Regioselective Synthesis of Acyclic *cis*-Enediynes via an Acid-Catalyzed Rearrangement of 1,2-Dialkynylallyl Alcohols. Syntheses, Computational Calculations, and Mechanism†

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Received December 21, 1998

A novel synthesis of acyclic *cis*-enediynes **2** has been established by an acid-catalyzed rearrangement of 1,2-diyn-2-propen-1-ols **1** possessing a C_3-aryl group in the presence of water, alcohols, or thiols. Reactivity of allyl alcohols and regio- and cis/trans diastereoselectivity of the allylic migration were examined. In the presence of (±)-10-camphorsulfonic acid (CSA), the parent allyl alcohol **5** and the C_3-methyl-substituted **9** failed to give enediynes, whereas the C_3-aryl-substituted **12** and **29** underwent the allylic rearrangement to provide predominantly *cis*-enediynes **16** and **31** at room temperature or below. Under similar acidic conditions, enediyne alcohol **13** produced **16b** and **16d** with the same regio- and cis/trans diastereoselectivity observed for **12**. Allyl alcohol **30**, an isomer of **29**, also provided enediynes **31c** and **32c** after a prolonged reaction (90 h) at room temperature in the presence of CSA and EtOH. These results suggested that the same allylic cations were obtained from allyl alcohols **12** and **13** or **29** and **30** even though the ease of ionization differed for each substrate. Involvement of allylic cations in the product-forming step was confirmed by the finding that chiral allyl alcohols (−)-**12** and (−)-**18c** furnished racemic products. In general, the *p*-MeOPh-substituted allyl alcohol **29** gave a better regioselectivity than the Ph-substituted **12**. In the reactions with alcohols, the regioisomeric ratios were 100:0 (**31**:**33**) for **29** and ca. 96:4 (**16**:**17**) for **12**; the ratios decreased to ca. 90:10 (**31**:**33**) for **29** and ca. 70:30 (**16**:**17**) for **12** when thiols were used. The cis/trans diastereoselectivity is higher for allyl alcohol **12** (100% for **16** at 20 °C) compared to that for **29** (**31**:**32** = 80:20−94:6 at 0 °C). Computational calculations at the RHF/3-21G level, carried out on the model compounds and allylic cations, indicated that nucleophilic trapping takes place preferentially at the C_3 carbon to form the thermodynamically much more stable enediynes. Under the best reaction conditions (1 equiv of CSA and 2 equiv of EtOH in CH_2Cl_2, 20 °C), a number of acyclic *cis*-enediynes can be synthesized in three steps from the commercially available α-bromocinnamaldehyde (**10**).

Introduction

The naturally occurring enediynes[1,2] are a novel class of antitumor antibiotics that possess a 1,5-diyn-3-ene core constrained in a 9- or 10-membered ring. At present, the enediyne antibiotics include the representative structures of neocarzinostatin chromophore,[3] calicheamicin γ_1^I,[4] esperamicin A_1,[5] namenamicin,[6] dynemicin A,[7] kedarcidin chromophore,[8] C-1027 chromophore,[9] maduropeptin chro-

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† As a result of attachment of the oxygenated substituent (Y = OH, OR) at the allylic carbon of enediynes **2**, the trisubstituted olefins possess the *E* configuration. To be consistent with the nomenclature of disubstituted enediynes, we use cis and trans designations in the text. The *cis*-enediynes have the alkynyl groups on the same side of the double bond.

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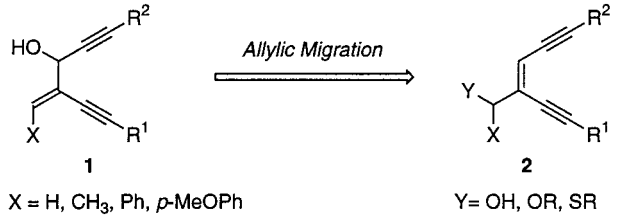
10.1021/jo982476v CCC: $18.00
Published on Web 06/15/1999

