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From Highly Enantioselective Catalytic Reaction of 1,3-Diynes with Aldehydes to Facile Asymmetric Synthesis of Polycyclic Compounds

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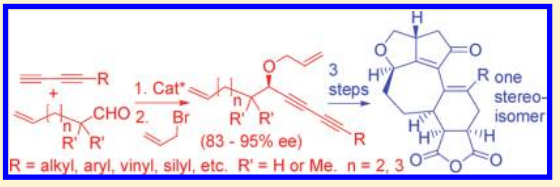
Supporting Information

ABSTRACT: (*S*)-1,1′-Binaphth-2-ol (BINOL) in combination with $ZnEt_2$, $Ti(O^iPr)_4$, and biscyclohexylamine was found to catalyze the highly enantioselective (83−95% ee) addition of various 1,3-diynes to aldehydes of diverse structures. This method provides a convenient pathway to generate a number of optically active dienediynes as the acyclic precursors to polycyclic compounds. The chiral dienediynes undergo highly chemoselective Pauson−Khand (PK) cycloaddition in benzaldehyde by using $[Rh(cod)Cl]_2$ as the catalyst in the presence of *rac*-BINAP. High diastereoselectivity (up to >20:1) has also been achieved with the chiral dienediyne substrates containing a bulky substituent adjacent to the chiral center. In the presence of the Grubbs II catalyst, ring-closing enyne metathesis of the PK cycloaddition products led to the formation of the desired 5,5,7- and 5,5,8-fused tricyclic compounds. Further highly diastereoselective Diels−Alder reaction of a 5,5,7-tricyclic compound with maleic anhydride produced a 5,5,7,6-polycyclic product. The asymmetric synthesis of polycyclic compounds from optically active dienediynes has established a novel and efficient synthetic route to the structural framework of many biologically significant molecules.



INTRODUCTION

Polycyclic systems containing medium-sized rings are frequent structural motifs in nature. Among these polycyclic systems, the fused 5,7- and 5,8-carbocycles comprise the structural core of a variety of natural products, as well as commonly being embedded in more complex polycyclic ring structures. For example, the fused 5,7-ring system of the perhydroazulene skeleton is a common structural feature of the large guaiane family of sesquiterpenes (Figure 1).[1] Due to their wide and promising biological activity,[1] members of the guaiane family have been frequent targets of total synthesis. These include the biologically active dimeric guaianolide (+)-absinthin,[2] (+)-arglabin, an inhibitor of farnesyl transferase and subsequently the RAS proto-oncogene,[3] and (+)-chinensiolide B, shown to be active against liver and lung cancer cells lines.[4] Most recently, several elegant syntheses of englerin A, a selective and highly potent inhibitor of renal cancer cell lines, have been reported.[5]

Daphnane diterpenes[6] possessing 5,7,6-fused carbocycles, and the structurally related tiglianes[7] possessing a 5,7,6,3-ring system, also make up important families of natural products with an extensive range of biological activity (Figure 2). The daphanes include gnididin, gniditrin, and gnidicin, which possess anti-leukemic activity,[6c] and the tiglianes are best exemplified by phorbol,[7a] a potent tumor promoter useful in studies of the mechanism of carcinogenesis. Other derivatives of the phorbol structure have been shown to have anti-tumor and anti-HIV activity.[7a]

Additionally, interesting and biologically active natural products containing fused 5,8-carbocycles are also common.[8] These are exemplified in Figure 3 by dumorenol and its derivatives,[9]

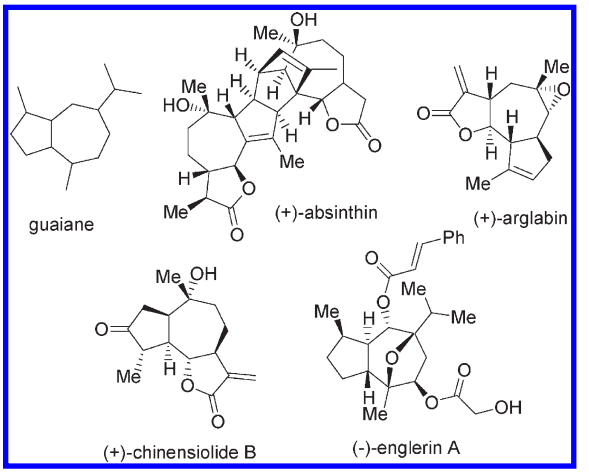


Figure 1. Biologically active members of the guaiane family.

(+)-asteriscanolide,[10] kalmanol,[11] (+)-epoxydictymene,[12] and variecolin, a potent immunosuppressant.[13] Interestingly, the 5,5,8-ring system is a common structural feature among several of these natural products.

Given the wide array of biologically active natural products containing fused 5,7- and 5,8-ring systems and the more complex 5,7,6- and 5,5,8-polycyclic ring systems, a flexible route to enantioselectively access these types of structures from readily available acyclic precursors would be attractive. Recently we have

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studied the formation of optically active 5,5- and 5,6-fused rings via a highly diastereoselective intramolecular Pauson−Khand (PK) reaction[14] of enynes derived from chiral propargylic alcohols (Scheme 1).[15] These enynes are readily accessible in high optical purity by employing a catalytic enantioselective alkyne addition to aldehydes developed in our laboratory. Using this method, optically active bicyclic cyclopentenone ring systems bearing a variety of substituents can be isolated as a single diastereomer. Our laboratory has also conducted the ring-closing enyne metathesis[16] of propargylic alcohol-based enynes to generate the optically active dienes as shown in Scheme 1. Others have applied the enyne metathesis to the construction of the medium-sized seven- and eight-membered rings.[17] As entropy loss is a significant challenge for the formation of eight-membered rings, rings present in the enyne precursor are known to be beneficial for promoting the reaction.[17a]

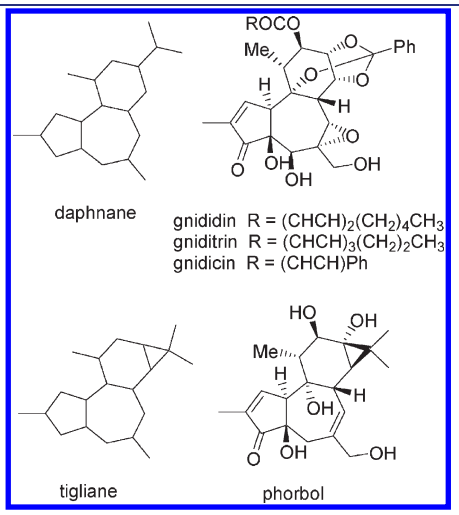


Figure 2. Daphnane and tigliane ring systems and biologically active derivatives.

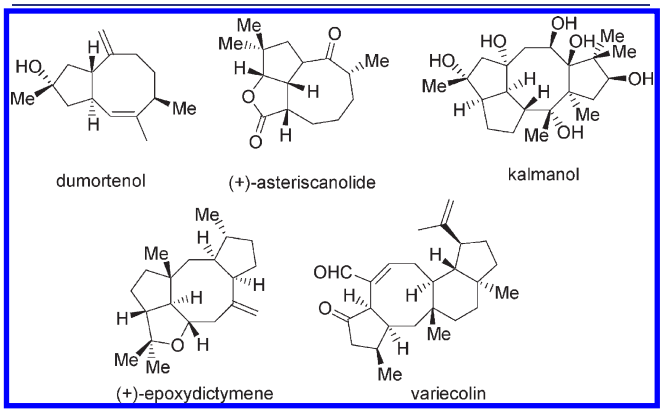
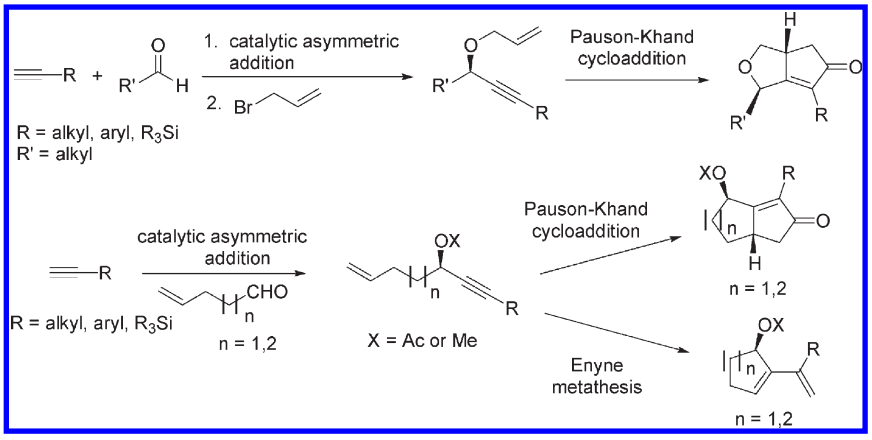


Figure 3. Polycyclic systems containing 5,8-fused ring systems.

