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Catalytic Asymmetric Synthesis of Chiral Propargylic Alcohols for the Intramolecular Pauson−Khand Cycloaddition

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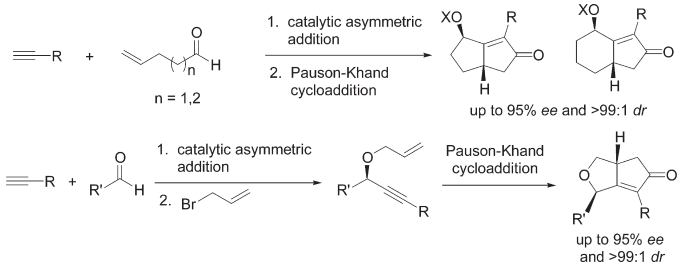

Several methods for the catalytic asymmetric alkyne addition to aldehydes are used to prepare the propargylic alcohol-based chiral en-ynes. Protection of the propargylic alcohols with either an acetyl or a methyl group allows the resulting en-ynes to undergo the intramolecular Pauson−Khand reaction to form the corresponding optically active 5,5- and 5,6-fused bicyclic products with high diastereoselectivity and high enantiomeric purity. In the major product, the propargylic substituent and the bridgehead hydrogen are cis with respect to each other on the fused bicyclic rings. The enantiomeric purity of the propargylic alcohols generated from the asymmetric alkyne addition is maintained in the cycloaddition products. The allylic ethers of the chiral propargylic alcohols are prepared which can also undergo the highly diastereoselective Pauson−Khand cycloaddition with retention of the high enantiomeric purity. This study has shown that the size of the substituents at the propargylic position as well as on the alkyne is important for the diastereoselectivity with the greater bulkiness of the substituents giving higher diastereoselectivity.

Introduction

Propargylic alcohols are synthetically very useful functional organic molecules. During the past decade, a number of catalysts have been developed for the asymmetric alkyne addition to aldehydes to generate chiral propargylic alcohols.[1] For example, chiral ligands such as **1**−**3** in combination with $Zn(OTf)_2$ or ZnR_2 (R = Et or Me) were found to catalyze the reaction of alkynes and aldehydes with high enantioselectivity.[2] We[3a] and Chan[4] found that 1,1′-bi-2-naphthol (BINOL, **4**) in combination with $Ti(O^iPr)_4$ and ZnR_2 catalyzed the alkyne addition to aromatic aldehydes with high enantioselectivity. We further demonstrated that the BINOL-$ZnEt_2$-$Ti(O^iPr)_4$ catalyst system was also highly enantioselective for the alkyne addition to aliphatic aldehydes and α,β-unsaturated aldehydes.[3b] This process required a preheating of a terminal alkyne with $ZnEt_2$ in toluene at

(1) (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.

(2) (a) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688. (c) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8–9. (d) Wolf, C.; Liu, S. *J. Am. Chem. Soc.* **2006**, *128*, 10996–10997. (e) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760–13761. (f) Trost, B. M.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010**, *132*, 5186–5192.

(3) (a) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855–1857. (b) Gao, G.; Moore, D.; Xie, R. G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143–4146. (c) Gao, G.; Xie, R. G.; Pu, L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5417–5420. (d) Gao, G.; Wang, Q.; Yu, X. Q.; Xie, R. G.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 122–125.

(4) (a) Lu, G.; Li, X. S.; Chan, A. S. C. *Chem. Commun.* **2002**, 172–173. (b) Li, X. S.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636–12637.

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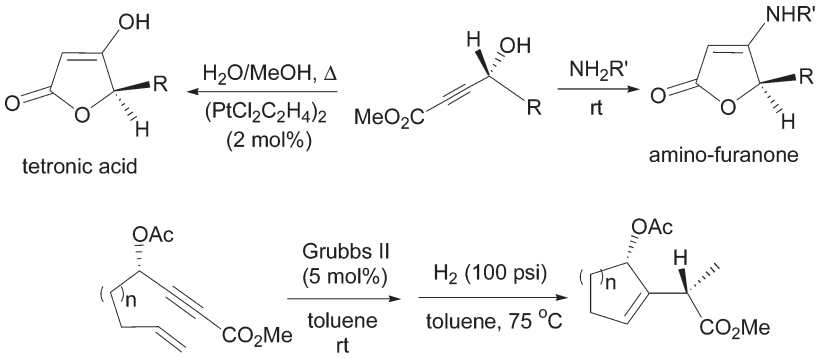
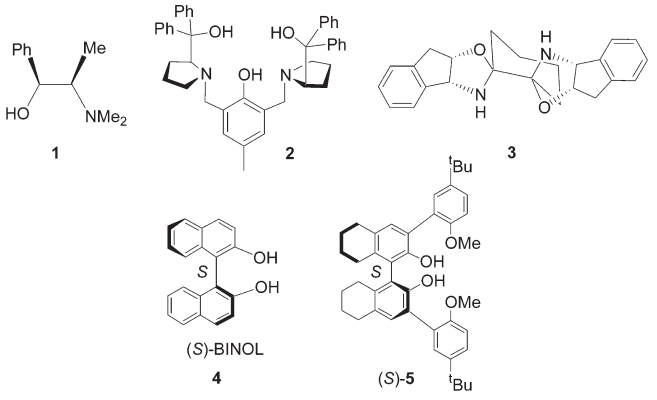
SCHEME 1. Conversion of Chiral Propargylic Alcohols to Other Products

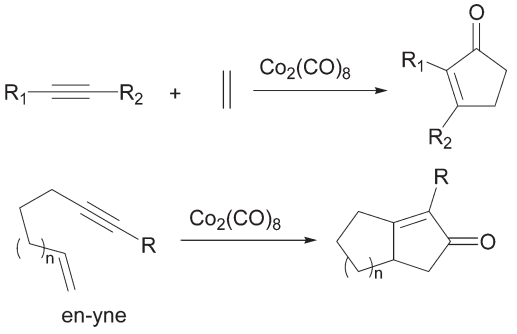


reflux in order to prepare the nucleophilic alkynylzinc reagent. Addition of hexamethylphosphoramide (HMPA) to the BINOL-$ZnEt_2$-$Ti(O^iPr)_4$ system was found to allow the reaction of functionalized alkynes with aromatic and α,β-unsaturated aldehydes to be conducted entirely at room temperature with high enantioselectivity.[3c,d] The Lewis base additive HMPA accelerated the reaction of $ZnEt_2$ with the terminal alkynes to generate the alkynylzinc nucleophiles at room temperature. Later, You and co-workers reported that *N*-methylimidazole (NMI) could be used in place of HMPA to increase the efficiency of the BINOL-$ZnEt_2$-$Ti(O^iPr)_4$ catalyst system.[5] We recently found that using biscyclohexylamine (Cy_2NH) in place of HMPA or NMI as a Lewis base additive greatly improved the asymmetric addition of linear alkyl alkynes to linear aldehydes.[6] We also reported that the 3,3′-substituted H_8BINOL derivative (*S*)-**5** in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ catalyzed the highly enantioselective addition of a variety of alkynes to a range of aldehydes at room temperature.[7]



With the use of the chiral catalysts based on BINOL and its derivative **5**,[3,6,7] we have prepared structurally diverse chiral propargylic alcohols with high enantiomeric purity. This has allowed us to explore their applications in the synthesis of various chiral organic compounds.[7b,8] As shown in Scheme 1, we have conducted the catalytic hydration of chiral propargylic alcohols to generate tetronic acids[8a] and the amine addition to produce amino furanones.[8b] We have also performed a tandem ring-closing metathesis and hydrogenation reaction in the presence of the Grubbs carbene catalyst to generate functional cycloalkenes.[7b]

SCHEME 2. Intermolecular and Intramolecular PK Reactions



The Pauson−Khand (PK) reaction is a powerful tool to construct cyclopentenones.[9] Discovered first as an intermolecular reaction in the early 1970s,[10] the PK reaction is a formal [2 + 2 + 1] cycloaddition of an alkyne, alkene, and carbon monoxide (Scheme 2). A decade later, Schore and coworkers pioneered the intramolecular reaction,[11] opening the access to multicyclic ring structures through this methodology (Scheme 2). Although propargylic alcohol-based enynes including propargyl allyl ethers have been used for the PK reaction, most of the work was conducted on achiral or racemic propargylic alcohols.[12] In cases where enantiomerically enriched propargylic alcohols were used, often additional chiral centers were present for the isolation of the enantiomers and to contribute to the stereocontrol of the reaction.[13,14] We have investigated the use of the catalytic asymmetric alkyne addition to aldehydes to prepare chiral en-ynes of high enantiomeric purity for the intramolecular

(5) Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 5457–5460.
(6) Du, Y. H.; Turlington, M.; Zhou, X.; Pu, L. *Tetrahedron Lett.* **2010**, *51*, 5024–5027.
(7) (a) Turlington, M.; DeBerardinis, A. M.; Pu, L. *Org. Lett.* **2009**, *11*, 2441–2444. (b) Yue, Y.; Turlington, M.; Yu, X.-Q.; Pu, L. *J. Org. Chem.* **2009**, *74*, 8681–8689.
(8) (a) Rajaram, A. R.; Pu, L. *Org. Lett.* **2006**, *8*, 2019–2021. (b) Zhou, L.-H.; Yu, X.-Q.; Pu, L. *J. Org. Chem.* **2009**, *74*, 2013–2017.
(9) Selected reviews: (a) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297–341. (b) Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657–1668. (c) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3283. (d) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32–42. (e) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328–2336.
(10) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1971**, 36. (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 975–977. (c) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.
(11) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436–5438.

