoselectivity. The propargylic alcohols produced from ethyl propiolate showed slightly higher diastereoselectivity than those from methyl propiolate. When the propargylic alcohols obtained from the aliphatic alkyne addition to aldehydes were examined for the tandem RCM hydrogenation, high diastereoselectivity was observed (up to 16:1 as indicated by ^{1}H NMR spectroscopy), but the products could not be fully purified. For the propargylic alcohols prepared from the phenylacetylene addition to aldehydes, introduction of H_2 to the RCM products could not lead to hydrogenation.

Summary

We have prepared 3- or 3,3′-anisyl substituted optically active BINOL, H_4BINOL, and H_8BINOL derivatives and

studied their use in the catalytic asymmetric reaction of alkynes with aldehydes. It was found that the H_8BINOL derivative (*S*)-**7** in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ is a generally enantioselective catalyst for the reaction of structurally diverse alkynes with a variety of aldehydes at room temperature. The resulting optically active propargylic alcohols can undergo an efficient RCM reaction in the presence of the Grubbs II catalyst to generate chiral functional cycloalkenes. We have further found a highly chemoselective tandem RCM hydrogenation reaction of some of the chiral propargylic alcohols. These findings expand the application of the chiral propargylic alcohols in the synthesis of chiral functional organic compounds.

Experimental Section

Preparation and Characterization of (*S*)-3,3′-Bis(5-*tert*-butyl-2-methoxyphenyl)-5,6,7,8-tetrahydro-1,1′-binaphthyl-2,2′-diol, (*S*)-6. Under nitrogen, 2-((1′*S*)-2,2′-bis(methoxymethoxy)-3′-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)-5′,6′,7′,8′-tetrahydro-1,1′-binaphthyl-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.15 g, 5 mmol), 2-bromo-4-*tert*-butyl-1-methoxybenzene (4.86 g, 20 mmol, 4 equiv), and $Pd(PPh_3)_4$ (410 mg, 0.5 mmol, 10 mol %) were placed in a 2-necked flask equipped with a reflux condenser that was connected with a vacuum adaptor. Degassed THF (50 mL) and 2 M K_2CO_3 (40 mL) were cannula-transferred into the flask. To ensure the removal of oxygen, the reaction vessel was freeze-pumped at −78 °C and refilled with nitrogen three times. The reaction mixture was then heated at 95 °C for 24 h. After being cooled to room temperature, the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with 2 M HCl (3 × 40 mL), dried, and concentrated. The crude product was dissolved in CH_2Cl_2 (25 mL) and trifluoroacetic acid (5 mL) was added. After the mixture was stirred at room temperature for 10 h, it was concentrated and purified by column chromatograph on silica gel eluted with 10% EtOAc/hexanes to give (*S*)-**6** as a white solid in 84% yield. An ee value of 99% was determined by HPLC analysis (Chiralcel OD column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 305 nm, retention time t_{major} = 24.37 min and t_{minor} = 33.45 min). $[\alpha]_D$ −39.1 (*c* 0.72, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.42 (s, 9H), 1.70−1.77 (m, 2H), 1.80−1.87 (m, 2H), 2.27−2.37 (m, 1H), 2.51−2.61 (m, 1H), 2.94 (t, 2H, *J* = 6.0 Hz), 3.85 (s, 3H), 3.86 (s, 3H), 5.88 (s, 1H), 6.04 (s, 1H), 6.97 (d, 1H, *J* = 8.4 Hz), 7.03 (d, 1H, *J* = 8.4 Hz), 7.21 (s, 1H), 7.38−7.45 (m, 3H), 7.46−7.52 (m, 3H), 7.57 (d, 1H, *J* = 2.4 Hz), 7.88−7.93 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 27.4, 29.8, 31.9, 34.6, 55.4, 111.0, 111.2, 117.8, 122.3, 123.8, 124.8, 125.8, 126.0, 126.4, 126.6, 127.0, 127.1, 128.5, 129.2, 129.4, 129.9, 130.0, 130.2, 130.8, 132.3, 133.2. HRMS (MH^+) for $C_{42}H_{47}O_4$ calcd 615.3474, found 615.3474.