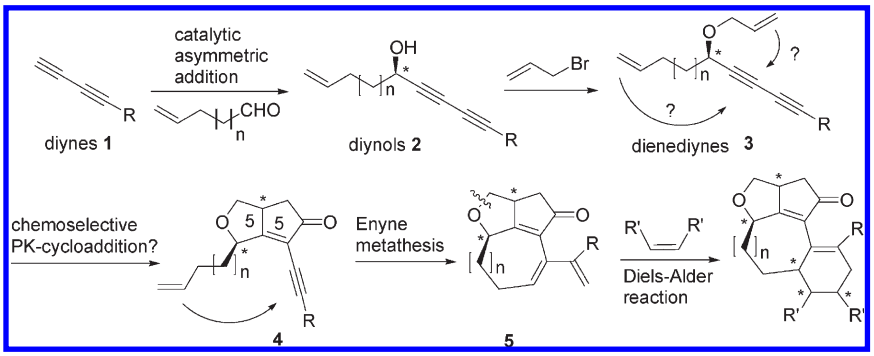
While the intramolecular PK reaction from simple enynes as shown in Scheme 1 provides efficient access to 5,5- and 5,6-bicyclic systems, it has met with limited success in the formation of medium-sized ring systems,[18] often requiring embedded aromatic rings in the enyne to facilitate the reaction.[19] More importantly, the resulting bicyclic products from simple alkynes would lack the functionality to quickly establish more complex polycyclic structures. In order to develop a facile acyclic precursor route to the optically active polycyclic systems containing medium-sized fused rings, we propose to synthesize the optically active dienediynes (**3**) from the asymmetric 1,3-diyne (**1**) addition to enals followed by treatment of the resulting enediynol (**2**) with allyl bromide (Scheme 2). These substrates could potentially undergo a chemoselective PK reaction to give the 5,5-bicyclic compounds **4** and retain the unreacted functional groups for the subsequent enyne metathesis to generate the medium-sized rings to form the 5,5,7- and 5,5,8-tricyclic products **5**. If one of the ether bonds in the hydrofuran ring of **5** could be cleaved, it would furnish the 5,7- and 5,8-carbocycles. Furthermore, these polycyclic substrates would contain an embedded 1,3-diene which could participate in the Diels−Alder cycloadditions to form the 5,7,6-carbocycles present in the daphnanes and tiglianes. The array of synthetic options available from this route prompted us to explore the viability of this pathway.

The success of this strategy requires enantioselective 1,3-diyne addition to enals to generate the chiral diynols **2**. The chiral center established in this step could direct the formation of the additional chiral centers in the subsequent cyclization steps. Although a number of catalytic systems have been reported for the highly enantioselective catalytic addition of alkynes to aldehydes in recent years,[20] enantioselective additions of diynes have proved more challenging. In 2003, Carreira and co-workers were able to access the biologically active strongylodiols from the addition of a diyne to aliphatic aldehydes.[21] While good enantioselectivities could be obtained (80−82% ee), 4 equiv of the chiral ligand, (+)-*N*-methylephedrine, and slow addition of the

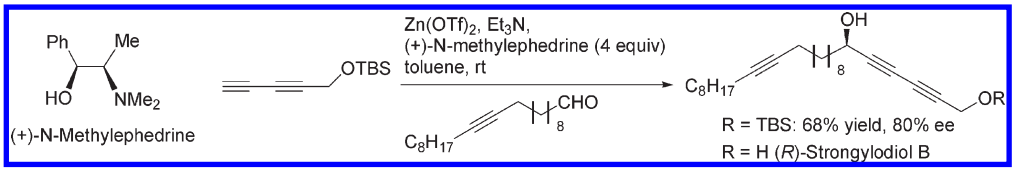
Scheme 1. Pauson−Khand Reaction and Enyne Metathesis of the Optically Active Propargylic Alcohol-Based Enynes



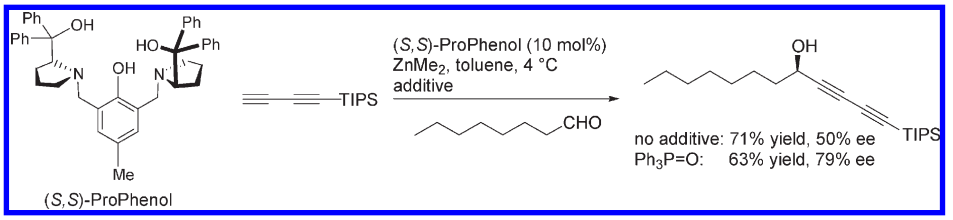
Scheme 2. Chiral Dienediynes as Acyclic Precursors to Polycyclic Compounds



Scheme 3. Enantioselective Addition of a Diyne to an Aldehyde



Scheme 4. (*S,S*) ProPhenol-Catalyzed Enantioselective Diyne Addition to Octyl Aldehyde



aldehyde with a syringe pump were required for good enantiocontrol (Scheme 3).

Recently, Trost and co-workers demonstrated a catalytic enantioselective diyne addition to aldehydes by using a chiral amino alcohol, ProPhenol (Scheme 4).[22] While the ProPhenol catalyst has been highly successful in a variety of alkyne additions to aldehydes,[23] the initial application of this catalytic system for the addition of buta-1,3-diynyltriisopropylsilane to octyl aldehyde resulted in only moderate enantioselectivity (50% ee, Scheme 4). It was then found that the enantioselectivity could be improved to 79% ee by using triphenylphosphine oxide (TPPO) as an additive. In this manner, high enantioselectivities were achieved for the addition of buta-1,3-diynyltriisopropylsilane to benzaldehyde (87% ee) and a range of *trans*-α,β-unsaturated aldehydes (84−97% ee) utilizing 10 mol % of the (*S,S*)-ProPhenol ligand. Other aliphatic aldehydes also proved to be challenging in the addition of buta-1,3-diynyltriisopropylsilane, resulting in enantioselectivities ranging from 67 to 83%.

These reports demonstrate the challenges associated with the diyne nucleophiles for the asymmetric addition to aldehydes in comparison with simple alkynes. We investigated the application of the 1,1′-binaphth-2-ol (BINOL)−$ZnEt_2$−$Ti(O^iPr)_4$ catalytic system, previously developed in our laboratory for the alkyne addition to aldehydes,[24] to the asymmetric diyne addition to aldehydes. In this paper, we report our development of highly enantioselective catalysts for the additions of a variety of diynes to aldehydes, which allowed the synthesis of the chiral dienediynes **3** with high optical purity. We conducted chemoselective and diastereoselective PK cycloaddition of the chiral dienediynes followed by enyne metathesis to construct a series of structurally interesting and optically active polycyclic compounds containing medium-sized rings.

RESULTS AND DISCUSSION

1. Enantioselective 1,3-Diyne Addition to Aldehydes. In 2002, we[24a] and Chan[25] found that BINOL in combination with $Ti(O^iPr)_4$ and ZnR_2 (R = Et or Me) was a highly enantioselective catalytic system for the reaction of alkynes with aromatic aldehydes to generate optically active propargylic alcohols. We later expanded this system to aliphatic and α,β-unsaturated aldehydes.[24b] Since this method required heating the terminal alkyne with $ZnEt_2$ in toluene at reflux in order to prepare the alkynylzinc nucleophile, it was not applicable for sensitive alkynes. To circumvent the elevated temperature required to form the alkynylzinc, we discovered that the addition of hexamethylphosphoramide (HMPA) allowed the reaction to be performed entirely at room temperature, since the Lewis basic additive HMPA accelerates the reaction of $ZnEt_2$ with terminal alkynes.[26] Later, You and co-workers revealed that *N*-methylimidazole is a more efficient Lewis basic additive than HMPA.[27]

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Scheme 5. (*S*)-BINOL-Catalyzed 6-Phenylhexa-1,3-diyne Addition to Benzaldehyde

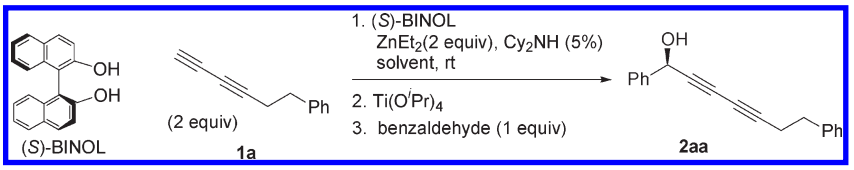
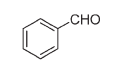
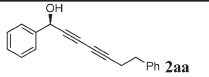
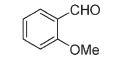
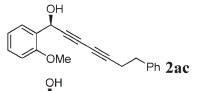
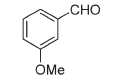
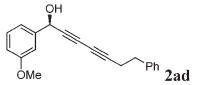
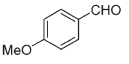
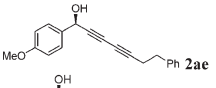
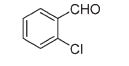
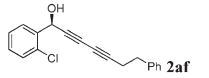
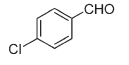
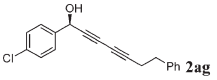
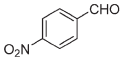
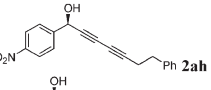
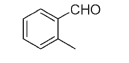
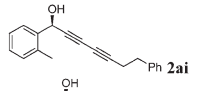
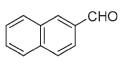
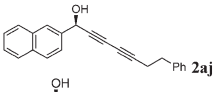
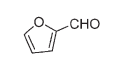
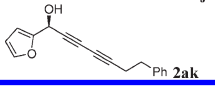


Table 1. Optimization of Conditions for the Reaction of the Diyne 1a with Benzaldehyde Catalyzed by (*S*)-BINOL−$ZnEt_2$−Cy_2NH−$Ti(O^iPr)_4$[a]

entry	BINOL (mol %)	solvent	time, 1st step (h)	$Ti(O^iPr)_4$ (mol %)	yield (%)	ee (%)[c]
1	20	THF	24	50	41	68
2	20	CH_2Cl_2	24	50	77	94
3	20	toluene	24	50	51	96
4	20	Et_2O	24	50	98	95
5	20	Et_2O	24	100	94	93
6	20	Et_2O	16	25	91	86
7	20	Et_2O	16	50	97	94
8	20	Et_2O	8	50	85	91
9	**10**	**Et_2O**	**16**	**25**	**96**	**94**
10	5	Et_2O	16	12.5	98	78
11[b]	**10**	**Et_2O**	**16**	**25**	**95**	**94**

[a] Unless otherwise indicated, the following conditions were employed: To a solution (3 mL) of the diyne (2 equiv) under nitrogen, (*S*)-BINOL, Cy_2NH (5 mol %), and $ZnEt_2$ (2 equiv) were added, and the reaction mixture was stirred at room temperature. $Ti(O^iPr)_4$ was then added and mixed for 1 h. Benzaldehyde (0.25 mmol) was added, and the resulting mixture was stirred for 3 h. [b] $Ti(O^iPr)_4$ and the aldehyde were added in the same step. [c] Enantiomeric excess was determined by HPLC analysis (Chiralpack AD-H column).