SCHEME 3. Asymmetric Alkyne Addition to Enals To Prepare Chiral En-Ynes

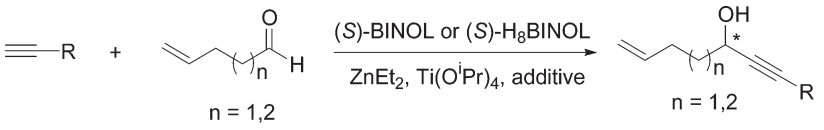
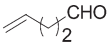
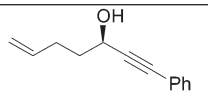
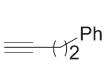
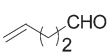
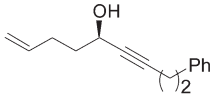
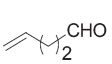
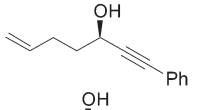
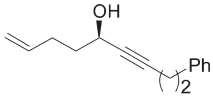
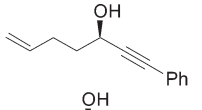
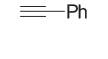
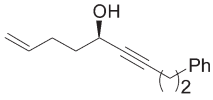
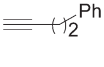
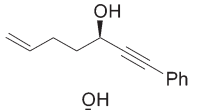
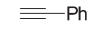
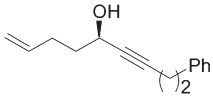
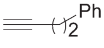
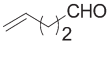
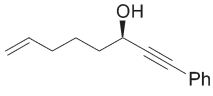
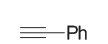
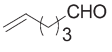
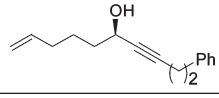


TABLE 1. Results for the Asymmetric Alkyne Addition to Enals in the Presence of BINOL-$ZnEt_2$-$Ti(O^iPr)_4$ with or without Lewis Base Additives

Entry	Alkyne	Aldehyde	Ligand	Additive	Product	Yield (%)	ee (%)[d]
1[a]			(*S*)-BINOL	NMI		32	68
2[a]			(*S*)-BINOL	NMI		26	69
3[b]			(*S*)-BINOL	HMPA		92	81
4[b]			(*S*)-BINOL	HMPA		28	82
5[c]			(*S*)-BINOL	-		88	94
6[c]			(*S*)-BINOL	-		95	95
7[c]			(*S*)-H_8BINOL	-		87	91
8[c]			(*S*)-H_8BINOL	-		66	91
9[c]			(*S*)-BINOL	-		87	93
10[c]			(*S*)-BINOL	-		83	90

[a]Under nitrogen, a ligand (0.1 mmol, 20 mol %), NMI (0.025 mmol, 0.05 equiv), alkyne (1 mmol, 2 equiv), and $ZnEt_2$ (1 mmol, 2 equiv) were stirred in CH_2Cl_2 (6 mL) for 2 h at rt. $Ti(O^iPr)_4$ (0.5 mmol, 1 equiv) was added and the mixture was stirred for 1 h, followed by the addition of 4-pentenal (0.5 mmol). [b]Under nitrogen, a ligand (0.2 mmol, 40 mol %), HMPA (1 mmol, 2 equiv), alkyne (2 mmol, 4 equiv), and $ZnEt_2$ (2 mmol, 4 equiv) were stirred in CH_2Cl_2 (6 mL) for 1 h at rt. $Ti(O^iPr)_4$ (0.5 mmol, 1 equiv) was added and the mixture was stirred for 1 h, followed by the addition of 4-pentenal (0.5 mmol). [c]Under nitrogen, an alkyne (2 mmol, 4 equiv) and $ZnEt_2$ (2 mmol, 4 equiv) were heated at reflux in toluene (1 mL) for 4 h. Et_2O (8 mL), ligand (0.2 mmol, 40 mol %), and $Ti(O^iPr)_4$ (0.5 mmol, 1 equiv) were added and the reaction mixture was stirred for 1 h at rt followed by the addition of 4-pentenal (0.5 mmol). [d]Determined by HPLC analysis with a Chiralcel OD or Chiralpak AD-H column.

PK reaction. Two types of chiral en-ynes are prepared which are observed to undergo highly diastereoselective intramolecular PK cycloaddition with retention of their enantiomeric purity. Herein, these results are reported.

Results and Discussion

a. Using (*S*)-BINOL as the Chiral Ligand. 1. Catalytic Asymmetric Alkyne Additions to Enals To Generate Chiral Propargylic Alcohol-Based En-Ynes. We have examined the reaction of alkynes with enals in the presence of (*S*)-BINOL-$ZnEt_2$-$Ti(O^iPr)_4$ with or without the Lewis base additives to prepare the chiral propargylic alcohol-based en-ynes (Scheme 3) for the intramolecular PK reaction.

(12) (a) Magnus, P.; Exon, R.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861–5869. (b) Pearson, A. J.; Dubbert, R. A. *Organometallics* **1994**, *13*, 1656–1661. (c) Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396–1406. (d) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5881–5898. (e) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286–1288. (f) Berk, S. C.; Robert, B.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8593–8601. (g) Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1997**, *62*, 3762–3765. (h) Quintal, M. M.; Closser, K. D.; Shea, K. M. *Org. Lett.* **2004**, *6*, 4949–4952. (i) Ajamian, A.; Gleason, J. L. *Org. Lett.* **2001**, *3*, 4161–4164. (j) Moradov, D.; Quntar, A.A A A.; Youssef, M.; Smoum, R.; Rubinstein, A.; Srebnik, M. *J. Org. Chem.* **2009**, *74*, 1029–1033.

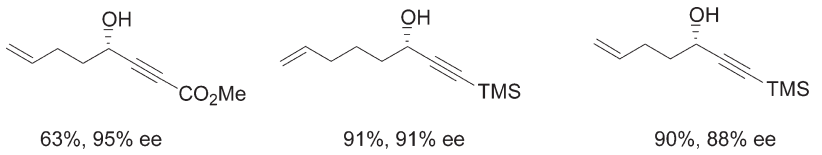
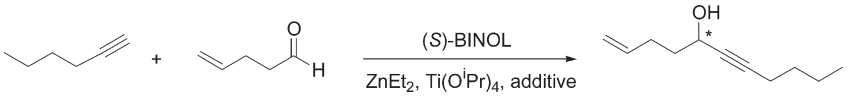


FIGURE 1. Chiral En-Ynes Prepared by Using (*S*)-**5**.

SCHEME 4. Asymmetric Addition of a Linear Alkyl Alkyne to a Linear Aldehyde



The results are summarized in Table 1. In entries 1 and 2, NMI was used as the additive to allow the reaction to be conducted at room temperature but the enantioselectivity was low.[5,6] When HMPA was used as the additive,[3c,d] the enantioselectivity was much higher (entries 3 and 4). When our original BINOL-catalyzed procedure involving the heating of the alkyne with $ZnEt_2$ in toluene at reflux in the first step was used,[3a,b] excellent ee values and yields were obtained for the addition of both the aryl and alkyl alkynes to 4-pentenal (entries 5 and 6). When the partially hydrogenated BINOL, H_8BINOL, was used, the ee was slightly lower (entries 7 and 8). The addition of the alkynes to 5-hexenal by heating the alkynes with $ZnEt_2$ in toluene and using BINOL as the catalyst also gave high ee values and yields (entries 9 and 10).