mophore,[10] and N1999A2.[11] Since the pioneer contributions by Bergman,[12a−d] Masamune,[12e] and Wong,[12f] it has been known that the naturally occurring and synthetic enediynes can undergo a thermal cycloaromatization to form 1,4-benzenoid diradical species. The latter causes DNA strand cleavage through abstraction of hydrogen atoms from the sugar−phosphate backbone.[1,2,13] Syntheses of naturally occurring enediynes and analogues have been the focus of many research efforts in recent years.[1a,g,h,14] In general, enediynes are prepared by a Pd(0)−Cu(I)-mediated cross-coupling reaction of vinyl dihalides or analogues with terminal acetylenes under the Sonogashira conditions[15] in good to excellent chemical yields. The geometry of enediynes so prepared is determined and predictable by that of the vinyl dihalides or analogues. The most important variation to the Sonogashira procedure is the Stille cross-coupling[16] of (*Z*)-1,2-bis(trimethylstannyl)ethene with iodoalkynes catalyzed by Pd(0). The latter method is particularly efficient for construction of cyclic enediynes.[17] Alternatively, a number of methods have been developed to synthesize *cis*-enediynes by introducing the double bond into 1,5-diyne derivatives. These methods include the reductive elimination,[18] the acid-[19] or base-induced[20] elimination of alcohols, the elimination of diol using the Corey−Winter reagent,[21] the benzylic oxidation,[22] the Norrish Type II reaction,[23] the rearrangement of allyl alcohols,[24] and the Diels−Alder and retro-Diels−Alder reactions.[25] In some of the above-mentioned preparations, control of the cis/trans diastereoselectivity in the formation of acyclic enediynes needs further improvement.[23] Nevertheless, these methods provide the chemical basis for enediyne prodrug[26] design and synthesis. During our studies on the formation of enediynes via an allylic rearrangement conceptually related to the mechanism of action of maduropeptin chromophore-derived artifacts,[10] we have been successful in conversion of 1,5-diyne derivatives **1** into *cis*-enediynes **2** via the corresponding allylic mesylate[24a] or the allylic cation intermediate under acidic conditions.[24b,c] In this article, we disclose a full account of the acid-catalyzed transformation of **1** into **2** (Scheme 1) with emphases on the substrate structural requirement and control of the regio- and cis/trans diastereoselectivity.

Scheme 1



1 X = H, CH_3, Ph, *p*-MeOPh

2 Y= OH, OR, SR

Results and Discussion

Synthesis of Enediynes. The parent allyl alcohol **5** was prepared from α-bromoacrolein (**3**)[27] as illustrated in Scheme 2. Addition of the lithium salt of phenyl propargyl sulfide[28] (LiC≡CCH_2SPh) to **3** gave 2-bromoallyl alcohol **4** in 51% yield. Cross-coupling of **4** with 6-methoxy-1-hexyne in the presence of 5 mol % of Pd(PPh_3)$_4$, 20 mol % of CuI, and 2 equiv of Et_3N in THF (20 °C, 4 h) afforded 1,2-dialkynylallyl alcohol **5** in 95% yield. Treatment of **5** with 1 equiv of (±)-10-camphorsulfonic acid (CSA) and 2 equiv of EtOH in dry CH_2Cl_2 (20 °C, 24 h) did not provide the expected product **6a** or **6b**. The starting material was recovered (80%). Compound **5** remained unchanged even in the presence of

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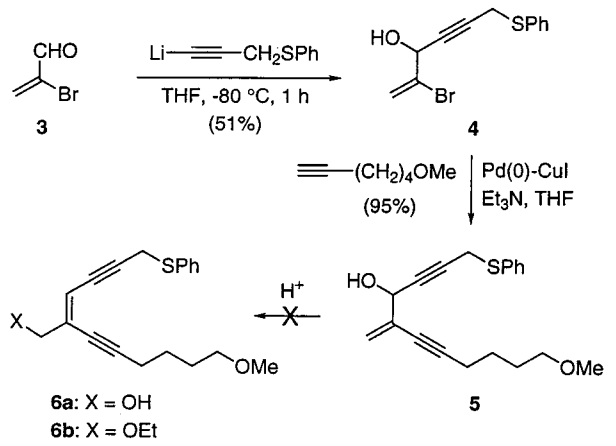
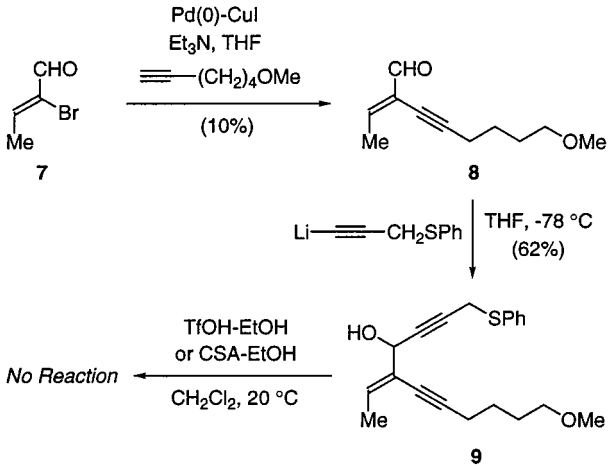
Scheme 2