Table 2. Addition of the Diyne 1a to Aromatic Aldehydes Catalyzed by (*S*)-BINOL−$ZnEt_2$−Cy_2NH−$Ti(O^iPr)_4$[a]

entry	aldehyde	product	yield (%)	ee (%)[b]
1		 **2aa**	95	94
2		 **2ac**	81	91
3		 **2ad**	96	90
4		 **2ae**	94	94
5		 **2af**	92 92	79 89[b]
6		 **2ag**	94	92
7		 **2ah**	56	90
8		 **2ai**	98 98	74 92[b]
9		 **2aj**	98	93
10		 **2ak**	89	85

[a] Unless indicated otherwise, the following stoichiometry of the reagents was used: diyne:$ZnEt_2$:Cy_2NH:(*S*)-BINOL:$Ti(O^iPr)_4$:aldehyde = 2:2:0.05:0.1:0.25:1. [b] Diyne:$ZnEt_2$:Cy_2NH:(*S*)-BINOL:$Ti(O^iPr)_4$:aldehyde = 2:2:0.05:0.2:0.50:1. [c] Determined by HPLC analysis (Chiralcel OD, OB-H, or Chiralpak AD-H column).

Recently, we further reported that the use of biscyclohexylamine (Cy_2NH) as a Lewis base additive significantly improves the asymmetric addition of linear alkyl alkynes to linear aldehydes.[28] Since 1,3-diynes possess an extended linear steric environment as result of the additional triple bond, we chose to begin our investigations of the catalytic asymmetric diyne addition to aldehydes with Cy_2NH as the Lewis basic additive in the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$ catalyst system.

1.1. Reaction of the Diyne ***1a*** *with Aromatic Aldehydes.* We identified 6-phenylhexa-1,3-diyne, **1a**, as an easily accessible and robust diyne for our initial screening experiments. We explored various conditions for the reaction of **1a** with benzaldehyde in the presence of (*S*)-BINOL, $ZnEt_2$, $Ti(O^iPr)_4$, and Cy_2NH at room temperature to generate the diynol product **2aa** (Scheme 5), and the results are summarized in Table 1. The reactions were conducted in three steps. In the first step, **1a** (2 equiv), (*S*)-BINOL, $ZnEt_2$ (2 equiv), and Cy_2NH (5 mol %) were stirred in a solvent under nitrogen. In the second step, $Ti(O^iPr)_4$ was added to mix for 1 h. In the third step, benzaldehyde (1 equiv) was added to react for 3 h to give the addition product. Table 1 shows the variation of the solvent, the reaction time in the first step, and the amounts of (*S*)-BINOL and $Ti(O^iPr)_4$ in order to optimize the reaction conditions. Entries 1−4 demonstrate that high enantioselectivity can be obtained in CH_2Cl_2, toluene, and Et_2O, but THF is not a good solvent for this reaction. Among these four experiments, entry 4 was the one that also showed high enantioselectivity for the simple alkyne addition to aldehydes. By varying the reaction time in the first step, in which the diynylzinc species is formed, it was found that 16 h was optimal to provide maximum yield and enantioselectivity (entries 7 and 8).[29] In entry 9, we reduced the amount of (*S*)-BINOL to 10 mol % and the amount of $Ti(O^iPr)_4$ to 25 mol %, which gave almost the same result as entry 4. However, further reducing the amount of (*S*)-BINOL to 5 mol % and that of $Ti(O^iPr)_4$ to 12.5 mol % gave reduced enantioselectivity, though the yield was still high (entry 10). In entry 11, the conditions of entry 9 were employed but the reaction process was simplified by combining the steps 2 and 3 into one step; that is, $Ti(O^iPr)_4$ and benzaldehyde were added consecutively and stirred for 3 h. This gave the same high yield and enantioselectivity as entry 9.

The conditions of entry 11 in Table 1 were applied to the reaction of **1a** with a variety of aromatic aldehydes, and the results

Scheme 6. (*S*)-BINOL-Catalyzed Addition of the Diyne 1a to Valeraldehyde

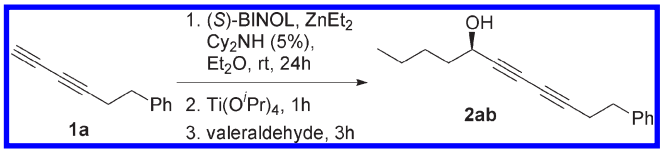


Table 3. Optimization of Conditions for the Reaction of the Diyne 1a with Valeraldehyde Catalyzed by (*S*)-BINOL−$ZnEt_2$−Cy_2NH−$Ti(O^iPr)_4$[a]

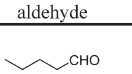
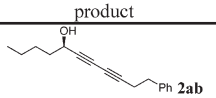
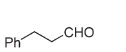
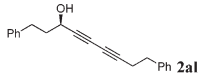
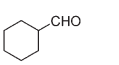
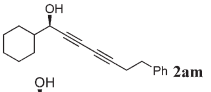
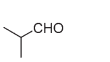
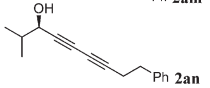
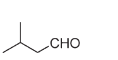
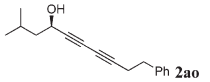
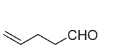
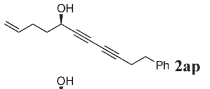
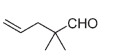
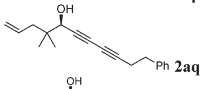
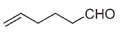
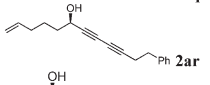
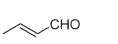
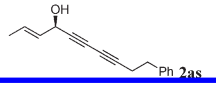
entry	BINOL (mol %)	diyne and $ZnEt_2$ (equiv)	solvent	time, 1st step (h)	$Ti(O^iPr)_4$ (mol %)	yield (%)	ee (%)[d]
1	10	2	Et_2O	16	25	96	66
2	20	2	Et_2O	24	50	97	82
3	20	2	THF	24	50	58	60
4	20	2	CH_2Cl_2	24	50	95	62
5	20	2	toluene	24	50	55	84
6[b]	20	2	Et_2O	16	50	64	59
7	20	1.5	Et_2O	16	50	62	50
8	30	2	Et_2O	16	75	83	69
9	30	3	Et_2O	16	75	95	85
10	**40**	**3**	**Et_2O**	**16**	**100**	**91**	**92**
11	40	2	Et_2O	16	100	82	69
12	40	2	Et_2O	16	50	88	60
13[c]	**40**	**3**	**Et_2O**	**16**	**100**	**92**	**92**

[a] Unless otherwise indicated, the following conditions were employed: A diyne was dissolved in a solvent (3 mL). (*S*)-BINOL, Cy_2NH (5 mol %), and $ZnEt_2$ were added, and the mixture was stirred at room temperature. $Ti(O^iPr)_4$ was then added and mixed for 1 h. Valeraldehyde (0.25 mmol) was added ,and the resulting mixture was stirred for 3 h. [b] Aldehyde was added at 0 °C, and the reaction was maintained at 0 °C until quenched. [c] $Ti(O^iPr)_4$ and the aldehyde were added in the same step. [d] Enantiomeric excess was determined by HPLC analysis (Chiralcel OD column).

are summarized in Table 2. As shown in Table 2, high enantioselectivities were obtained for the diyne addition to aromatic aldehydes containing either electron-donating or -withdrawing groups at the *o*-, *m*-, or *p*-positions. In the case of two *o*-substituted benzaldehydes, *o*-chlorobenzaldehyde and *o*-methylbenzaldehyde (entries 5 and 8), the amount of (*S*)-BINOL was increased to 20 mol % and that of $Ti(O^iPr)_4$ to 50 mol % in order to obtain high ee's. 2-Naphthaldehyde and 2-furaldehyde also furnished the diynol products with good yield and enantioselectivity (entries 9 and 10).

1.2. Reaction of the Diyne ***1a*** *with Aliphatic Aldehydes and Enals.* We also investigated the more challenging asymmetric diyne addition to aliphatic aldehydes. The reaction conditions for the addition of the diyne **1a** to a linear aliphatic aldehyde, valeraldehyde, were screened (Scheme 6). As shown in Table 3, when the conditions of entry 9 in Table 1 were applied for the addition to valeraldehyde, much lower enantioselectivity was observed (66% ee, entry 1). Increasing the amount of (*S*)-BINOL to 20 mol % and that of $Ti(O^iPr)_4$ to 50 mol % improved the enantioselectivity to 82% ee (entry 2). Further increasing the amount of (*S*)-BINOL to 30 mol % and that of $Ti(O^iPr)_4$ to 75 mol % but maintaining the amounts of the diyne and $ZnEt_2$ each at 2 equiv gave lower enantioselectivity (69% ee, entry 8).