We also studied the reaction of a linear alkyl alkyne, 1-hexyne, with 4-pentenal (Scheme 4). Using (*S*)-BINOL as the ligand and the conditions in the footnote c of Table 1 gave the corresponding propargylic alcohol product with 83% ee and 76% yield. Recently, we found that the use of Cy_2NH (5 mol %) as the additive is superior to NMI and it allows the linear alkyl alkyne addition to linear aldehydes to be conducted at room temperature with good enantioselectivity.[6] For the reaction of 1-hexyne with 4-pentenal in the presence of (*S*)-BINOL (20 mol %), $ZnEt_2$ (2 equiv), $Ti(O^iPr)_4$ (0.5 equiv), and Cy_2NH (5 mol %) in diethyl ether at room temperature, the propargylic alcohol product was obtained with 87% ee and 63% yield.[6] When the reaction was carried out by doubling the amount of (*S*)-BINOL, $ZnEt_2$, and $Ti(O^iPr)_4$ and still using 5 mol % Cy_2NH, the product was obtained with 89% ee and 73% yield.

b. Using the H_8BINOl Derivative (*S*)-5 as the Chiral Ligand. Following our recently reported procedure,[7] we have used the chiral ligand (*S*)-**5** (20 mol %) in combination with $ZnEt_2$ (2 equiv) and $Ti(O^iPr)_4$ (50 mol %) in a mixed solvent of diethyl ether/THF (1:5) to catalyze the functional alkyne addition to enals at room temperature to generate the propargylic alcohol-based chiral en-ynes shown in Figure 1. We find that for the reaction of methyl propiolate with 4-pentenal and that of trimethylsilyl acetylene with 5-hexenal, the observed enantioselectivities are very close to those reported. However, for the reaction of trimethylsilyl acetylene with 4-pentenal, the observed enantioselectivity (88% ee) is lower than that reported (95% ee).[7b] These ee values were determined by using the ^{1}H NMR spectra of their esters prepared with (*R*)-PhCH(OAc)CO_2H. The discrepancy in ee is found to be due to the use of two different NMR integration programs with MestReC (version 4.9.9.6) being the previously used and MestReNova (version 6.0.2−5475) the current one. HPLC (chiral columns) analysis of the analogous compounds has confirmed the accuracy of the current NMR integration program. We also tested the use of the two (*S*)-BINOL methods (methods I and II in the footnote of Table 2) for the trimethylsilyl acetylene addition to 4-pentenal, which gave 84% ee (37% yield) and 85% ee (58% yield), respectively. Thus, (*S*)-**5** is better than (*S*)-BINOL for the trimethylsilyl acetylene addition to 4-pentenal and these two ligands give the opposite enantiomers of the product.

2. Reaction of Chiral Propargylic Alcohols with Allyl Bromide To Prepare Chiral En-Ynes. We have prepared another type of chiral en-ynes from the reaction of the chiral propargylic alcohols, generated from the catalytic asymmetric alkyne addition, with allyl bromide (Scheme 5). As shown in Table 2, the three different methods described in the above section were used for the catalytic asymmetric alkyne addition to aldehydes to generate the corresponding propargylic alcohols with 81−95% ee. The reactions of these propargylic alcohols with allyl bromide in entries 1−4 were conducted in the presence of KOH in DMSO at room temperature to form the chiral propargyl allyl ethers. The reaction with allyl bromide in entry 5 was conducted by treatment with ^{n}BuLi (1 equiv) at −78 °C in THF followed by the addition of allyl bromide.

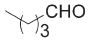
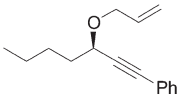
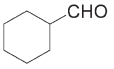
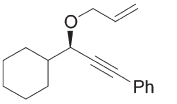
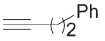
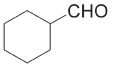
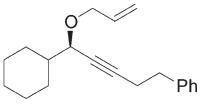
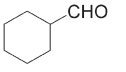
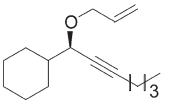
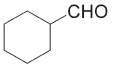
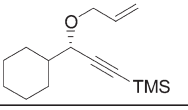
3. The Intramolecular PK Reactions of the Chiral Propargylic Alcohol-Based En-Ynes. With the chiral propargylic alcohol-based en-ynes in hand we explored their intramolecular PK reactions to generate various bicyclic enones. For a number of years after its discovery the PK reaction suffered from low yields and a narrow substrate scope, but recent advances in the use of promoters have greatly expanded the utility of this reaction.[9] We chose to employ the amine oxides

(13) (a) Almansa, C.; Moyano, A.; Serratosa, F. *Tetrahedron* **1988**, *44*, 2657–2662. (b) Alcaide, B.; Polanco, C.; Sierra, A. A. *J. Org. Chem.* **1998**, *63*, 6786–6796. (c) Mukai, C.; Kim, J. S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem.* **1999**, *64*, 6822–6832. (d) Mukai, C.; Sonobe, H.; Kim, J. S.; Hanaoka, M. *J. Org. Chem.* **2000**, *65*, 6654–6659. (e) Ishikawa, T.; Shimizu, K.; Ishii, H.; Ikeda, S.; Saito, S. *J. Org. Chem.* **2001**, *66*, 3834–3847. (f) Mukai, C.; Kozaka, T.; Suzuki, Y.; Kim, I. J. *Tetrahedron Lett.* **2002**, *43*, 8575–8578. (g) Ishikawa, T.; Ishii, H.; Shimizu, K.; Nakao, H.; Urano, J.; Kudo, T.; Saito, S. *J. Org. Chem.* **2004**, *69*, 8133–8135. (h) Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, *61*, 4053–4065.

(14) (a) Honda, T.; Kaneda, K. *J. Org. Chem.* **2007**, *72*, 6541–6547. (b) The asymmetric homoallylzinc addition to a Co-coordinated propargyl aldehyde was used to generate chiral propargylic alcohols for the intramolecular PK reaction: Stumpf, A.; Hwang, S. H.; Kim, J. S.; Jeong, N. *Bull. Korean Chem. Soc.* **2004**, *25*, 1621–1622.

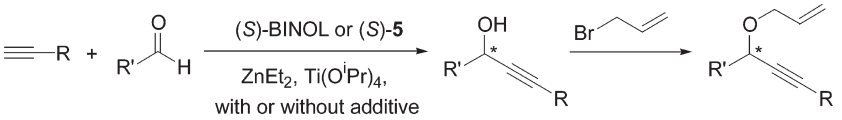
(15) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289.

TABLE 2. Preparation of the Chiral Propargyl Allyl Ethers

Entry	Alkyne	Aldehyde	Method[a]	Propargylic Alcohol Yield(%)	Propargylic Alcohol ee(%)[b]	Chiral En-Yne Product[c]	Yield (%)
1			I	89	95		73
2			I	88	96		69
3			I	94	84		73
4			II	84	81		57
5			III	88	88		73

[a]Method I: Under nitrogen, an alkyne (2 mmol, 4 equiv) and $ZnEt_2$ (205 μL, 2 mmol, 4 equiv) were heated at reflux in toluene (1 mL) for 4 h. Et_2O (8 mL), (*S*)-BINOL (57.2 mg, 0.2 mmol, 40 mol %), and $Ti(O^iPr)_4$ (150 μL, 0.5 mmol, 1 equiv) were added and the reaction mixture was stirred for 1 h at rt followed by the addition of an aldehyde (0.5 mmol). Method II: Under nitrogen, (*S*)-BINOL (57.2 mg, 0.2 mmol, 40%), Cy_2NH (5 μL, 0.025 mmol, 5 mol %), 1-hexyne (230 μL, 2 mmol, 4 equiv), and $ZnEt_2$ (205 μL, 2 mmol, 4 equiv) were combined in Et_2O (6 mL) and the mixture was stirred at rt for 24 h. $Ti(O^iPr)_4$ (150 μL, 0.5 mmol, 1 equiv) was added and the mixture was stirred for 1 h, followed by the addition of an aldehyde (0.5 mmol). Method III: Under nitrogen, (*S*)-**5** (61.9 mg, 0.1 mmol, 20 mol %), $ZnEt_2$ (103 μL, 1 mmol, 2 equiv), and an alkyne (1 mmol, 2 equiv) were combined in Et_2O (1 mL) and the mixture was stirred for 16 h. THF (5 mL) and $Ti(O^iPr)_4$ (74 μL, 0.25 mmol, 50 mol %) were added and the mixture was stirred for 1 h followed by addition of an aldehyde (0.5 mmol). [b]Determined by chiral HPLC analysis (Chiralcel OD column) for entries 1 and 2, and by analysis of the ^1H spectra of the esters prepared with (*R*)-PhCH(OAc)CO_2H for entries 3−5. [c]For entries 1−4: A propargylic alcohol (1 equiv) and allyl bromide (3 equiv) were dissolved in DMSO (0.1 M). Powdered KOH (2 equiv) was added and the reaction was stirred for 1.5 h. Entry 5: A propargylic alcohol (1 equiv) was dissolved in THF (0.2 M) and the mixtue was cooled to −78 °C. ^{n}BuLi (1 equiv) was added. After 10 min, allyl bromide (8 equiv) was added. The reaction was warmed to −40 °C, DMSO (2 equiv) was added, and the reaction was allowed to warm to rt overnight.