Scheme 3



trifluoromethanesulfonic acid [TfOH (1 equiv), EtOH, 20 °C, 24 h]. These results indicate that ionization of **5** cannot take place under the acidic conditions.

The methyl analogue **9** was synthesized from α-bromocrotonaldehyde (**7**)[29] as shown in Scheme 3. A sequence different from Scheme 2 was used to introduce the two alkynyl units into **7**. In contrast to **4**, a similar cross-coupling of 3-methyl-2-bromoallyl alcohol, formed from **7** and LiC≡CCH$_2$SPh, failed to provide the desired product. Therefore, bromination of (*E*)-crotonaldehyde (Br_2, CH_2Cl_2, 0 °C) followed by treatment with Et_3N (20 °C, 1 h) afforded α-bromocrotonaldehyde (**7**) in 72% overall yield. Cross-coupling of **7** with 6-methoxy-1-hexyne [5 mol % of Pd(PPh_3)$_4$, 20 mol % of CuI, 2 equiv of Et_3N, THF, 20 °C, 5 h] gave eneyne aldehyde **8** in only 10% yield. We attempted to improve efficiency of the reaction but failed. Addition of LiC≡CCH$_2$SPh to **8** in THF (−78 °C, 1 h) afforded 1,2-dialkynylallyl alcohol **9** in 62% yield. Unfortunately, treatment of **9** with CSA or TfOH (1 equiv) in the presence of EtOH (2 equiv) in dry CH_2Cl_2 (20 °C, 24 h) failed to form any product; the starting allyl alcohol **9** was recovered. At this point, we realized that a better stabilizing group for the allylic cation intermediate is required to facilitate the ionization of 1,2-dialkynylallyl alcohols.

We considered the phenyl analogue **12** as a suitable substrate for the acid-catalyzed rearrangement at room temperature in the expectation that the phenyl ring could facilitate ionization of the allyl alcohol. We prepared 1,2-dialkynylallyl alcohol **12** from the commercially available α-bromocinnamaldehyde (**10**)[30] in two steps as shown in Scheme 4. The Pd(0)−Cu(I)-catalyzed cross-coupling of **10** with 6-methoxy-1-hexyne under the standard conditions [5 mol % of Pd(PPh_3)$_4$, 20 mol % of CuI, 2 equiv of Et_3N, THF, 20 °C, 1 h] furnished eneyne aldehyde **11** in 90% yield. Addition of LiC≡CCH$_2$SPh to **11** (THF, −78 °C, 0.5 h) gave **12** in 79% yield. It was very encouraging to find that treatment of **12** with 1 equiv of CSA in dry CH_2Cl_2 (20 °C, 16 h) produced the desired *cis*-enediyne **13** (56%) together with a 34:66 mixture of two isomeric allyl alcohols **14** and **15** (26% combined yield). We monitored the conversion of **12** (1 equiv of CSA, CD_2Cl_2, 20 °C) by ^{1}H NMR spectroscopic analysis. The compositions of the reaction mixture against time are plotted in Figure 1, featuring a gradual decrease of **12** and increases of the three products **13**−**15** over the first 3 h. Because of overlap of the signals of **14** and **15** with others in the ^{1}H NMR spectra of the reaction mixtures, their ratios could not be determined separately by the integrations. After 3 h reaction, an equilibrium mixture of **12**:**13**:(**14**+**15**) in the ratio of 6.5:58.5:35.0 was obtained. These results indicate that our desired *cis*-enediyne **13** is thermodynamically much more stable than **12** and is formed preferentially during the rearrangement. This is further supported by the significant difference in the reaction time of **12** and **13** for acid-catalyzed ionization to form the same allylic cation in the presence of nucleophiles (vide infra).