Table 4. Addition of the Diyne 1a to Aliphatic Aldehydes Catalyzed by (*S*)-BINOL−$ZnEt_2$−Cy_2NH−$Ti(O^iPr)_4$[a]

entry	aldehyde	product	yield (%)	ee (%)[b]
1		 **2ab**	92	92
2		 **2al**	93	88
3		 **2am**	91	91
4		 **2an**	95	90
5		 **2ao**	90	87
6		 **2ap**	80	92
7		 **2aq**	82	89
8		 **2ar**	86	90
9		 **2as**	99	92

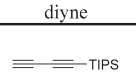
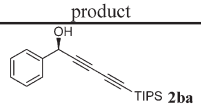
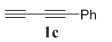
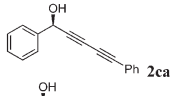
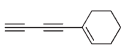
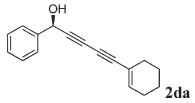
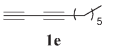
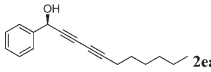
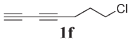
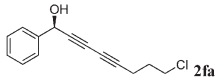
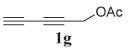
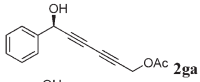
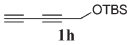
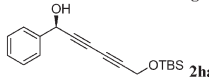
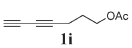
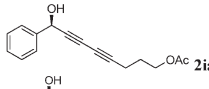
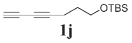
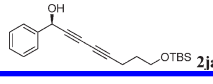
[a] Diyne:$ZnEt_2$:Cy_2NH:(*S*)-BINOL:$Ti(O^iPr)_4$:aldehyde = 3:3:0.05:0.4:1:1. [b] Determined by HPLC analysis (Chiralcel OD, OB-H, or Chiralpak AD-H column).

This indicates that the ratio of the chiral ligand versus the diynylzinc nucleophile should be important for the reaction. On the basis of the conditions of entry 8, the amounts of the diyne and $ZnEt_2$ were increased to 3 equiv, which gave improved enantioselectivity (85% ee, entry 9). Further increasing the amount of (*S*)-BINOL to 40 mol % and $Ti(O^iPr)_4$ to 100 mol % and maintaining the amounts of the diyne and $ZnEt_2$ each at 3 equiv gave a high enantioselectivity of 92% ee (entry 10). The procedure of entry 10 was simplified by combining steps 2 and 3 with the consecutive addition of $Ti(O^iPr)_4$ and the aldehyde, which gave the same high yield and excellent enantioselectivity (92% yield and 92% ee, entry 13). In this procedure, the chiral ligand BINOL can be easily recovered by elution from the column after isolation of the diynol product.

The conditions of entry 13 in Table 3 were applied to the reaction of **1a** with a variety of aliphatic aldehydes and enals. As the results summarized in Table 4 demonstrate, high enantioselectivities were achieved for the reactions of linear, α-branched, and β-branched aliphatic aldehydes (87−92% ee, entries 1−5). Excellent results were also obtained for the reaction a variety of enals (89−92% ee, entries 6−8), which are important for the proposed construction of polycyclic compounds. Finally, an α,β-unsaturated enal, *trans*-crotonaldehyde, was also found to be well-suited for this catalytic system (92% ee, entry 9).

1.3. Reaction of Various Diynes with Aldehydes of Diverse Structures. We explored the catalytic asymmetric addition of other diynes besides **1a** to aldehydes. Table 5 summarizes the results for the reaction of various diynes with benzaldehyde by using the conditions of entry 11 in Table 1. It shows that the catalytic system is compatible with a wide range of functional

Table 5. Addition of Various Diynes to Benzaldehyde in the Presence of the (*S*)-BINOL−$ZnEt_2$−Cy_2NH−$Ti(O^iPr)_4$ Catalyst System[a]

entry	diyne	product	yield (%)	ee (%)[b]
1	 1b	 2ba	98	91
2	 1c	 2ca	98	88
3	 1d	 2da	99	90
4	 1e	 2ea	87	94
5	 1f	 2fa	95	91
6	 1g	 2ga	87	83
7	 1h	 2ha	95	94
8	 1i	 2ia	78	86
9	 1j	 2ja	97	92

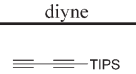
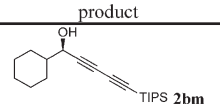
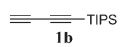
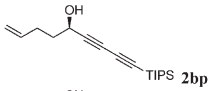
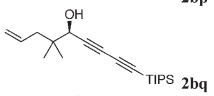
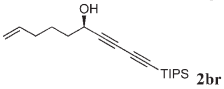
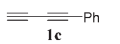
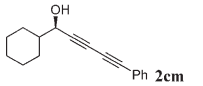
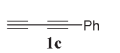
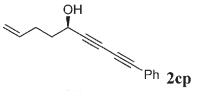
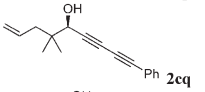
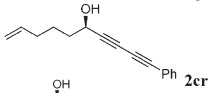
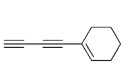
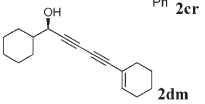
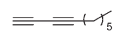
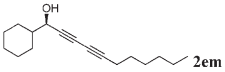
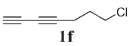
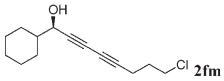
[a] Diyne:$ZnEt_2$:Cy_2NH:(*S*)-BINOL:$Ti(O^iPr)_4$:aldehyde = 2:2:0.05:0.1:0.25:1. [(b)] Determined by HPLC analysis (Chiralcel OD, OB-H, or Chiralpak AD-H column).

diynes. Excellent yields and high enantioselectivities were obtained for the diynes substituted with a triisopropylsilyl (TIPS) (91% ee, entry 1), a phenyl (88%, entry 2), and a cyclohexenyl (90% ee, entry 3). The effect of a variety of alkyl substituents on the diyne was also investigated, which revealed high enantioselectivity for those containing a linear alkyl group (94% ee, entry 4), a halogen substituent (91% ee, entry 5), and various hydroxyl protecting groups (83−94% ee, entries 6−9).

The addition of the functional diynes to a variety of aliphatic aldehydes and enals was conducted by applying the conditions of entry 13 in Table 3. As the results summarized in Table 6 show, the reactions of linear or branched aliphatic aldehydes and several enals with the diynes all gave excellent results (85−95% ee). These findings represent the most generally enantioselective catalytic system for the reaction of various diynes with aldehydes of diverse structures. The enediynol products obtained in entries 2−4 and 6−8 of Table 6 and entries 6−8 of Table 4 provide the starting materials of high optical purity for the asymmetric synthesis of the chiral polycyclic compounds discussed in the next section.

2. Diastereoselective Pauson−Khand Reaction of the Optically Active Dienediynes. Having established efficient catalytic systems to access the optically active enediynols, we converted these substrates to the optically active dienediynes for the subsequent PK cycloaddition study. As shown in Scheme 7a, deprotonation of the optically active enediynols at low temperatures with ^{n}BuLi followed by treatment with allyl bromide afforded the optically active dienediynes in high yields with retention of the enantiomeric purity. The racemic dienediynes were

Table 6. Addition of Diynes to Aliphatic Aldehydes and Enals Catalyzed by (*S*)-BINOL−$ZnEt_2$−Cy_2NH−$Ti(O^iPr)_4$[a]

entry	diyne	product	yield (%)	ee (%)[b]
1	 1b	 2bm	99	89
2	 1b	 2bp	94	95
3	1b	 2bq	98	88
4	1b	 2br	87	91
5	 1c	 2cm	98	92
6	 1c	 2cp	97	90
7	1c	 2cq	97	89
8	1c	 2cr	73	91
9	 1d	 2dm	99	90
10	 1e	 2em	97	86
11	 1f	 2fm	98	85
12	1h	2hm	98	91
13	1h	2ht	89	88
14	1j	2jm	99	92

[a] Diyne:$ZnEt_2$:Cy_2NH:(*S*)-BINOL:$Ti(O^iPr)_4$:aldehyde = 3:3:0.05:0.4:1:1. [b] Determined by HPLC analysis (Chiralcel OD, OB-H, or Chiralpak AD-H column).

easily prepared in one pot from a diyne as shown in Scheme 7b; they were used to screen conditions for the PK reaction.

2.1. Using Stoichiometric $Co_2(CO)_8$. The intramolecular PK reaction of enynes in the presence of stoichiometric $Co_2(CO)_8$ has been extensively studied.[14] Recently, we reported that the optically active propargylic alcohol-based enynes can undergo highly diastereoselective PK cycloaddition in the presence of $Co_2(CO)_8$ and *N*-methylmorpholine oxide (NMO) with retention of the enantiomeric purity, as shown by the example in Scheme 8.[15,30]

We applied the reaction conditions in Scheme 8 to the PK cycloaddition of the dienediynes. Because these dienediynes, such as **3ar** in Scheme 9, contained multiple reactive sites, we were conscious of several challenges unique to these substrates. First, would the cobalt be able to coordinate to the inner triple

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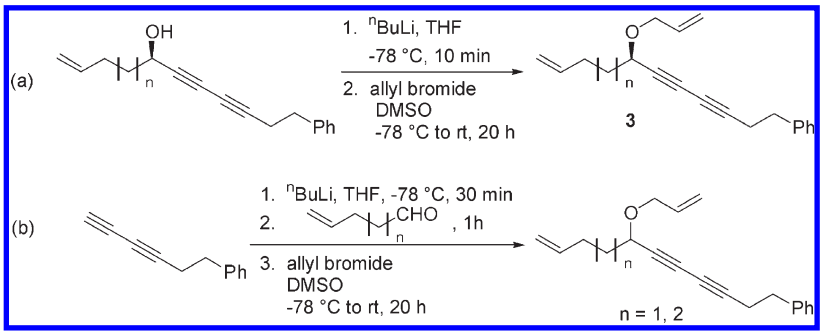
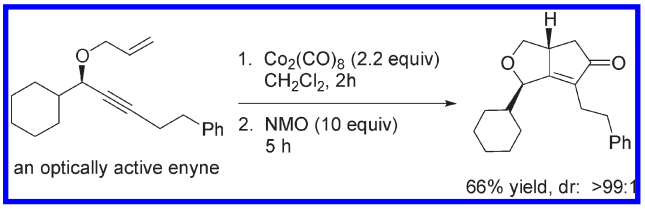
Scheme 7. Preparation of Optically Active and Racemic Dienediynes



Scheme 8. Highly Diastereoselective PK Reaction of the Propargylic Alcohol-Based Enyne



bond of the diyne effectively enough to promote the cyclization? It is expected that the initial coordination of the outer triple bond would be sterically more favorable, which could hinder the coordination of a second equivalent of cobalt to the inner triple bond. Second, two alkenes were present in the substrate, raising the question of chemoselectivity. There was some precedent that the allyloxy double bond should be favored for the PK cycloaddition,[31] but would this pathway predominate to a great enough extent to yield one cycloaddition product? In addition, will the enyne product **4ar** undergo further PK cycloaddition?