SCHEME 5. Asymmetric Alkyne Addition to Enals To Prepare the Chiral Propargyl Allyl Ethers



discovered by Schreiber[15] and Jeong[16] because they are the most popular and effective promoters of the PK reaction. The amine oxides are thought to accelerate the reaction by oxidizing one of the carbon monoxide ligands in the intermediate cobalt−alkyne complex, releasing carbon dioxide and opening a coordination site for the alkene on one of the cobalt atoms. The use of amine oxides has made it possible to perform the reaction at room temperature or below, where traditionally elevated temperatures are required for the dissociation of a carbon monoxide ligand to open a coordination site on cobalt. The amine oxides commonly used are *N*-methylmorpholine *N*-oxide (NMO), introduced by Schreiber, and trimethylamine *N*-oxide (TMANO), introduced by Jeong. In most cases, we used NMO since this compound is much less expensive.

a. Using En-Ynes Prepared from 4-Pentenal To Generate the 5,5-Fused Bicyclic Products. We investigated the intramolecular PK reaction of the propargylic alcohol-based en-ynes prepared from the asymmetric alkyne addition to 4-pentenal to generate the 5,5-fused bicyclic products (Scheme 6). The results are summarized in Table 3. We found that the direct use of the propargylic alcohol could not give the desired product (entry 1). Therefore, the acetyl-protected en-ynes were prepared by treatment of the alcohols with acetic anhydride in the presence of DMAP. These substrates were then treated with $Co_2(CO)_8$ (1.2 equiv) in methylene chloride at room temperature followed by addition of NMO (method A). As shown in entries 2−4, the PK cycloaddition products were obtained with excellent diastereoselectivity from various propargylic acetates. However, when the acetate of the propargylic alcohol prepared from the trimethylsilyl acetylene addition to 4-pentenal was used, the desired PK reaction product could not be obtained (entry 5). Removal of the TMS group allowed the formation of the cycloaddition product in good yield but with significantly reduced diastereoselectivity (entry 6). When the cobalt complex of the acetate was heated in acetonitrile at 72−75 °C (method B), its decomposition was observed rather than the desired PK cycloaddition (entry 7). We then replaced the acetyl protecting group with a more stable methyl

(16) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204.

SCHEME 6. Intramolecular PK Reaction of the En-Ynes Derived from the Asymmetric Alkyne Addition to 4-Pentenal

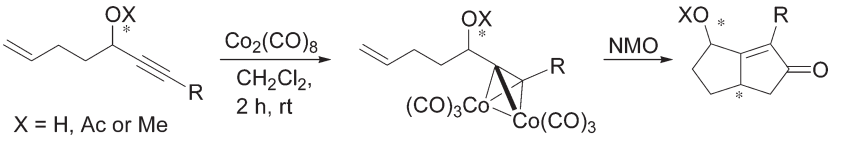
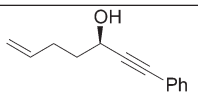
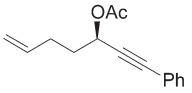
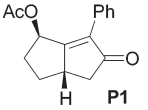
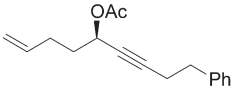
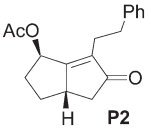
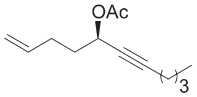
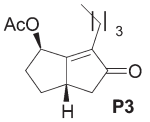
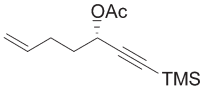
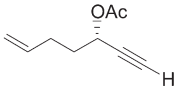
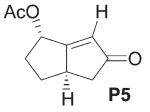
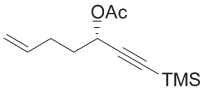
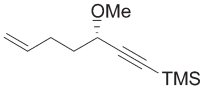
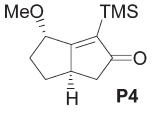
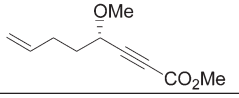


TABLE 3. Results for the Intramolecular PK Reaction To Form the 5,5-Fused Bicyclic Products

Entry	Enyne	ee	Method[a]	Product	Yield[b]	dr[c]
1		94	A	-	-	-
2		94	A	 **P1**	94	95:5
3		95	A	 **P2**	81	93:7
4		89	A	 **P3**	85	95:5
5		88	A	-	-	-
6		88	A	 **P5**	83	75:25
7		88	B	-	-	-
8		88	B	 **P4**	69	>99:1
9		95	A, B	-	-	-

[a]Method A: An en-yne (0.25 mmol) and $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) were combined in CH_2Cl_2 (12.5 mL, 0.02 M) and the mixture was stirred for 2 h. NMO (293 mg, 2.5 mmol, 10 equiv) was added and the reaction was stirred for 3−5 h. Method B: An en-yne (0.25 mmol) and $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) were combined in CH_2Cl_2 (10 mL, 0.025 M) and the mixture was stirred for 2 h. CH_2Cl_2 was removed under vacuum and MeCN (10 mL, 0.025 M) was added. The reaction was heated at 72−75 °C for 24 h. [b]Combined yield of diastereomers. [c]Diastereomers observed by ^{1}H NMR and dr quantified by HPLC analysis (Chiralpak AD-H column).

group. As shown in entry 8, using method B led to the formation of the biscyclopentanoid product from the methyl ether of the propargylic alcohol with very high diastereoselectivity. The en-yne prepared from methyl propiolate addition to 4-pentenal could not undergo the intramolecular PK reaction by using either method A or B (entry 9). Substrates like this are historically challenging for the PK reaction.

The diastereoselectivities in Table 3 were determined by HPLC analysis with a Chiralpak AD-H column. To determine the enantiomeric purity of the PK cycloaddition product, we prepared the racemic version of the en-yne in entry 2 and found that the enantiomers of the cycloaddition product could be resolved by using a HPLC-Chiralpak AD-H column. This analysis showed that the enantiomeric purity of the starting en-yne in entry 2 was maintained in the product (94% ee). We also found that the diastereoselectivity for the racemic en-yne in the PK reaction was the same as that observed for the enantiomerically enriched one. Thus, the intermolecular interaction of the chiral en-yne had minimum effect on the intramolecular cyclization.

In our experiments, the major diastereomer in each of the PK reactions shown in Table 3 could be easily separated by column chromatography, allowing the isolation of a single stereoisomer for these reactions. The products were determined to be the cis-bicyclic compounds (Figure 2) by correlation

with the known chemical shifts of the related compounds.[17a] The NMR signal of H_a was shown to have a more upfield chemical shift in the cis isomer than that in the trans isomer. All of the products in Table 3 manifested this diagnostic chemical shift pattern. For example, for the product in entry 2, the H_a in the major cis diastereomer resonated at 5.7 ppm while H_a in the minor trans diastereomer resonated at 6.4 ppm. The assignment of the stereochemistry in these products is in accord with the well-documented literature precedent for this type of PK transformation.[17,18]

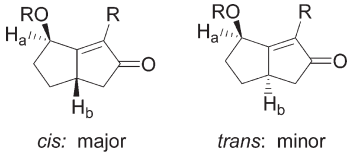


FIGURE 2. The cis and trans isomers of the 5,5-fused bicyclic products.

b. Using En-Ynes Prepared from 5-Hexenal To Generate the 6,5-Fused Bicyclic Products. We also studied the intramolecular PK reaction of the chiral propargylic alcohol-based en-ynes prepared from the asymmetric alkyne addition to 5-hexenal to generate the 6,5-fused bicyclic products (Scheme 7). The results are summarized in Table 4. When the acetate of the propargylic alcohol-based en-yne was used, only a very small amount of the cycloaddition product was obtained (entry 1). This suggests that there should be competition between the decomposition of the propargylic acetate and the cycloaddition. Formation of the 5,5-bicyclic product shown in entry 2 of Table 3 might be faster than the formation of the 6,5-bicyclic product here, resulting in the completely different reaction outcome. We thus replaced the acetyl protecting group with a more stable methyl group that allowed the cycloaddition (method A) to proceed smoothly to give the desired 6,5-bicyclic products with