The structures of allyl alcohols **12**−**15** were assigned according to the chemical shifts of the vinyl and methine protons and the NOE data as depicted in Figure 2. Positions of the double bonds in **12**−**15** are determined by the absence or presence of a NOE between the vinyl and *ortho* benzene protons. For compounds **12** and **15**, NOEs of 14.5% and 4.0% were observed among the vinyl and *ortho* benzene protons, respectively, upon irradiation at the vinyl proton; a NOE was not detected between the methine and *ortho* benzene protons when the methine proton was irradiated. The small NOE value of 4.0% between the vinyl and *ortho* benzene protons in **15** (only one enantiomer shown) indicates that the benzene ring is not coplanar with the double bond. This also explains the NOE (5.8%) between the methine proton and the other *ortho* benzene proton in **15**. For compounds **13** and **14**, NOE values between the vinyl and *ortho* benzene protons were not recorded. Instead, NOEs between the methine and *ortho* benzene protons were noted (7.2% and 10.9%, respectively) upon irradiation at the methine proton. These data revealed that the double bond in **13** and **14** is not conjugated with the benzene ring. The cis relationship of the two alkynyl groups in **13** was unequivocally confirmed by a well-established chemical transformation.[24a]

We investigated the acid-catalyzed transformation of **12** and **13** in the presence of nucleophiles such as alcohols and thiols. Scheme 5 and Table 1 show the results of the reactions of allyl alcohols **12** and **13** with a number of alcohols and thiols catalyzed by CSA. It is interesting to realize that only two regioisomers, **16** and **17**, were formed in these reactions. The major products were

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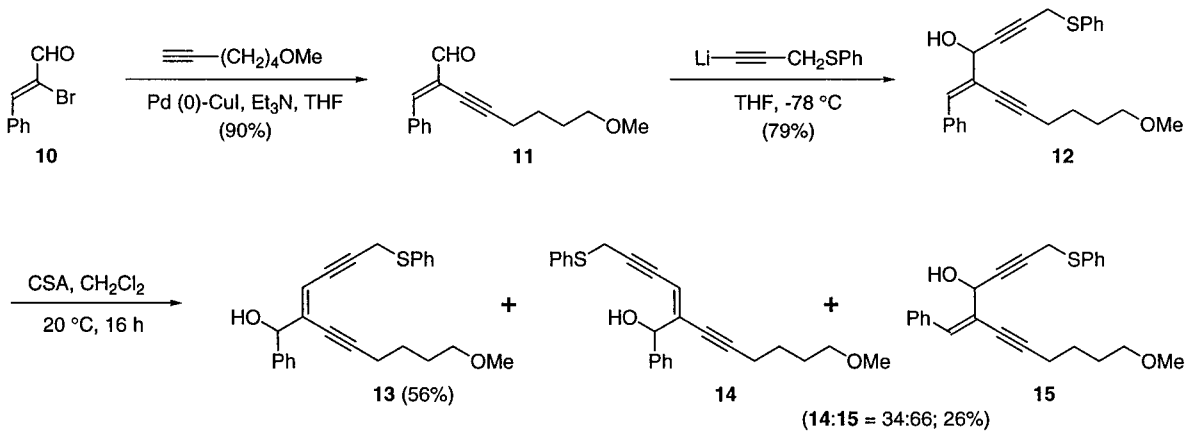
Scheme 4



determined as *cis*-enediynes **16**; *trans*-enediynes were not detected in any reaction. The following aspects can be summarized from Table 1: (a) reactions in alcoholic solvents are much slower than in CH_2Cl_2 (entries 1 and 2 versus entry 3) perhaps as a result of the competition of solvent molecules for protonation, (b) the regioselectivity of **16**:**17** is higher for reactions of alcohols (ca. 96:4) compared with those of thiols (ca. 70:30) regardless of the bulkiness of the nucleophiles, and (c) enediyne alcohol **13** gave the same products as **12** under the same acidic conditions (entries 8 and 9 versus entries 3 and 5) after a prolonged reaction. This last observation suggests that allyl alcohols **12** and **13** share the same reactive intermediate in the reactions. Moreover, enediyne alcohol **13** is confirmed to be thermodynamically much more stable than 1,5-diyne alcohol **12**.