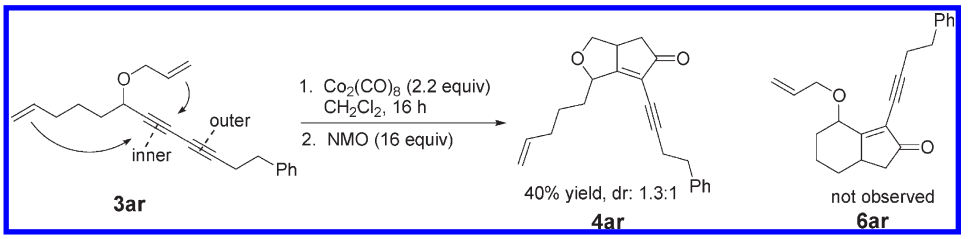
We conducted the reaction of **3ar** in the presence of 2.2 equiv of $Co_2(CO)_8$ and 16 equiv of NMO at room temperature (Scheme 9). This, however, led to the formation of only a very small amount of the cycloaddition product. Realizing that a longer time might be required for the complexation of the cobalt to both alkynes of **3ar**, we extended the first step reaction time from 2 to 16 h. Upon treatment with NMO, the 5,5-cycloaddition product **4ar** was generated in moderate yield (~40%) without the formation of **6ar**. This reveals that the allyl ether reaction pathway was favored exclusively, and high chemoselectivity could be achieved with these substrates. However, unlike the high diastereoselectivity we observed for the PK cycloaddition of the propargylic alcohol-based enyne as shown in Scheme 8, the PK cycloaddition of **3ar** proceeded with little diastereoselectivity (1.3:1). Attempts to improve the yield and diastereoselectivity of the $Co_2(CO)_8$-mediated reaction by applying the various reaction conditions and promoters that were found to be effective for the propargylic alcohol-based enynes[15] were unsuccessful. Thermal reaction conditions employing reflux in acetonitrile or toluene, and common promoters such as *n*-butyl methyl sulfide in dichloroethane at 83 °C[32] and tetramethylthiourea under reflux in toluene,[33] all failed to produce more than trace amounts of the desired cycloaddition product.

2.2. Using Transition Metal Catalysts. We then explored the *catalytic* PK cycloaddition of the dienediynes in the presence of various transition metal complexes. In recent years, a variety of transition metal complexes have been utilized, including Ti,[34] Zr,[35] Ni,[36] Mo,[37] Ru,[38] Rh,[39] Ir,[40] and Pd,[41] for the catalytic PK-type reactions in the presence of a CO source.[42] We tested several of the more widely applied and commercially available catalytic systems. It was found that the $[Cp_2Ti(CO)_2]$[34] and $PdCl_2$—thiourea[41] catalytic systems led to the opposite diastereomers of the cycloaddition product from **3ar**, but the yields were very low (10—25%). The $[Cp_2Ti(CO)_2]$-catalyzed reaction yielded *cis*-**4ar** in 10:1 dr, and the $PdCl_2$—thiourea-catalyzed reaction yielded *trans*-**4ar** in 8:1 dr (Scheme 10). Using the $[Ir(cod)Cl_2]$-BINAP[40] catalytic system failed to generate the cycloaddition product.

In 2002, Shibata and co-workers reported a $[Rh(cod)Cl]_2$—phosphine (cod = 1,5-cyclooctadiene) catalytic system employing an aldehyde as the solvent and CO source, alleviating the need to use toxic carbon monoxide gas.[43] We applied this catalytic system to the reaction of the dienediyne **3ap** with an aldehyde as the CO source (Table 7). As shown in entry 1 of Table 7, using *rac*-BINAP and *trans*-cinnamaldehyde afforded the product **4ap** with 64% yield and 2:1 dr. We then screened a variety of aromatic and vinyl aldehydes as the CO source at various reaction temperatures. When the reaction temperature was reduced to 80 °C with cinnamaldehyde as the CO source, the product was still obtained but without improvement in dr (entry 2). Switching to the sterically bulkier α-methyl-*trans*-cinnamaldehyde improved the diastereoselectivity to 3:1 dr (entry 3). However, lowering the reaction temperature to 80 °C for this aldehyde resulted in only a minimal amount of the desired product. When benzaldehyde was used as the CO donor, reducing the temperature from 120 to 80 °C significantly improved the diastereoselectivity (entries 4 and 5). A variety of *ortho*- and *para*-substituted aromatic aldehydes containing electron-donating or -withdrawing groups were then screened but did not further enhance the diastereoselectivity (entries 6—10). All the experiments in Table 7 were found to proceed with high chemoselectivity, without the observation of the reaction of the other alkene unit.

As shown in Table 7, the conditions of entry 5 provided the desired PK cycloaddition product from the dienediyne **3ap** with practically useful yield and diastereoselectivity as well as high chemoselectivity. In addition, no further PK cycloaddition of the enyne product **4ap** was observed. On the basis of these conditions, we studied the PK cycloaddition of the optically active **3ap** (92% ee). As shown in entry 1 of Table 8, when $[Rh(cod)Cl]_2$ was increased to 15 mol % and *rac*-BINAP to 30 mol %, the optically active product *cis*-**4ap** was obtained with 62% yield and 4:1 dr. We applied these conditions to the PK

Scheme 9. $Co_2(CO)_8$-Mediated PK Reaction of the Dienediyne 3ar



Scheme 10. Transition Metal-Catalyzed PK Cycloaddition of the Dienediyne 3ar

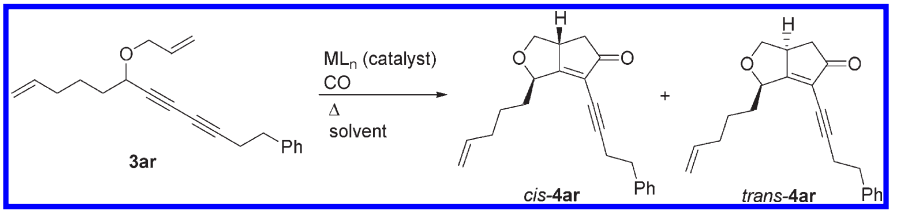
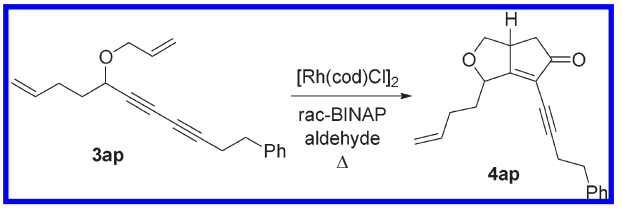
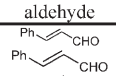
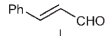
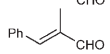
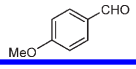


Table 7. [Rh(cod)Cl]$_2$−Phosphine-Catalyzed PK Cycloaddition of 3ap with Various Aldehydes as the CO Source[a]

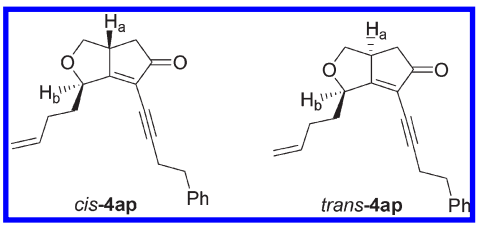


entry	aldehyde	T (°C)	Time (h)	Yield	dr[b]
1		120	5	64	2:1
2		80	16	69	2:1
3		100	14	46	3:1
4		120	5	49	2:1
5		**80**	**16**	**60**	**4:1**
6		100	16	65	2:1
7		100	16	37	3:1
8		100	16	47	3:1
9		80	16	38	4:1
10		80	16	32	4:1

[a] Dienediyne:[Rh(cod)Cl]$_2$:*rac*-BINAP:aldehyde = 1:0.10:0.20:20. [b] Ratio of *cis*:*trans* determined by integration of the ^{1}H NMR spectra.