SCHEME 7. Intramolecular PK Reaction of the En-Ynes Derived from the Asymmetric Alkyne Addition to 5-Hexenal

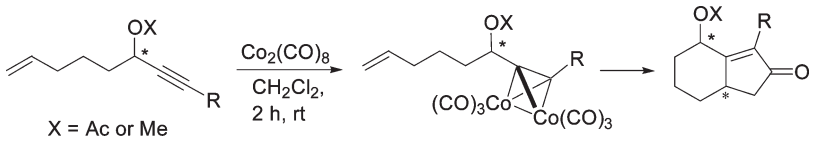
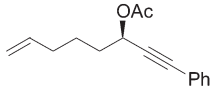
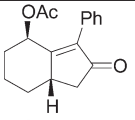
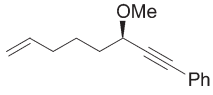
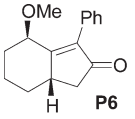
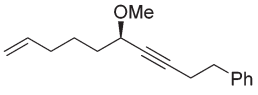
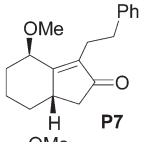
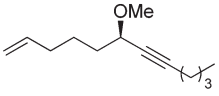
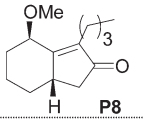
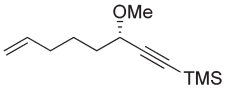
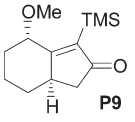
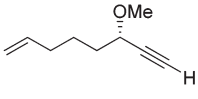
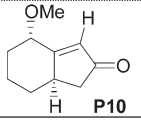


TABLE 4. Results for the Intramolecular PK Reactions To Form the 6,5-Fused Bicyclic Products

Entry	Enyne	ee	Method[a]	Product	Yield[b]	dr[c]
1		93	A		Very low	
2		93	A	 **P6**	93	92:8
3		90	A	 **P7**	77	93:7
4		83	A	 **P8**	79	95:5
5		91	B	 **P9**	47	94:6
6			C		56	94:6
7			D		81	87:13
8		91	A	 **P10**	61	84:16

[a]Method A, B: See Table 3. Method C: An en-yne (0.25 mmol) and $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) were combined in CH_2Cl_2 (5 mL, 0.05 M) and the mixture was stirred for 2 h. CH_2Cl_2 was removed under vacuum and 1,4-dioxane (5 mL, 0.05 M) and *n*-butyl methyl sulfide (465 μL, 3.79 mmol, 15.15 equiv) were added. The reaction was heated at 100 °C for 16 h. Method D: An en-yne (0.25 mmol) and $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) were combined in toluene (5 mL, 0.05 M) and the mixture was stirred for 2 h. TMTU (132 mg, 1 mmol, 4 equiv) was added and the reaction was heated at 112 °C for 16 h. [b]Combined yield of diastereomers. [c]Diastereomers observed by ^{1}H NMR and dr quantified by HPLC analysis (Chiralpak AD-H or Chiralcel OD column).

excellent diastereoselectivity and yield (entry 2). The reactions of two other methyl ethers of the propargylic alcohol-based en-ynes with the use of method A also gave high diastereoselectivities and yields (entries 3 and 4). For the en-yne prepared from the trimethylsilyl acetyelene addition, when method B was used, the desired cycloaddition product was obtained with high diastereoselectivity

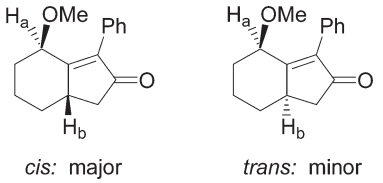
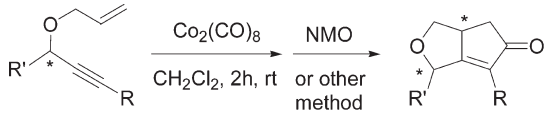


FIGURE 3. The cis and trans isomers of the 6,5-fused bicyclic products.

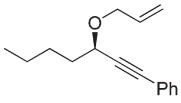
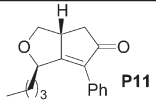
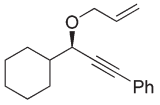
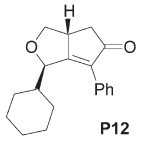
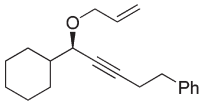
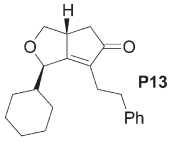
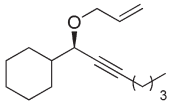
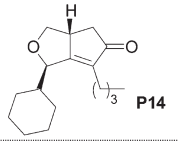
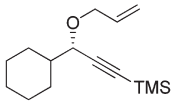
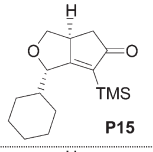
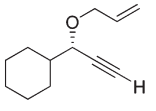
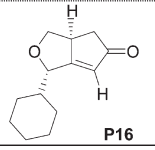
SCHEME 8. Intramolecular PK Reaction of the Chiral Propargyl Allyl Ethers



but in lower yield (entry 5). A different promoter *n*-butyl methyl sulfide was used in place of NMO for the cycloaddition and an elevated reaction temperature of 100 °C was applied (method C)[19] that gave an increased yield also with the same high diastereoselectivity (entry 6). When tetramethylthiourea (TMTU) was used as the promoter under the refluxing toluene condition,[20] the product was obtained in high yield with a small reduction in diastereoselectivity (entry 7). When the TMS group on the alkyne was removed, the resulting en-yne underwent the PK reaction in the presence of NMO with lower diastereoselectivity (entry 8). This is similar to that observed in the formation of the fused 5,5-bicyclic product in entry 6 of Table 3. The stereochemistry of the cycloaddition is sensitive to the size of the substituent on the alkyne with the smaller substituent giving lower selectivity.

In accord with literature precedence,[17c] the cis structure is assigned to the major diastereomer of the 6,5-fused bicyclic products (Figure 3). This assignment is supported by the NOESY spectra of the product in entry 2 of Table 4. Both the major and minor diastereomers of the product in entry 2 were isolated. The NOESY spectrum of the minor diastereomer indicates an NOE effect between H_a and H_b that is absent in the major diastereomer. That is, the minor diastereomer is the trans isomer and the major diastereomer is the cis isomer. The high enantiomeric purity of the propargylic

TABLE 5. Results for the Intramolecular PK Reactions of the Chiral Propargylic Allylic Ethers

Entry	Enyne	ee	Method[a]	Product	Yield[b]	dr[c]
1		95	A	 P11	82	87:13
2		96	A	 P12	83	>99:1
3		84	A	 P13	66	>99:1
4		81	A	 P14	64	>99:1
5		88	A	 P15	33	>99:1
6			B		31	>99:1
7			E		50	>99:1
8		88	A	 P16	55	65:35

[a]Method A, B: See Table 3. Method E: An en-yne (0.2 mmol, 1 equiv), $Co_2(CO)_8$ (78.7 mg, 0.23 mmol, 1.15 equiv), and 4-Å MS (8 wt. equiv) were combined in CH_2Cl_2 (5 mL, 0.04 M) and the mixture was stirred for 2 h. The reaction mixture was cooled to −20 °C and TMANO (120.2 mg, 1.6 mmol, 8 equiv) was added over 10 min. After bubbling the reaction mixture with compressed air (passed through a drying filter) for 20 min the reaction was warmed to rt and stirred 16 h. [b]Combined yield of diastereomers. [c]Diastereomers observed by ^{1}H NMR and dr quantified by chiral HPLC analysis (Chiralpak AD-H and Chiralcel OD column).

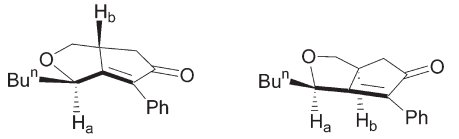


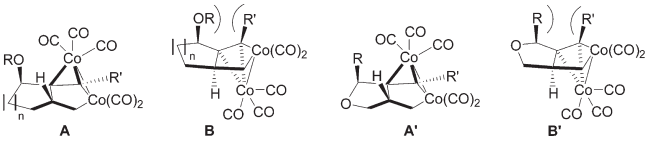
FIGURE 4. The cis and trans isomers of the 5,5-fused bicyclic products from the propargyl allyl ethers.

alcohol starting material was found to be maintained in the 6,5-fused bicyclic product by analyzing the racemic product in entry 2 with a HPLC-Chiralcel OB-H column.

c. Using the Chiral Propargyl Allyl Ethers for the PK Reaction. The PK reactions of the chiral en-ynes made of the propargyl allyl ethers are studied (Scheme 8). The results are summarized in Table 5. In most cases, NMO served as an efficient promoter for the cycloaddition. For the en-yne prepared from a linear aldehyde, the observed dr was 87:13 (entry 1). This diastereoselectivity was greatly enhanced when the en-ynes prepared from the reaction of cyclohexanecarboxaldehyde, a branched aliphatic aldehyde, with a variety of alkynes were used. For these substrates only one diastereomer was observed in the cycloaddition product (entries 2−7). For the en-yne prepared from trimethylsilylacetylene, three methods were tested to promote the cycloaddition. As shown in entries 5 −7, all three methods gave high diastereoselectivity. Using NMO as the promoter (method A, entry 5) or heating in acetonitrile (method B, entry 6) gave lower yield than using TMANO as the promoter in the presence of air (method E, entry 7).[21] The small hydrogen substituted alkyne gave much lower diastereoselectivity (entry 8) than those bearing an alkyl, aryl, or trimethylsilyl substituent (entries 2−7).