We examined the effect of the alkynyl groups in the allyl alcohols **18a**−**c**[24a] on the regioselectivity of the allylic rearrangement (Table 2). Exposure of **18a**−**c** to CSA and EtOH in dry CH_2Cl_2 at 20 °C gave *cis*-enediynes **19a**−**c** in good to excellent yield. The phenylacetylenic group at C_1 of the allyl alcohols enhanced the reactivity and reduced the reaction time from 93 h for **18a** to 45 h for **18b** and from 3 h for **12** (Table 1, entry 3) to 2 h for **18c**. Regioselectivity of the allylic rearrangement was also improved for **18b**,**c** (single isomer formed) versus 94:6 for **18a** and 96:4 for **12** (Table 1, entry 3), respectively.

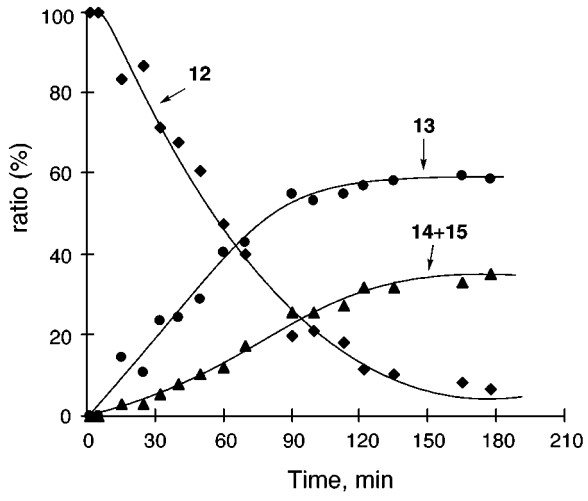


Figure 1. Conversion of **12** in the presence of 1.0 equiv of CSA in CD_2Cl_2 at 20 °C as monitored by ^1H NMR on a 400 MHz instrument. The relative ratios of **12**−**15** were obtained by integrations of the vinyl and methine protons, respectively.

***p*-MeOPh-Substituted Allyl Alcohols.** The successful transformation of **12** into *cis*-enediynes **16** prompted us to synthesize the *p*-MeOPh-substituted substrate **29** to examine the possibility of effecting the allylic rearrangement under milder acidic conditions. 1,2-Dialkynylally alcohols **29** and **30** were synthesized from *p*-anisaldehyde (**21**) according to Scheme 6. The Horner−Wadsworth−Emmons reaction of trimethyl phosphonoacetate with **21** (*n*-BuLi, THF, −78 °C, then 20 °C, 5 h) afforded α,β-unsaturated ester **22** in quantitative yield. Addition of Br_2 to **22** followed by Et_3N-mediated elimination of HBr (20 °C, 16 h) produced an inseparable mixture of α-bromo-α,β-unsaturated esters **23** and **24** in the ratio