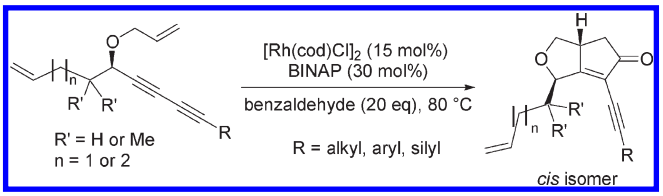
cycloaddition of other optically active dienediynes, and the results are summarized in Table 8. As shown by entries 1−6, the optically active dienediynes with alkyl, aryl, and triisopropylsilyl substituents on the alkyne underwent the catalytic PK cycloaddition chemoselectively in the presence of the catalyst [Rh(cod)Cl]$_2$ and *rac*-BINAP in benzaldehyde to give the 5,5-fused bicyclic products with 48−78% yield and 3:1−4:1 dr. Importantly, the diastereomers could be separated by column chromatography, providing the optically active and densely functionalized bicyclic products as a single stereoisomer. We further found that, when the steric bulkiness adjacent to the chiral center of the substrates was increased, the diastereoselectivity of the catalytic PK cycloaddition was greatly enhanced. As shown in entries 7−9, excellent diastereoselectivity up to >20:1 dr was achieved with 51−71% yield. Analysis of the racemic and optically active product in entry 2 by chiral HPLC (Chiralpak AD-H column) confirmed that the cyclization proceeded without loss of enantiomeric purity. These results represent the first diastereoselective PK cycloaddition of 1,3-diyne substrates.

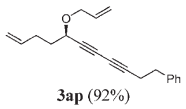
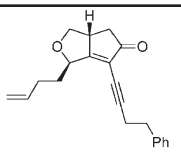
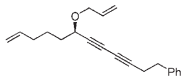
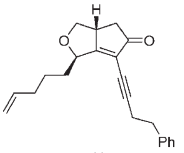
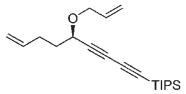
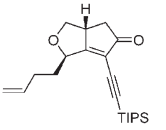
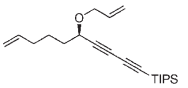
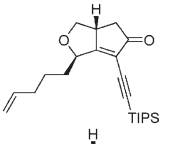
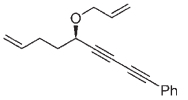
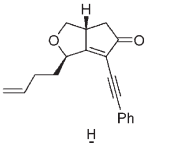
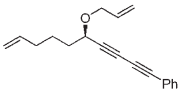
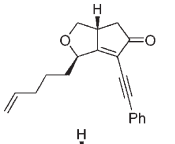
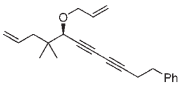
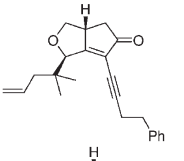
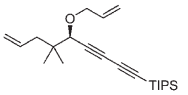
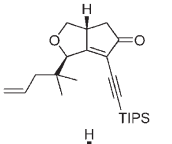
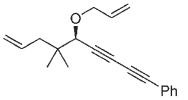
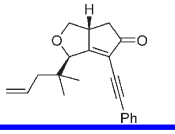
The *cis* and *trans* stereoisomers of the PK cycloaddition of the dienediynes were determined on the basis of the correlation with known chemical shifts of the analogous cycloaddition products derived from enynes.[15] For example, for product **4ap**, H_b resonates at δ 4.66 in the *cis* isomer (major), while in the *trans* isomer (minor) H_b resonates at δ 4.79; that is, the *cis* isomer gives a more upfield H_b signal than the *trans* isomer. All of the products in Table 8 manifested this diagnostic chemical shift pattern. Analyses of the major and minor diastereomers of **4ap** by NOESY spectroscopy support this structural assignment. A nuclear Overhauser effect (NOE) was observed between H_a and H_b in the minor diastereomer but not in the major diastereomer. Therefore, the minor diastereomer is determined to be the *trans* isomer and the major one the *cis* isomer.



Scheme 11 shows a proposed mechanism for the Rh(I)-catalyzed PK cycloaddition of the dienediynes.[43] This mechanism consists of two catalytic cycles, the first involving the

Table 8. [Rh(cod)Cl]$_2$–BINAP-Catalyzed PK Cycloaddition of Optically Active Dienediynes[a]



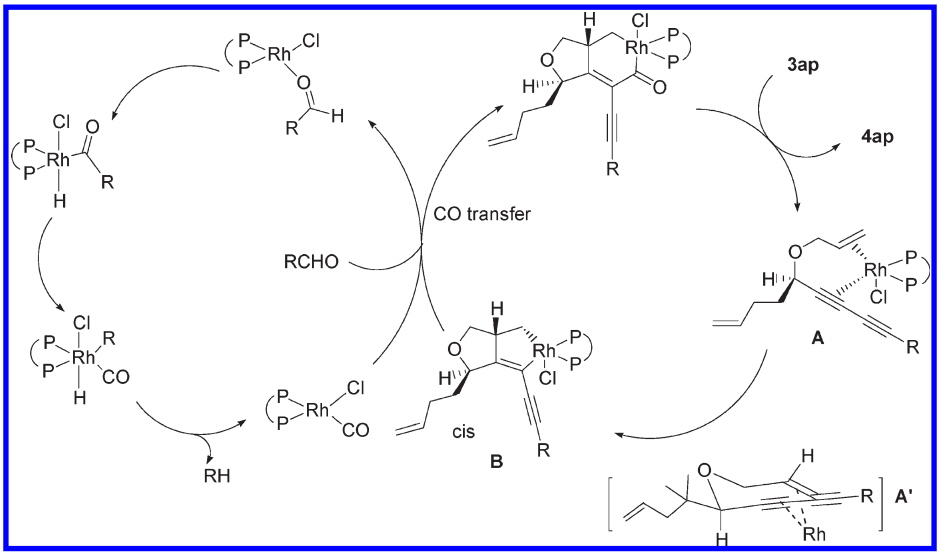
Entry	Dienediyne (ee)	Time (h)	Product	Yield (%)	dr [b]
1	 **3ap** (92%)	16	 **4ap**	62	4:1
2	 **3ar** (90%)	20	 **4ar**	73	4:1
3	 **3bp** (95%)	16	 **4bp**	76	4:1
4	 **3br** (91%)	16	 **4br**	60	3:1
5	 **3cp** (90%)	10	 **4cp**	57	3:1
6	 **3cr** (91%)	16	 **4cr**	48	4:1
7	 **3aq** (89%)	36	 **4aq**	51	17:1
8	 **3bq** (88%)	60	 **4bq**	68	>20:1[c]
9	 **3cq** (89%)	18	 **4cq**	71	18:1

[a] Dienediyne:[Rh(cod)Cl]$_2$:*rac*-BINAP:benzaldehyde = 1:0.15:0.30:20. [b] Ratio of *cis*:*trans* determined by integration of ^{1}H NMR spectra. [c] Only one diastereomer was observed.

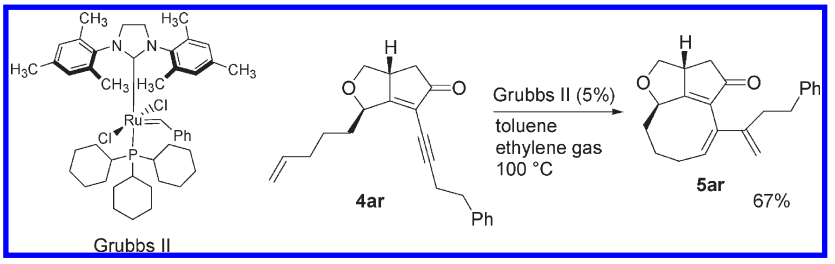
established decarbonlyation pathway. On the basis of a series of studies, Shibata and co-workers proposed that the CO is transferred directly from the decarbonylation cycle without the generation of free CO gas. The second catalytic cycle involves the coordination of the enyne to the rhodium center and its subsequent cyclization. In this mechanism the key diastereoselective step involves the cyclization of intermediate **A** to generate **B**. We propose a chairlike transition state for this cyclization step, especially when there is a bulky substituent adjacent to the chiral center, as shown in entries 7–9 in Table 8. The correspoding chairlike transition state **A′**, with the bulky alkyl group at the equatorial position, would lead to the observed predominate *cis* products.

3. Ring-Closing Metathesis To Construct the 5,5,7- and 5,5,8-Tricyclic Compounds. After the construction of the 5,5-fused bicyclic compounds from the optically active dienediynes,

Scheme 11. Proposed Mechanism for the $[RhCl(CO)_2]_2$–Phosphine-Catalyzed PK Cycloaddition of Dienediyne 3ap with Aldehydes as a CO Source