The cis diastereomer is expected to be the major product for the PK reaction of the propargyl allyl ethers. Analyses of the major and minor diastereomers of the product in entry 1 by NOESY spectroscopy support this structural assignment. A NOE effect is observed between H_a and H_b in the minor diastereomer but not in the major diastereomer (Figure 4). Therefore, the minor diastereomer is determined to be the trans isomer and the major one to be the cis isomer. Notably, formation of the related trans isomer as the major product was recently reported via a PK-type reaction in the presence of a $PdCl_2$-thiourea catalyst.[22] This method in combination with our work should provide access to all four possible stereoisomers of the products with high optical purity. In our study, the high enantiomeric purity of the propargylic alcohol is found to be maintained in the PK cycloaddition product by analyzing the racemic product in entry 2 with a HPLC-Chiralcel OD column.

4. Discussion about the Stereoselectivity of the Intramolecular PK Reaction of the Chiral Propargylic Alcohol-Based En-Ynes. Magnus[12a,18] and others[17] have proposed a mechanistic explanation for the formation of the cis isomer in the intramolecular PK reaction of the en-ynes analogous to those described above. According to the proposed mechanism, the stereo discriminating step occurs during the formation of the cobalt-metallocycles. Between the two possible metallocycle intermediates **A** and **B**, **B** should be less favorable because of the 1,3-pseudoaxial steric interactions between the OR and R′ groups. This interaction is not present in the metallocycle **A**, which makes its formation more favorable to give the cis product as the major diastereomer. This mechanism is consistent with our observation that a larger R′ group on the alkyne gives much higher diastereoselectivity than when R′ is a hydrogen atom. The same mechanistic explanation can be extended to the PK reaction of the propargyl allyl ethers as shown in the more favorable intermediate metallocycle **A**′ and the less favorable one **B**′. We have found that when the R group of the aldehyde starting material is a bulkier cyclohexyl ring, the diastereoselectivity is much greater than when R is a linear alkyl group, and a bulkier R′ group on the alkyne also gives much higher diastereoselectivity than when R′ is a hydrogen atom.



Summary

We have demonstrated that the use of the catalytic asymmetric alkyne addition methodology developed in our laboratory can provide rapid access to a variety of chiral propargylic alcohol-based en-yne precursors with high enantiomeric purity for the PK reaction. With the protection of the propargylic alcohols with either an acetyl or a methyl group, the resulting en-ynes can undergo intramolecular PK reaction to form the corresponding optically active 5,5- and 5,6-fused bicyclic products with high diastereoselectivity. In the major product, the propargylic substituent and the bridgehead hydrogen are cis with respect to each other on the fused bicyclic rings. The high enantiomeric purity of the propargylic alcohols is maintained in the PK cycloaddition products. The chiral propargyl allyl ethers are also found to undergo highly diastereoselective PK cycloaddition with retention of enantiomeric purity. Thus, the chiral information in these en-yne precursors is efficiently transferred to the fused bicyclic products. These findings expand the utility of the chiral propargylic alcohols as precursors for diastereoselective transformation.

Experimental Section

General Procedures for the Intramolecular PK Reaction. Method A. Under nitrogen in a 25 mL flame-dried flask, an en-yne substrate (0.25 mmol, 1 equiv) was dissolved in CH_2Cl_2 (12.5 mL, 0.02 M). $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv)

(17) (a) Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett*. **1995**, *36*, 5761–5764. (b) Mukai, C.; Kim, J. S.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2903–2915. (c) Mukai, C.; Kim, J. S.; Uchiyama, M.; Hanaoka, M. *Tetrahedron Lett*. **1998**, *39*, 7909–7912. (d) Castro, J.; Moyano, A.; Pericas, M. A.; Antoni Riera, A. *Tetrahedron* **1995**, *51*, 6541–6556. (e) Breczinski, P. M.; Stumpf, A.; Hope, H.; Krafft, M. E.; Casalnuovo, J. A.; Schore, N. E. *Tetrahedron* **1999**, *55*, 6797–6812.

(18) Magnus, P.; Principe, L. M. *Tetrahedron Lett*. **1985**, *26*, 4851–4854.

(19) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771.

(20) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett*. **2005**, *7*, 593–595.

(21) (a) Velcicky, J.; Lanver, A.; Lex, J.; Prokip, A.; Wieder, T.; Schmalz, H. G. *Chem.—Eur. J*. **2004**, *10*, 5087–5110. (b) Lanver, A.; Schmalz, H. G. *Eur. J. Org. Chem*. **2005**, 1444–1458.

(22) Lan, Y.; Deng., L.; Liu, J.; Wang, C.; Wiest, O.; Yang, Z.; Wu, Y.-D. *J. Org. Chem*. **2009**, *74*, 5049–5058.

was added and the reaction mixture was stirred for 2 h, during which formation of the cobalt-complexed en-yne was observed by TLC analysis. To the dark amber colored solution was added *N*-methylmorpholine *N*-oxide (293 mg, 2.5 mmol, 10 equiv). The reaction was monitored by TLC. After the consumption of the cobalt-complexed en-yne (3−5 h), the cobalt blue solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (10−40% ethyl acetate) yielded a mixture of diastereomers. Both diastereomers were observable by ^{1}H NMR spectroscopy, and the diastereomeric ratio was determined by HPLC equipped with a Chiralcel OD or Chiralpak AD-H column. The major diastereomer was separated by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (10−40% ethyl acetate).

Method B. Under nitrogen in a 25 mL flame-dried flask, an en-yne substrate (0.25 mmol, 1 equiv) was dissolved in CH_2Cl_2 (10 mL, 0.025 M). $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) was added and the flask was fitted with a stopcock vacuum/nitrogen adaptor. After 2 h, the solvent was removed under vacuum, and the resulting amber colored oil was redissolved in acetonitrile (10 mL, 0.025 M). The flask was connected with a flame-dried reflux condenser fitted with a stopcock vacuum/nitrogen adaptor and the reaction mixture was heated at 72−75 °C for 24 h. The dark colored solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (0−30% ethyl acetate) yielded the product (in some cases as a mixture of diastereomers). The diastereomers were observable by ^{1}H NMR, and the diastereomeric ratio was determined by HPLC equipped wih a Chiralcel OD or Chiralpak AD-H column. The major diastereomer was separated by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (0−30% ethyl acetate).

Method C. Under nitrogen in a 25 mL flame-dried flask, an en-yne substrate (0.25 mmol, 1 equiv) was dissolved in CH_2Cl_2 (5 mL, 0.05 M). $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) was added and the flask was fitted with a stopcock vacuum/nitrogen adaptor. After 2 h, the solvent was removed under vacuum, and the resulting amber colored oil was redissolved in 1,4-dioxane (5 mL, 0.05 M). *n*-Butyl methyl sulfide (465 μL, 3.79 mmol, 15.15 equiv) was then added. The flask was connected with a flame-dried reflux condenser fitted with a stopcock vacuum/nitrogen adaptor and the reaction mixture was heated at 100 °C for 16 h. The dark colored solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (0−30% ethyl acetate) yielded the product (**P9**) as a mixture of diastereomers. The diastereomers were observable by ^{1}H NMR, and the diastereomeric ratio was determined by HPLC equipped with a Chiralcel OD column. The major diastereomer was separated by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (0−30% ethyl acetate).