Preparation of (*S*)-3,3′-Bis(5-*tert*-butyl-2-methoxyphenyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diol, (*S*)-7. Under nitrogen, (*S*)-3,3′-dibromoH_8BINOL (2.0 g, 4.4 mmol), 2-(5-*tert*-butyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.85 g, 13.3 mmol, 3 equiv), and $Pd(PPh_3)_4$ (512 mg, 0.4 mmol, 10 mol %) were placed in a 2-necked flask equipped with a reflux condenser that was connected with a vacuum adaptor. Degassed dimethoxyethane (25 mL) and 2 M Na_2CO_3 (20 mL) were cannula-transferred into the flask. To ensure the removal of oxygen, the reaction vessel was freeze-pumped at −78 °C and refilled with nitrogen three times. The reaction mixture was then heated at 95 °C for 24 h. After being cooled to room temperature, the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with 2 M HCl (3 × 40 mL), dried, and concentrated. The residue was purified by column chromatography on silica gel eluted with 8% EtOAc/hexanes to afford (*S*)-**7** as a white solid in 94% yield (2.57 g). A small amount of (*S*)-**8** was also obtained. Prior to use in catalysis, (*S*)-**7** was dissolved in CH_2Cl_2 and stirred with 2 equiv of trifluoroacetic acid for 1 h to remove trace metal impurities. After flash chromatography over silica gel, the product was dried by dissolving in THF and pumping under vacuum.

Characterization of (*S*)-7: 98% ee determined by HPLC analysis (Chiralcel OD column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 254 nm, retention time t_{major} = 18.71 min and t_{minor} = 22.98 min). $[\alpha]_D$ −7.01 (*c* 1.14, THF). ^{1}H NMR (75 MHz, $CDCl_3$) δ 1.34 (s, 18H), 1.77 (br, 8H), 2.27−2.35 (m, 2H), 2.50−2.58 (m, 2H), 2.84 (br, 4H), 3.81 (s, 6H), 5.85 (s, 2H), 6.91 (d, 2H, *J* = 8.7 Hz), 7.05 (s, 2H), 7.35 (d, 2H, *J* = 8.4 Hz), 7.43 (d, 2H, *J* = 2.4 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 23.2, 23.2, 27.2, 29.4, 31.5, 34.2, 56.0, 110.7, 124.0, 124.0, 125.4, 127.0, 129.4, 129.5, 131.3, 136.5, 144.2, 148.7, 153.5. HRMS (MH^+) for $C_{42}H_{51}O_4$ calcd 619.3782, found 619.3792.

Characterization of (*S*)-8: 99% ee determined by HPLC analysis (Chiralcel OD column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 254 nm, retention time t_{major} = 22.12 min and t_{minor} = 18.65 min). $[\alpha]_D$ −8.34 (*c* 1.01, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9), 1.72−1.81 (m, 8H) 2.16−2.46 (m, 4H), 2.76−2.84 (m, 4H), 3.84 (s, 3H), 5.12 (s, 1H), 6.08 (s, 1H), 6.94 (d, 1H, *J* = 8.4 Hz), 7.10 (s, 1H), 7.27 (s, 1H), 7.37−7.40 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 23.2, 23.3, 23.3, 27.3, 27.3, 29.4, 29.6, 31.8, 34.5, 56.4, 106.8, 111.1, 122.3, 124.5, 125.0, 126.1, 126.6, 129.8, 130.4, 131.2, 132.3, 132.4, 136.7, 137.0, 144.9, 147.4, 149.2, 153.5. HRMS (MH^+) for $C_{36}H_{39}O_3Br$ calcd 535.1842, found 535.1840.