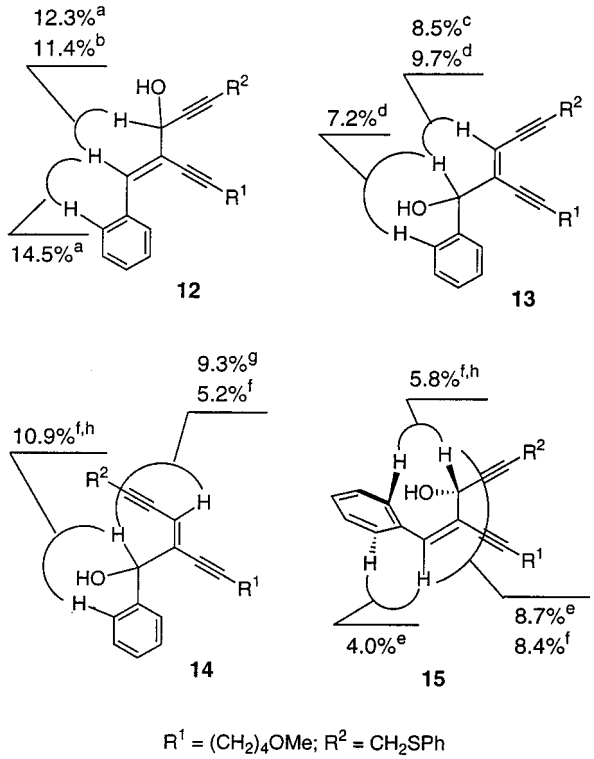


Figure 2. NOE experiments for compounds **12**−**15** measured on a 400 MHz instrument in $CDCl_3$ at room temperature: (a) irradiated at the vinyl proton at 6.75 ppm; (b) irradiated at the methine proton at 4.90 ppm; (c) irradiated at the vinyl proton at 5.95 ppm; (d) irradiated at the methine proton at 5.17 ppm; (e) irradiated at the vinyl proton at 6.06 ppm; (f) irradiated at the methine proton at 4.80 ppm for both **14** and **15**; (g) irradiated at the vinyl proton at 6.00 ppm; (h) assignment of 5.8% and 10.9% NOE to **14** and **15** is tentative.

Scheme 5

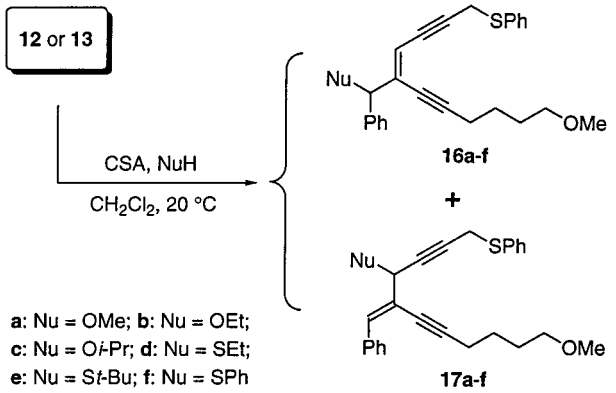
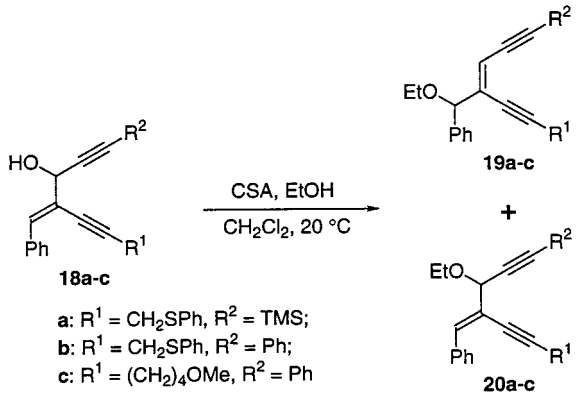


Table 1. Synthesis of Enediynes 16[a]

entry	substrate	NuH, *t* (h)	products (%)	ratio (**16**:**17**)
1[b]	**12**	MeOH, 48	**16a** (73); **17a** (2)	97:3
2[b]	**12**	EtOH, 120	**16b** (70); **17b** (3)	96:4
3	**12**	EtOH, 3	**16b** (71); **17b** (3)	96:4
4	**12**	*i*-PrOH, 4	**16c** (65); **17c** (3)	96:4
5	**12**	EtSH, 2.5	**16d** + **17d** (79)	67:33
6	**12**	*t*-BuSH, 2	**16e** + **17e** (61)	73:27
7	**12**	PhSH, 2.5	**16f** + **17f** (54)	69:31
8	**13**	EtOH, 48	**16b** (55); **17b**[c]	
9	**13**	EtSH, 48	**16d** + **17d** (61)	68:32

[a] Reactions were performed in CH_2Cl_2 in the presence of 1 mole equiv of CSA (0.16 M) and 2 mole equiv of nucleophile at 20 °C. [b] The nucleophile was used as solvent. [c] Not isolated.