Method D. Under nitrogen in a 25 mL flame-dried flask, an en-yne substrate (0.25 mmol, 1 equiv) was dissolved in toluene (5 mL, 0.05 M). $Co_2(CO)_8$ (102.6 mg, 0.3 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 2 h. To the resulting dark amber colored solution was added tetramethylthiourea (132 mg, 1 mmol, 4 equiv). The flask was connected with a flame-dried reflux condenser fitted with a stopcock vacuum/nitrogen adaptor and the reaction mixture was heated at 112 °C for 16 h. The dark colored solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (0−30% ethyl acetate) yielded the product (**P9**) as a mixture of diastereomers. The diastereomers were observable by ^{1}H NMR, and the diastereomeric ratio was determined by HPLC equipped with a Chiralcel OD column. The major diastereomer was separated by flash column chromatography on silica gel eluted with hexanes/ethyl acetate (0−30% ethyl acetate).

Method E. Under nitrogen in a 25 mL flame-dried flask, an en-yne substrate (0.2 mmol, 1 equiv) was dissolved in CH_2Cl_2 (5 mL, 0.04 M) containing activated 4-Å molecular sieves (8 wt equiv). $Co_2(CO)_8$ (78.7 mg, 0.23 mmol, 1.15 equiv) was added and the reaction mixture was stirred for 2 h, during which formation of the cobalt-complexed en-yne was observed by TLC analysis. The reaction mixture was cooled to −20 °C and TMANO (120.2 mg, 1.6 mmol, 8 equiv) was added in 4 equal portions over 10 min. The reaction mixture was then bubbled with compressed air (passed through a drying filter) for 20 min. The flask was then allowed to remain open to air, covering with drying tube. The cooling bath was removed and the reaction was allowed to warm to room temperature and stirred for 15 h. The cobalt blue solution was loaded onto a short silica gel column. Elution with hexanes/ethyl acetate (10−40% ethyl acetate) yielded the product (**P15**) as a single diastereomer.

Characterization of the PK Reaction Products. (1*R*,3a*S*)-5-Oxo-6-phenyl-1,2,3,3a,4,5-hexahydropentalen-1-yl acetate (P1): 94% yield. 95:5 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 254 nm, retention time: t_{major} = 56.3, 60.1, t_{minor} = 77.1. 94% ee determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 254 nm, retention time: t_{major} = 56.3, t_{minor} = 60.1. $[\alpha]^{25}_D$ −89.1 (*c* 0.89, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.37 (m, 3H), 5.65 (m, 1H), 3.22 (m, 1H), 2.90 (dd, 1H, *J* = 18.0, 6.6 Hz), 2.65 (p, 1H, *J* = 7.2 Hz), 2.31 (m, 2H), 2.17 (s, 3H), 1.94 (m, 1H), 1.17 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 175.7, 170.0, 138.3, 130.5, 128.8, 128.5, 128.0, 70.8, 43.1, 41.9, 35.1, 29.2, 21.2. HRMS (MH^+) calcd for $C_{16}H_{17}O_3$ 257.1183, found 257.1179.

(1*R*,3a*S*)-5-Oxo-6-phenethyl-1,2,3,3a,4,5-hexahydropentalen-1-yl acetate (P2): 81% yield. 93:7 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 235 nm, retention time: t_{major} = 39.7, 43.0, t_{minor} = 56.2. 94% ee determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 235 nm, retention time: t_{major} = 39.7, t_{minor} = 43.0. $[\alpha]^{25}_D$ −84.5 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (m, 5H), 5.17 (m, 1H), 2.94 (m, 1H), 2.85−2.75 (m, 1H), 2.66 (m, 4H), 2.11 (m, 3H), 2.01 (s, 3H), 1.82 (m, 1H), 0.95−0.82 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 176.1, 170.1, 141.3, 138.1, 128.7, 128.2, 125.9, 68.6, 42.3, 40.8, 33.7, 33.2, 28.9, 25.8, 21.0. HRMS (MH^+) calcd for $C_{18}H_{21}O_3$ 285.1496, found 285.1493.

(1*R*,3a*S*)-6-Butyl-5-oxo-1,2,3,3a,4,5-hexahydropentalen-1-yl acetate (P3): 85% yield. 95:5 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 221 nm, retention time: t_{major} = 7.6, t_{minor} = 9.6. $[\alpha]^{25}_D$ −91.9 (*c* 1.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (m, 1H), 3.02 (m, 1H), 2.69 (dd, 1H, *J* = 18.0, 6.0 Hz), 2.52 (p, 1H, *J* = 6.0 Hz), 2.24 (m, 3H), 2.07 (s, 3H), 2.06 (dd, 1H, *J* = 18.0, 3.0 Hz), 1.94 (m, 1H), 1.33 (m, 4H), 1.06 (p, 1H, *J* = 9.0 Hz), 0.88 (t, 3H, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 174.9, 170.2, 139.9, 68.8, 42.1, 41.3, 34.1, 30.3, 29.2, 23.6, 22.5, 21.0, 13.8. HRMS (MH^+) calcd for $C_{14}H_{21}O_3$ 237.1491, found 237.1485.

(4*S*,6a*R*)-4-Methoxy-3-(trimethylsilyl)-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (P4): 69% yield. >99:1 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 235 nm, retention time: t_{major} = 19.3. $[\alpha]^{25}_D$ 138.4 (*c* 1.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (m, 1H), 3.33 (s, 3H), 3.08 (m, 1H), 2.64 (dd, 1H, *J* = 18.0, 9.0 Hz), 2.24 (m, 2H), 2.03 (dd, 1H, *J* = 18.0, 3.0 Hz), 1.94 (m, 1H), 1.08 (m, 1H), 0.23 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 192.0, 139.0, 76.4, 56.2, 43.9, 43.7, 32.8, 28.1, −1.1. HRMS (MH^+) calcd for $C_{12}H_{21}O_2Si$ 225.1311, found 225.1308.

(1*S*,3a*R*)-5-Oxo-1,2,3,3a,4,5-hexahydropentalen-1-yl acetate (P5): 83% yield. 75:25 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 215 nm, retention time: t_{major} = 24.7, t_{minor} = 29.3. $[\alpha]^{25}_D$ 94.8 (*c* 0.67, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)

δ 6.13 (m, 1H), 5.67−5.63 (m, 1H), 3.12 (m, 1H), 2.69 (dd, 1H, J = 18.0 Hz, 6.0 Hz), 2.50 (p, 1H, J = 7.2 Hz), 2.31−2.22 (m, 1H), 2.11 (dd, 1H, J = 18.0 Hz, 3.0 Hz), 2.07 (s, 3H), 2.05−1.95 (m, 1H), 1.21−1.10 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 182.8, 170.3, 128.5, 69.5, 43.6, 42.6, 33.1, 28.9, 20.9. HRMS (MH^+) calcd for $C_{10}H_{13}O_3$ 181.0865, found 181.0873.

(4*R*,7a*S*)-4-Methoxy-3-phenyl-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (P6): 93% yield. 92:8 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 254 nm, retention time: t_{major} = 43.9, 45.8, t_{minor} = 56.8. 93% ee determined by HPLC analysis: Chiralpak OB-H column, 98:2 hexanes:^{i}PrOH, flow rate = 2 mL/min, λ = 254 nm, retention time: t_{major} = 17.1, t_{minor} = 12.8. $[\alpha]^{25}_D$ −96.6 (c 0.69, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 3H), 7.24 (m, 2H), 4.43 (t, 1H, J = 3.0 Hz), 3.19 (s, 3H), 3.07 (m, 1H), 2.74 (dd, 1H, J = 18.0, 6.0 Hz), 2.23 (m, 2H), 2.12 (dd, 1H, J = 18.0, 3.0 Hz), 1.92 (m, 1H), 1.57 (m, 2H), 1.18 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 174.2, 139.6, 130.8, 129.0, 128.3, 127.9, 72.9, 56.1, 41.7, 36.1, 35.6, 31.9, 19.7. HRMS (MH^+) calcd for $C_{16}H_{19}O_2$ 243.1385, found 243.1285.

(4*R*,7a*S*)-4-Methoxy-3-phenethyl-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (P7): 77% yield. 93:7 dr determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes:^{i}PrOH, flow rate = 0.3 mL/min, λ = 221 nm, retention time: t_{major} = 37.5, 38.5, t_{minor} = 44.5. $[\alpha]^{25}_D$ −58.3 (c 0.86, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 5H), 3.99 (t, 1H, J = 3.0 Hz), 3.09 (s, 3H), 2.62 (m, 6H), 2.05 (m, 1H), 1.93 (dd, 1H, J = 18.0, 3.0 Hz), 1.85 (m, 1H), 1.72 (m, 1H), 1.41 (m, 1H), 0.85 (m, 1H), 0.70 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 173.2, 141.2, 138.5, 128.7, 128.3, 126.0, 72.6, 55.9, 41.5, 36.2, 35.3, 34.0, 31.6, 25.0, 19.6. HRMS (MH^+) calcd for $C_{18}H_{23}O_2$ 271.1698, found 271.1688.