Preparation and Characterization of (*S*)-3-(5-*tert*-Butyl-2-methoxyphenyl)-6′-(2-*tert*-butyl-5-methoxyphenyl)-5,6,7,8-tetrahydro-1,1′-binaphthyl-2,2′-diol, (*S*)-10. (a) (*S*)-H_4BINOL (2.0 g, 6.79 mmol) was dissolved in CH_2Cl_2 (75 mL) and cooled to 0 °C. Bromine (0.73 mL, 14.3 mmol) was added in one portion, and after 30 min the reaction mixture was quenched with sodium sulfite (saturated, aqueous, 75 mL). The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2 (30 mL). The resulting organic layers were dried and concentrated, and purified by flash chromatography on silica gel (10% EtOAc/hexanes) to yield (*S*)-**9** as a white solid in 91% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59−1.62 (m, 2H), 1.71−1.75 (m, 2H), 2.00−2.08 (m, 1H), 2.16−2.24 (m, 1H), 2.78 (t, 2H, *J* = 3.3 Hz), 4.98 (d, 1H, *J* = 2.7 Hz), 5.16 (s, 1H), 7.08 (d, 1H, *J* = 9.0 Hz), 7.30 (d, 1H, *J* = 9.0 Hz), 7.40−7.44 (m, 2H), 7.77 (d, 1H, *J* = 9.0 Hz), 7.98 (d, 1H, *J* = 2.1 Hz). (b) Under nitrogen, (*S*)-**9** (2.0 g, 4.4 mmol), 2-(5-*tert*-butyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.85 g, 13.3 mmol, 3 equiv), and $Pd(PPh_3)_4$ (512 mg, 0.4 mmol, 10 mol %) were placed in a 2-necked flask equipped with a reflux condenser that was connected with a vacuum adaptor. Degassed 1,2-dimethoxyethane (25 mL) and 2 M Na_2CO_3 (20 mL) were cannula-transferred into the flask. To ensure the removal of oxygen, the reaction vessel was freeze-pumped at −78 °C and refilled with nitrogen three times. The reaction mixture was then heated at 95 °C for 24 h. After being cooled to room temperature, the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with 2 M HCl (3 × 40 mL), dried, and concentrated. The residue was purified by column chromatograph on silica gel eluted with 10% EtOAc/hexanes to afford (*S*)-**10** as a white solid in 89% yield. Prior to use in catalysis, (S)-**10** was dissolved in CH_2Cl_2 and stirred with 2 equiv of trifluoroacetic acid for 1 h to remove trace metal impurities. After flash chromatography over silica gel, the product was dried by dissolving in THF and pumping under. $[\alpha]_D$ −127.6 (*c* 1.04, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.38 (s, 9H), 1.68−1.70 (m, 2H), 1.80−1.89 (m, 2H), 2.25−2.45 (m, 1H), 2.90 (t, 1H, *J* = 6.6 Hz), 3.76 (t, 2H, *J* = 6.6 Hz), 3.82 (s, 3H), 3.85 (s, 3H), 5.26 (s, 1H), 5.84 (s, 1H), 6.96 (dd, 2H, *J* = 3.6, 8.7 Hz), 7.21 (s, 1H), 7.31−7.45 (m, 6H), 7.60 (dd, 1H, *J* = 1.8, 8.7 Hz), 7.89 (d, 1H, *J* = 8.7 Hz), 7.98 (s, 1H). ^{13}C NMR (75 MHz,

$CDCl_3$) δ 23.3, 25.9, 27.3, 29.7, 31.8, 34.4, 34.5, 55.9, 56.4, 68.2, 111.0, 115.9, 117.6, 119.8, 124.0, 125.1, 125.3, 126.1, 126.6, 128.7, 129.1, 129.4, 129.6, 130.2, 130.4, 130.5, 132.2, 132.9, 134.4, 138.7, 143.7, 144.6, 150.5, 151.0, 153.9, 154.7. HRMS (MH^+) for $C_{42}H_{47}O_4$ calcd 615.3469, found 615.3469.

General Procedure for the Asymmetric Alkyne Addition to Aldehydes. Under nitrogen, a chiral ligand (0.1 mmol, 20 mol %) was dissolved in THF (5 mL) (for addition to an aliphatic aldehyde) or THF/Et_2O (1:4, 5 mL) (for addition to an aromatic aldehyde) in a 10 mL flame-dried flask. $ZnEt_2$ (103 μL, 1 mmol, 2 equiv) and an alkyne (1 mmol, 2 equiv) were added sequentially and the mixture was stirred at room temperature for 16 h, yielding a light yellow solution. $Ti(O^iPr)_4$ (74 μL, 0.25 mmol, 50 mol %) was then added and the reaction mixture was stirred for 1 h. To the resulting dark orange solution was added an aldehyde and the reaction was monitored by using TLC or NMR. Upon consumption of the aldehdye, the reaction was quenched with saturated aqueous ammonium chloride (5 mL). The reaction mixture was extracted three times with CH_2Cl_2 and the organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The residue was purified by flash chromatography on silica gel. An initial eluent of 2:1 CH_2Cl_2: hexanes cleanly separated the ligand from the product. Then, the column was eluted with hexanes/ethylacetate (10−20% ethyl acetate) to give the product as an oil.