Table 2. Synthesis of Enediynes 19[a]



entry	substrate, *t* (h)	products (%)	ratio (**19**:**20**)
1	**18a**, 93	**19a** + **20a** (70)	94:6
2	**18b**, 45	**19b** (82); **20b** (0)	100:0
3	**18c**, 2[b]	**19c** (65); **20c** (0)	100:0

[a] Reactions were performed in the presence of 0.5 mole equiv of CSA (0.043−0.048 M) and 4 mole equiv of EtOH. [b] One mole equivalent of CSA (0.062 M) and 2 mole equiv of EtOH were used.

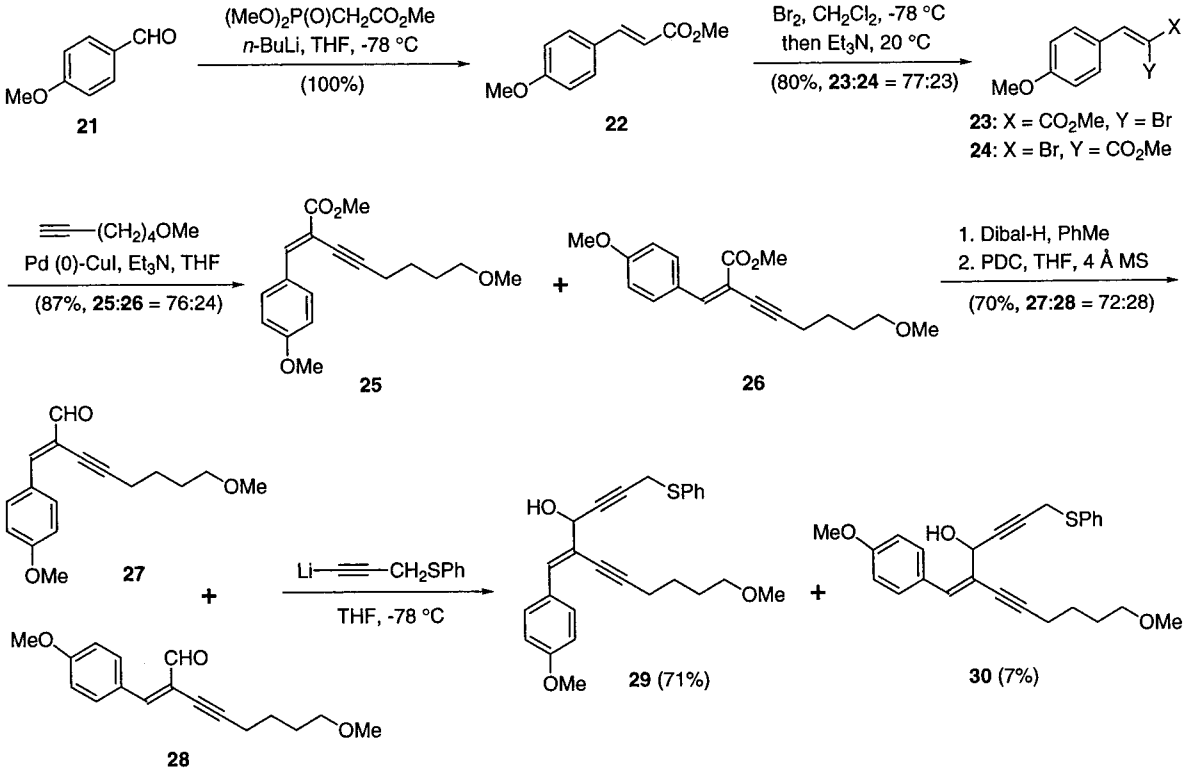
of 77:23 (80% combined yield).[31] The mixture of **23** and **24** was used in the cross-coupling reaction with 6-methoxy-1-hexyne [5 mol % of $Pd(PPh_3)_4$, 20 mol % of CuI, 2 equiv of Et_3N, THF, 20 °C, 22 h] to give eneyne esters **25** and **26** in 86% yield with a similar isomeric ratio of 76:24. Conversion of the ester group in **25** and **26** into the corresponding formyl group was achieved by the reduction (DIBAL-H, PhMe, −78 °C, 2 h, 87%) and oxidation (PDC, 4 Å MS, THF, 20 °C, 4.5 h, 81%) sequence. *It is critical to use THF as the solvent for the PDC oxidation to obtain the minor aldehyde* ***28****, which could not be isolated from the same oxidation in* CH_2Cl_2. Fortunately, the isomeric aldehydes **27** and **28** can be separated by repeated flash column chromatography over silica gel; however, we used the mixture for the following reaction. Addition of $LiC{\equiv}CCH_2SPh$ to **27** and **28** (THF, −78 °C, 1 h) furnished the allyl alcohols **29** and **30** in 71% and 7% isolated yield, respectively. Compounds **29** and **30** were separated by flash column chromatography over silica gel, but some mass of the minor isomer **30** was lost during the repeated separation process. NOE experiments were carried out for compounds **29** and **30** (Figure 3). Irradiation at the vinyl proton (6.73 ppm) of **29** gave 16.5% and 17.2% enhancement of the signals of the methine proton and the *ortho* proton of the *para*-methoxyphenyl group, respectively. Irradiation at the methine proton (4.92 ppm) of **29** resulted in 13.3% NOE for the vinyl proton only. Similar NOE effects between the methine/vinyl protons and the aryl/vinyl protons were also observed for compound **30** even though the NOE effects are stronger than those of compound **15** (Figure 2).