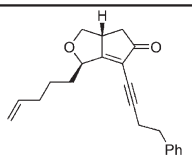
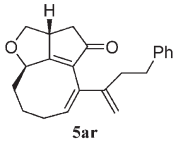
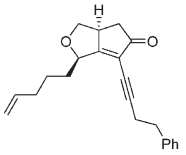
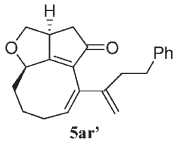
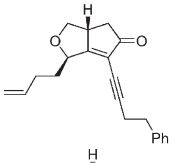
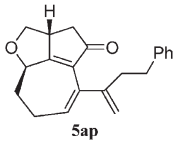
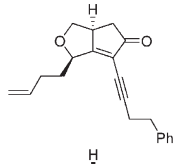
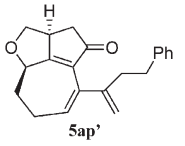
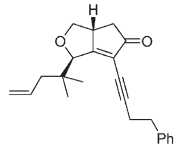
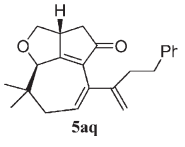
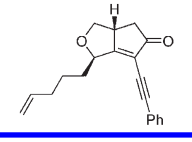
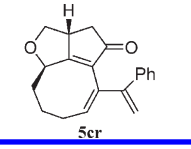
Scheme 12. Ring-Closing Enyne Metathesis of 4ar in the Presence of the Grubbs II Catalyst and Ethylene Gas



we explored their ring-closing metathesis to construct the desired 5,5,7- and 5,5,8-polycyclic products with medium-sized rings. We began by testing the Grubbs II catalyst with compound **4ar**. However, this reaction did not proceed under ambient or elevated temperatures (refluxing in CH_2Cl_2 or toluene), returning only the starting material. These failures were not unprecedented, considering Chang and co-workers' study of conjugated 1,3-enynes in enyne metathesis in which they found that the conjugated enynes deactivated the Grubbs I and II catalysts, preventing both intermolecular enyne metathesis and alkene metathesis.[44] As ethylene gas has been demonstrated to promote enyne metathesis for difficult substrates,[45] we conducted the enyne metathesis of **4ar** in the presence of ethylene gas (1 atm). No reaction was observed at room temperature. We then tested the reaction in a sealed tube at elevated temperature by first bubbling the solution with ethylene gas for 2 min. Promisingly, employing 5 mol % of Grubbs II catalyst in CH_2Cl_2 at 45 °C provided partial conversion to the desired eight-membered-ring product. Heating to 100 °C in toluene in a sealed tube fully consumed the starting material, providing the product **5ar** in 67% yield (Scheme 12). This result is listed as entry 1 in Table 9, which summarizes the ring-closing enyne metathesis of the 5,5-bicyclic compounds. Compound **4ar′** is the *trans* diastereomer of **4ar**, and it was isolated as the minor isomer from the PK cycloaddition. As shown in entry 2 of Table 9, when **4ar′** was subjected to the ring-closing enyne metathesis, it was found that addition of a second portion of the Grubbs II catalyst was necessary after 12 h in order to ensure the completion of the reaction. This gave the *trans* diastereomeric 5,5,8-tricyclic product **5ar′** in 68% yield. Compound **4ap** was found to be unstable at 100 °C in toluene. When metathesis of **4ap** was carried out at a reduced temperature of 45 °C in CH_2Cl_2, the desired product **5ap** was obtained in 63% yield after the addition of the second portion of the catalyst (entry 3). In contrast, compound **4ap′**, the *trans* diastereomer of **4ap**, was found to undergo metathesis at 100 °C to give **5ap′** in 73% yield, without the need to add a second portion of the catalyst. In entry 5, the bulkier compound **4aq** underwent metathesis at 100 °C to give **5aq** in 51% yield, with the addition of a second portion of the catalyst after 12 h. No product was obtained when metathesis of **4aq** was conducted at 45 °C in CH_2Cl_2. Compound **4cr** underwent metathesis at 100 °C to give **5cr** in 73% yield, with the addition of a second portion of the catalyst (entry 6). The results in Table 9 demonstrate that both of the diastereomers of the 5,5,7- and 5,5,8-tricyclic compounds can be readily obtained.

4. Highly Diastereoselective Diels–Alder Reaction To Construct a Fused 5,5,7,6-Polycyclic Compound. One important feature of using enyne metathesis to access the optically active 5,5,7- and 5,5,8-polycyclic ring systems is that this method

Table 9. Ring-Closing Enyne Metathesis To Access Optically Active Polycyclic Compounds Containing Seven- and Eight-Membered Rings[a]

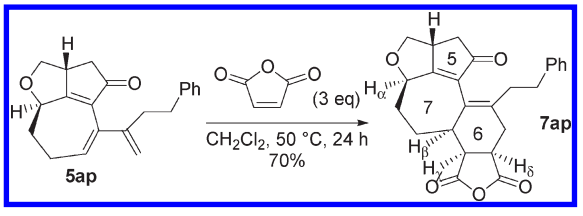
entry	Enyne		Grubbs II (mol %)	Reaction time (h)	Product	Yield (%)
1		**4ar**	5	17	 **5ar**	67
2[c]		**4ar'**	10	24	 **5ar'**	68
3[b,c]		**4ap**	15	24	 **5ap**	63
4		**4ap'**	5	17	 **5ap'**	73
5[c]		**4aq**	20	24	 **5aq**	51
6[c]		**4cr**	10	24	 **5cr**	73

[a] Enyne (0.025 M)/Grubbs II = 1:0.05−0.20 in toluene at 100 °C. All reactions were conducted in the presence of ethylene gas, bubbling the reaction mixture with ethylene for 2 min prior to heating. [b] CH_2Cl_2, 45 °C. [c] Grubbs II added in two portions. The second portion was added after 12 h, and the solution was bubbled with ethylene gas for 1.5 min prior to heating.

furnishes a conjugated diene functionality that can be exploited for the formation of more complex polycyclic structures. In particular, the newly formed dienes should allow access of the 5,7,6-carbocycles present in the daphnane and tigliane ring systems via Diels−Alder cycloaddition. To test this idea, we pursued the [4+2] cycloaddition of **5ap** with maleic anhydride. The reaction proceed at 50 °C in a sealed tube to cleanly furnish the cycloaddition product **7ap** as a single diastereomer in 70% yield, setting three new stereocenters (Scheme 13).

The stereochemistry of **7ap** was determined by NOESY and COESY 2D ^{1}H NMR analyses. We observed NOEs between H_β and H_χ and between H_χ and H_δ, consistent with the expected *endo* cycloaddition between maleic anhydride and a conjugated diene. The ^{1}H NMR signal of H_χ is observed at δ 3.26 (dd, $J_{H_\chi-H_\delta}$ = 9.75 Hz and $J_{H_\beta-H_\chi}$ = 5.25 Hz), and the coupling constants support the *syn* configuration of the three protons $H_{\beta-\delta}$ generated from the *endo* cycloaddition. A NOE between H_α and H_β was also observed. This indicates that the dienophile maleic anhydride approaches the diene unit of **5ap** from the top face in an *endo* fashion to generate the product **7ap**, in which the four bridge-head hydrogens $H_{\alpha-\delta}$ are all on the same side, as shown. The structural assignment for **7ap** is supported by a single-crystal X-ray analysis of this compound, as shown in Figure 4.

Scheme 13. [4+2] Cycloaddition of 5ap with Maleic Anhydride



One hypothesis for the preferred top face attack of the dienophile on **5ap** is that this approach avoids electronic repulsion between the carbonyl oxygen of maleic anhydride and the axial hydrogen atom H_α in the *endo* pathway, as shown in the proposed transition state **C**. That is, the chiral center established from the catalytic asymmetric diyne addition to aldehydes should have directed this asymmetric Diels−Alder reaction. Thus, the polycyclic compound **7ap** with five stereocenters has been constructed from the corresponding acyclic dienediyne in three

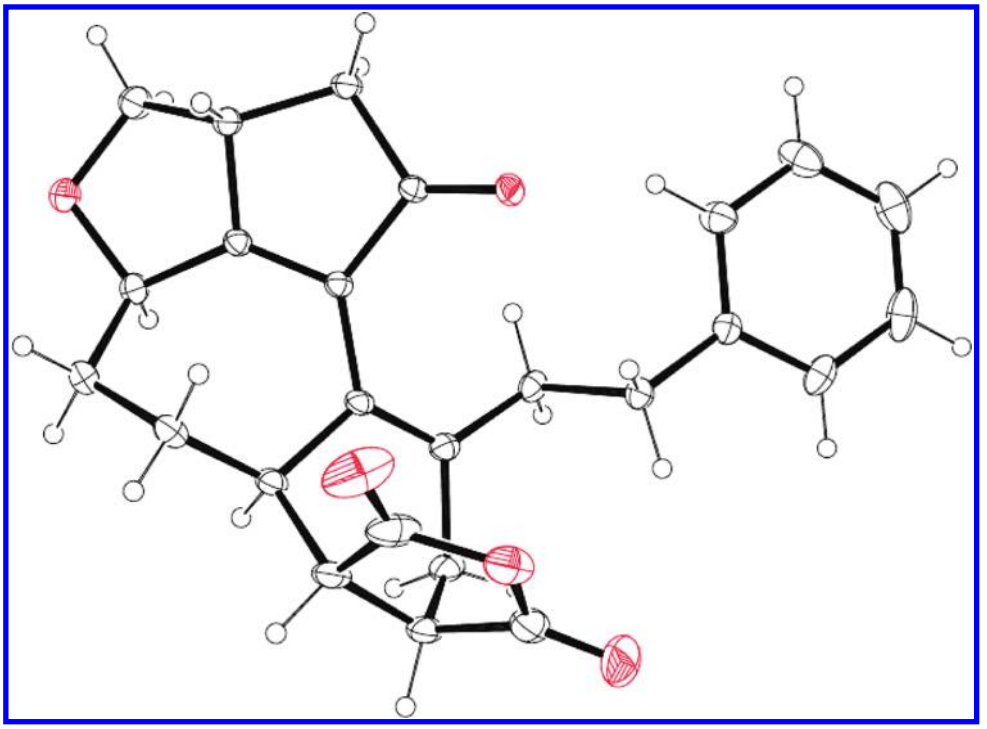
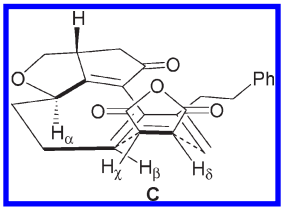


Figure 4. X-ray structure of **7ap**.

steps with high chemoselectivity and diastereoselectivity. The multiple functional groups in **7ap** should allow further structural elaboration of this compound.