An Example for the Characterization of the Optically Active Propargylic Alcohol Products. 1-Phenylnon-3-yn-5-ol, P-1: 78% yield. 84% ee determined by HPLC analysis (AD column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 221 nm, retention time t_{major} = 51.43 min and t_{minor} = 54.968 min). $[\alpha]_D$ −6.20 (*c* 0.34, THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93−0.98 (t, 3H, J = 7.2 Hz), 1.37−1.48 (m, 4H), 1.65−1.74 (m, 2H), 2.02 (br, 1H), 2.55 (td, 2H, J_t = 8.4 Hz, J_d = 2.1 Hz), 2.87 (t, 2H, J = 7.5 Hz), 4.37 (tt, 1H, J_1 = 6.6 Hz, J_2 = 2.1 Hz), 7.25−7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 21.2, 22.7, 27.6, 35.3, 38.1, 63.0, 82.5, 84.9, 126.6, 128.6, 128.7, 140.9. HRMS ($M - H^+$) for $C_{15}H_{19}O$ calcd 215.1430, found 215.1434.

General Procedure for the Ring-Closing Metathesis of the Optically Active Propargylic Alcohols. To a 10 mL round-bottomed flask were added a propargylic alcohol (1 equiv), Ac_2O (2 equiv), DMAP (0.1 equiv), and CH_2Cl_2 (5 mL) at room temperature. After the mixture was stirred for 10 min, it was passed through a short silica gel column eluted with 10% EtOAc/hexanes to give the Ac-protected propargylic alcohol. This compound (1 equiv) was then dissolved in toluene (0.14 M) and combined with Grubbs II (5 mol %) in a 50 mL round-bottomed flask under nitrogen. After the mixture was stirred at room temperature for 2 h, it was passed through a short silica gel column eluted with 10% EtOAc/hexanes to give the product.

An Example for the Characterization of the Ring-Closing Metathesis Products. 2-(1-Phenylvinyl)cyclopent-2-enyl acetate, P-7: 94% yield. $[\alpha]_D$ −19.67 (*c* 1.73, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92−1.98 (m, 1H), 2.05 (s, 3H), 2.36−2.45 (m, 2H), 2.57−2.61 (m, 1H), 5.15 (s, 1H), 5.22 (s, 1H), 5.92 (t, 1H, J = 2.7 Hz), 6.07−6.10 (m, 1H), 7.30−7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 31.2, 31.8, 79.3, 114.9, 127.6, 128.3, 128.5, 137.4, 141.8, 141.9, 144.2, 171.4. HRMS (M − H) for $C_{15}H_{15}O_2$ calcd 227.1067, found 227.1070.

General Procedure for the Tandem Ring-Closing Metathesis and Hydrogenation of the γ-Hydroxy-α,β-acetylenic Esters. In a 50 mL round-bottomed flask under nitrogen, an Ac group protected propargylic alcohol (1 equiv) was dissolved in toluene (0.14 M) and combined with Grubbs II (5 mol %). After the mixture was stirred at room temperature for 1 h, it was transferred to a parr reactor. Hydrogen (100 psi) was introduced and the reactor was heated at 75 °C with stirring for 10 h. The crude mixture was passed through a short silica gel column eluted with 20% EtOAc/hexanes to give the product.

An Example for the Characterization of the Tandem Ring-Closing Metathesis and Hydrogenation Products. Methyl 2-(5-acetoxycyclopent-1-enyl)propanoate, P-12: 88% yield. The ratio of the two diastereomers is 2:1, determined by analyzing the ^{1}H NMR spectrum. $[\alpha]_D$ −1.77 (*c* 1.10, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 3H, J = 7.2 Hz), 1.72−1.90 (m, 2H), 2.02 (s, 3H), 2.31−2.51 (m, 2H), 3.20−3.30 (m, 1H), 3.66 (s, 3H), 5.70−5.73 (m, 1H), 5.90 (br s, 1H). Following are the resolved signals of another diastereomer: δ 1.29 (d, 3H, J = 7.2 Hz), 3.68 (s, 3H), 5.86 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 21.5, 30.4, 31.2, 38.6, 52.2, 80.5, 132.9, 141.0, 171.2, 174.6. Following are the resolved signals of another diastereomer: δ 16.8, 39.6, 80.6, 132.7, 174.9. HRMS (MNa^+) for $C_{11}H_{16}O_4Na$ calcd 235.0946, found 235.0949.

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Supporting Information Available: Detailed synthesis and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.