(4*R*,7a*S*)-3-Butyl-4-methoxy-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (P8): 79% yield. 95:5 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 221 nm, retention time: t_{major} = 5.7, 6.1, t_{minor} = 6.8. $[\alpha]^{25}_D$ −118.0 (c 1.335, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (t, 1H, J = 3 Hz), 3.24 (s, 3H), 2.86 (m, 1H), 2.56 (dd, 1H, J = 18.0, 6.3 Hz), 2.20 (m, 4H), 1.94 (dd, 1H, J = 18.0, 3.0 Hz), 1.84 (1H), 1.58 (m, 1H), 1.37 (m, 5H), 1.01 (m, 1H), 0.90 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 172.2, 140.3, 72.8, 56.1, 41.5, 36.0, 35.5, 32.3, 31.1, 22.7, 22.5, 19.8, 13.9. HRMS (MH^+) calcd for $C_{14}H_{23}O_2$ 223.1698, found 223.1694.

(4*S*,7a*R*)-4-Methoxy-3-(trimethylsilyl)-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (P9): 47% yield. 94:6 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 221 nm, retention time: t_{major} = 5.5, t_{minor} = 7.1. $[\alpha]^{25}_D$ 100.8 (c 0.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (t, 1H, J = 3.0 Hz), 3.26 (s, 3H), 2.97 (m, 1H), 2.53 (dd, 1H, J = 18.0, 6.9 Hz), 2.17 (m, 2H), 1.92 (dd, 1H, J = 18.0, 2.4 Hz), 1.85 (m, 1H), 1.49 (m, 2H), 1.09 (m, 1H), 0.24 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ213.2, 188.4, 139.7, 74.5, 56.0, 42.6, 39.1, 36.1, 32.7, 19.5, −0.1. HRMS (MH^+) calcd for $C_{13}H_{23}O_2Si$ 239.1467, found 239.1468.

(4*S*,7a*R*)-4-Methoxy-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (P10): 61% yield. 84:16 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 235 nm, retention time: t_{major} = 11.2, t_{minor} = 15.6. $[\alpha]^{25}_D$ 76.9 (c 0.37, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (m, 1H), 4.23 (br s, 1H), 3.25 (s, 3H), 2.95 (m, 1H), 2.61 (dd, 1H, J = 18.0, 6.0 Hz), 2.20 (m, 1H), 2.16 (m, 1H), 2.00 (dd, 1H, J = 18.0, 1.8 Hz), 1.83 (m, 1H), 1.55 (m, 2H), 1.10 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 181.2, 129.2, 75.0, 56.3, 42.2, 37.7, 35.2, 32.6, 19.6. HRMS (MH^+) calcd for $C_{10}H_{15}O_2$ 167.1072, found 167.1074.

(1*R*,3a*R*)-1-Butyl-6-phenyl-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (P11): 82% yield. 87:13 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 14.5, 15.3, t_{minor} = 19.7. $[\alpha]^{25}_D$ 165.07 (c 1.28, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 5H), 4.81 (m, 1H), 4.39 (t, 1H, J = 6.0 Hz), 3.32 (m, 2H), 2.82 (dd, 1H, J = 18.0, 6.0 Hz), 2.30 (dd, 1H, J = 18.0, 3.0 Hz), 1.82 (m, 2H), 1.42 (m, 4H), 0.90 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 179.9, 135.0, 130.9, 128.5, 128.4, 128.2, 76.3, 71.2, 42.7, 39.7, 34.9, 27.5, 22.5, 13.9. HRMS (MH^+) calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1535.

(1*R*,3a*R*)-1-Cyclohexyl-6-phenyl-3a,4-dihydro-1*H*-cyclopenta-[*c*]furan-5(3*H*)-one (P12): 83% yield. >99:1 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 17.0. 96% ee determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 17.0, t_{minor} = 14.2. $[\alpha]^{25}_D$ 247.0 (c 2.18, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H), 4.72 (d, 1H, J = 3.0 Hz), 4.38 (t, 1H, J = 6.0 Hz), 3.36−3.25 (m, 2H), 2.80 (dd, 1H, J = 18.0, 6.0 Hz), 2.28 (dd, 1H, J = 18.0, 3.0 Hz), 1.72−1.56 (m, 6H), 1.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 179.6, 135.9, 131.2, 128.4, 128.2, 80.7, 71.2, 43.4, 43.1, 39.5, 29.4, 28.0, 26.2, 26.0. HRMS (MH^+) calcd for $C_{19}H_{23}O_2$ 283.1698, found 283.1699.

(1*R*,3a*R*)-1-Cyclohexyl-6-phenethyl-3a,4-dihydro-1*H*-cyclopenta-[*c*]furan-5(3*H*)-one (P13): 66% yield. >99:1 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 11.3. $[\alpha]^{25}_D$ 144.3 (c 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 5H), 4.21 (t, 1H, J = 6.0 Hz), 3.91 (d, 1H, J = 6.0 Hz), 3.01 (m, 2H), 2.80 (m, 2H), 2.56 (m, 3H), 2.05 (dd, 1H, J = 18.0, 3.0 Hz), 1.68 (m, 5H), 1.46 (m, 1H), 1.23 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 179.1, 141.2, 136.5, 128.5, 128.4, 126.2, 80.2, 71.4, 43.0, 42.6, 39.1, 33.4, 29.2, 28.8, 26.9, 26.2, 26.1, 25.9. HRMS (MH^+) calcd for $C_{21}H_{27}O_2$ 311.2011, found 311.2005.

(1*R*,3a*R*)-6-Butyl-1-cyclohexyl-3a,4-dihydro-1*H*-cyclopenta-[*c*]furan-5(3*H*)-one (P14): 64% yield. >99:1 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 7.2. $[\alpha]^{25}_D$ 71.2 (c 1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (d, 1H, J = 6.0 Hz), 4.29 (t, 1H, J = 6.0 Hz), 3.17 (m, 2H), 2.62 (dd, 1H, J = 18.0, 6.0 Hz), 2.20 (m, 2H), 2.06 (dd, 1H, J = 18.0 Hz, 2.7 Hz), 1.69 (m, 6H), 1.26 (m, 9H), 0.90 (t, 3H, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 177.7, 137.7, 80.3, 71.4, 42.9, 42.7, 38.9, 29.8, 29.1, 26.1, 26.0, 24.2, 22.7, 13.8. HRMS (MH^+) calcd for $C_{17}H_{27}O_2$ 263.2011, found 263.2007.

(1*S*,3a*S*)-1-Cyclohexyl-6-(trimethylsilyl)-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (P15): 50% yield. >99:1 dr determined by HPLC analysis: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 254 nm, retention time: t_{major} = 6.2. $[\alpha]^{25}_D$ −152.9 (c 0.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (d, 1H, J = 3.0 Hz), 4.29 (t, 1H, J = 6.9 Hz), 3.21 (m, 2H), 2.56 (dd, 1H, J = 18.0, 6.0 Hz), 2.05 (dd, 1H, J = 18.0, 3.6 Hz), 1.77 (m, 2H), 1.65 (m, 4H), 1.23 (m, 5H), 0.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 192.6, 136.3, 80.8, 71.0, 46.3, 42.8, 40.6, 30.0, 27.4, 26.5, 26.1, 26.0, −1.1. HRMS (MH^+) calcd for $C_{16}H_{27}O_2Si$ 279.1780, found 279.1778.

(1*S*,3a*S*)-1-Cyclohexyl-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (P16): 55% yield. 65:35 dr determined by HPLC analysis of the minor enantiomers since the peaks of these diastereomers are fully resolved: Chiralcel OD column, 98:2 hexanes:^{i}PrOH, flow rate = 1.0 mL/min, λ = 221 nm, retention time: t_{major} = 15.4, t_{minor} = 14.1. $[\alpha]^{25}_D$ −151.2 (c 0.62, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (s, 1H), 4.36 (d, 1H, J = 9.0 Hz), 4.31 (t, 1H, J = 6.0 Hz), 3.26 (m, 2H), 2.60 (dd, 1H, J = 18.0, 6.0 Hz), 2.11 (dd, 1H, J = 18.0, 3.0 Hz), 1.74 (m, 6H), 1.12 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 186.6, 125.3, 81.3, 71.3, 45.7, 41.7, 39.5, 29.1, 28.5, 26.2, 25.8. HRMS (MH^+) calcd for $C_{13}H_{19}O_2$ 207.1385, found 207.1377.

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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.