C

5. Summary. We have developed the highly enantioselective catalytic reaction of a variety of 1,3-diynes with aldehydes of diverse structures by using BINOL in combination with $ZnEt_2$, $Ti(O^iPr)_4$, and Cy_2NH at room temperature. This represents the most generally enantioselective catalyst system for the asymmetric diyne addition to aldehydes. With this method, optically active dienediynes are readily obtained, which allowed us to devise a new synthetic strategy to construct polycyclic compounds. $[Rh(cod)Cl]_2$ in combination with *rac*-BINAP was found to catalyze the highly chemoselective PK cycloaddition of the chiral dienediynes to generate the corresponding 5,5-bicyclic compounds. High diastereoselectivity was achieved for the substrates containing bulky substituents adjacent to the chiral center. Ring-closing enyne metathesis of the 5,5-bicyclic compounds catalyzed by the Grubbs II catalyst led to the formation of the desired 5,5,7- and 5,5,8-tricyclic products. Further highly stereoselective Diels–Alder reaction of a 5,5,7-tricyclic compound produced a 5,5,7,6-polycyclic product as a single stereoisomer in good yield. This work demonstrates that the chiral dienediynes are potentially useful for the asymmetric synthesis of the cyclic structural frameworks of a number of biologically significant molecules containing embedded medium-sized rings.

EXPERIMENTAL SECTION

General Data. All commercial chemicals were used as received unless otherwise noted. Cy_2NH was distilled prior to use. Commercial $ZnEt_2$ (95%) was used. Toluene, THF, and 1,4-dioxane were distilled over sodium and benzophenone under nitrogen atmosphere. Methylene chloride and diethyl ether were dried by passing through activated alumina columns under nitrogen. Solvents were stored over 4 Å molecular sieves. All aldehydes were passed through a plug of alumina and distilled from 4 Å molecular sieves prior to use and then stored under nitrogen atmosphere. All 1,3-diynes were stored at −15 °C in Et_2O solution. Prior to use, they were concentrated via rotary evaporation and then placed under high vacuum (except **1c**) for 15 min.

General Procedure for the Asymmetric Diyne Addition to Aromatic Aldehydes. Under nitrogen, to a Et_2O (3 mL) solution of a 1,3-diyne (0.5 mmol, 2 equiv) were added (*S*)-BINOL (>99% ee, 7.2 mg, 0.025 mmol, 10 mol %), Cy_2NH (2.5 μL, 0.0125 mmol, 5 mol %), and $ZnEt_2$ (51.3 μL, 0.5 mmol, 2 equiv), and the reaction mixture was stirred at room temperature for 16 h. $Ti(O^iPr)_4$ (18.5 μL, 0.0625 mmol, 25 mol %) and then an aldehyde (0.25 mmol, 1 equiv) were added, and the solution was stirred for 3 h, during which the aldehyde was completely consumed, as determined by TLC analysis. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted three times with CH_2Cl_2. The organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel, eluted with hexanes/ethyl acetate (0–15% ethyl acetate), to give the product in 56–99% yield and 83–94% ee. Note: The excess diyne can be easily recovered by first eluting the column with hexanes. The BINOL ligand can be recovered by eluting the column with hexanes/ethyl acetate (20% ethyl acetate).

General Procedure for the Asymmetric Diyne Addition to Aliphatic Aldehydes and Enals. Under nitrogen, to a Et_2O (3 mL) solution of a 1,3-diyne (0.75 mmol, 3 equiv) were added (*S*)-BINOL (>99% ee, 28.6 mg, 0.1 mmol, 40 mol %), Cy_2NH (2.5 μL, 0.0125 mmol,

5 mol %), and $ZnEt_2$ (76.9 μL, 0.75 mmol, 3 equiv), and the reaction mixture was stirred at room temperature for 16 h. Ti(O^iPr)4 (74 μL, 0.25 mmol, 100 mol %) and then an aldehyde (0.25 mmol, 1 equiv) were added, and the solution was stirred for 3 h, during which the aldehyde was completely consumed, as determined by TLC analysis. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted three times with CH_2Cl_2. The organic layer was dried with sodium sulfate and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel, eluted with hexanes/ethyl acetate (0−15% ethyl acetate), to give the product in 73−99% yield and 85−95% ee. Note: This reaction was successfully scaled up to 2 mmol of aldehydes. The excess diyne can be easily recovered by first eluting the column with hexanes. The BINOL ligand can be recovered by eluting the column with hexanes/ethyl acetate (20% ethyl acetate).

General Procedure for the Preparation of the Optically Active Dienediynes 3. Under nitrogen, to a THF (7.5 mL) solution of a diynol compound **2** (1.5 mmol, 1 equiv) at −78 °C was added ^{n}BuLi (1.5 mmol, 1 equiv), and the mixture was stirred for 10 min. Allyl bromide (1.04 mL, 12 mmol, 8 equiv) was then added, followed by the addition of DMSO (0.21 mL, 3.0 mmol, 2 equiv). The reaction flask was allowed to warm to room temperature overnight. Upon consumption of the starting material, the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL), extracted three times with CH_2Cl_2, dried with sodium sulfate, and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel, eluted with hexanes/ethyl acetate (0−5% ethyl acetate), to give the dienediyne products **3** in 82−93% yield.

General Procedure for the $[Rh(cod)Cl]_2$−BINAP-Catalyzed PK Cycloaddition of the Dienediynes Utilizing Benzaldehyde as the CO Source. Under nitrogen, in a flask equipped with a reflux condenser, a dienediyne **3** (0.25 mmol), $[Rh(cod)Cl]_2$ (18.5 mg, 0.038 mmol, 0.15 equiv), *rac*-BINAP (46.7 mg, 0.075 mmol, 0.30 equiv), and benzaldehyde (0.51 mL, 5 mmol, 20 equiv) were combined. The reaction was heated under nitrogen at 80 °C for the time indicated in Table 8, until the reaction was complete, as determined by TLC or crude ^{1}H NMR analysis. The reaction mixture was cooled to room temperature and purified by column chromatography. Benzaldehyde was eluted with 95:5 hexanes:EtOAc, and the product was eluted with 90:10 to 80:20 hexanes:EtOAc, depending on the substrate, to yield the *cis* diastereomer of the 5,5-bicyclic compound **4** as the major product in 48−73% yield and with 3:1 to >20:1 dr.

Ring-Closing Enyne Metathesis of the 5,5-Bicyclic Compounds 4. Under nitrogen, in a flame-dried vial, a 5,5′-bicyclic compound **4** (0.1 mmol, 1 equiv) was dissolved in toluene or CH_2Cl_2 (4 mL, 0.025 M). The Grubbs II catalyst (5−20 mol %, see Table 9) was added, and the vial was fit with a rubber septum. Ethylene gas was bubbled through the reaction solution for 2 min (venting with a needle through the septum). The septum was replaced with a screw cap, and the vial was tightly sealed (wrapping the cap with parafilm and electrical tape). The vial was heated at 100 or 45 °C for 17−24 h. As indicated in Table 9, for certain substrates, the reaction was first heated for 12 h and then allowed to cool to room temperature. Under nitrogen, a second portion of Grubbs II catalyst was added, the solution was bubbled with ethylene gas for 1.5 min, and the vial was resealed and heated for an additional 12 h. After completion of the reaction, the crude mixture was purified by column chromatography (75:25 hexanes:EtOAc) on silica gel to yield the product **5** in 51−73% yield. Note: Because of the sensitivity of the diene products, they should not be kept at room temperature for a long period of time and should be stored in dilute solution under nitrogen in a refrigerator.

Diels−Alder Reaction of 5ap with Maleic Anhydride. Under nitrogen, in a flame-dried vial, compound **5ap** (53 mg, 0.173 mmol, 1 equiv) was dissolved in CH_2Cl_2 (3.5 mL, 0.05 M). Maleic anhydride (51 mg, 0.52 mmol, 3 equiv) was added, and the vial was tightly sealed (wrapping the cap with parafilm and electrical tape). It was heated at 50 °C for 24 h, during which the starting material was consumed. The crude reaction mixture was then cooled to room temperature and purified by column chromatography (40:60 hexanes:EtOAc) on silica gel to yield the product **7ap** as a white solid in 70% yield as a single stereoisomer. $[\alpha]_D^{25}$ = 11.4 (c = 0.35, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (m, 2H), 7.14 (m, 1H), 7.05 (m, 2H), 4.28 (t, 1H, J = 7.5 Hz), 4.21 (m, 1H), 3.48 (m, 1H), 3.26 (dd, 1H, J = 9.75, 5.25 Hz), 3.16 (dd, 1H, J = 11.0, 8.0 Hz), 3.09 (m, 1H), 2.86 (m, 2H), 2.66 (dd, 1H, J = 16.0, 6.0 Hz), 2.61 (m, 1H), 2.55 (m, 1H), 2.36 (m, 3H), 2.17 (m, 1H), 2.08 (m, 2H), 1.89 (m, 1H), 1.81 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.0, 184.8, 173.6, 171.4, 141.6, 140.8, 130.0, 128.5, 128.2, 126.9, 125.8, 74.6, 72.6, 46.9, 43.2, 42.7, 40.8, 38.1, 37.9, 33.8, 30.0, 29.1, 27.4. IR (cm^{-1}): 3059, 3025, 2926, 2855, 1844, 1771, 1705, 1673, 1618, 1602, 1495, 1452, 1441. HRMS (MH^+) for $C_{25}H_{24}O_5$: calcd, 405.1702; found, 405.1700.

■ ASSOCIATED CONTENT

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

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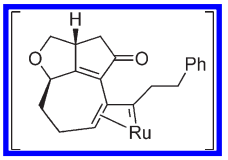

This intermediate could consume the Grubbs II catalyst and decompose after extended exposure to elevated temperatures. For a DFT study of the mechanism of enyne metathesis and the effect of ethylene gas, see: Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444–7457.

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