With compounds **29** and **30** in hand, we examined the allylic rearrangement under different acidic conditions (Scheme 7 and Table 2). Treatment of **29** with 1 equiv of CSA in the presence of 2 equiv of EtOH at 20 °C for only 15 min afforded a mixture of **31c** and **32c** (77:23) in 78% yield (entry 1). The enhanced reactivity of **29** toward ionization was further demonstrated in entries 2 and 3. A weaker acid, CF_3CO_2H, promoted the allylic migration of **29** to form **31c** and **32c** (82:18, 68%) after 48 h at 20 °C (entry 2), or a catalytic amount of CSA (0.2 equiv) completed the same transformation of **29** in 2 h at 20 °C (entry 3). In the latter reaction, the rearranged *cis*-enediyne alcohol **31a** (Nu = OH) was isolated in 15% yield; this product could be suppressed by using 4 equiv of EtOH (entry 5). The allylic migration of **29** took place sluggishly in refluxing formic acid (6 equiv) in the presence of EtOH (2 equiv), and after 66 h, the formic acid adducts were isolated in 20% yield (data not listed in Table 2). Selectivity for the formation of enediynes **31c** and **32c** was affected by the acid, the amount of acid, and the reaction temperature (entries 1−4). To balance the reaction time and the selectivity, a set of reaction conditions (0.5 equiv of CSA, 4 equiv of EtOH, 0 °C) was developed as illustrated in entry 5. From 1,2-dialkynyl-allyl alcohol **29**, *cis*-enediyne **31c** could be isolated in 94:6 ratio and in excellent yield.

Reactions of different alcohols (4 equiv) with **29** catalyzed by 0.5 equiv of CSA at 0 °C were compared (Table 3, entries 5−8). With increasing bulkiness of the alcohols in the order of MeOH, EtOH, *i*-PrOH, and *t*-BuOH, the reaction time increased accordingly from 3.5 to 7, 9, and 23 h, and the combined yield of enediynes **31** and **32** decreased from 90% to 89%, 77%, and 20%. The diminished reactivity of *t*-BuOH due to steric hindrance resulted in the formation of the dimeric ethers **35** (78%) as the major products, arising from the addition of the rearranged allyl alcohol **31a** or **32a** to the reactive intermediates. The isolated **35** was a very complex and inseparable mixture of at least three components that were confirmed by ^1H NMR and MS data. The dimeric ether **35** was also obtained from the reaction of *i*-PrOH (11%, entry 7). Diastereoselectivity among *cis*- and *trans*-enediynes **31b**−**e** and **32b**−**e** varied from 94:6 to 82:18.

(31) (*Z*)- and (*E*)-3-(*p*-Methoxyphenyl)-2-bromo-propenoate, see: Le Menn, J.-C.; Saarrazin, J.; Tallec, A. *Can. J. Chem.* **1989**, *67*, 1332. Assignment of the (*Z*) and (*E*) isomers seems not correct.

Scheme 6



Primary alcohols offered the best cis/trans diastereoselectivity (94:6) in favor of *cis*-enediynes **31b**,**c**. The isomer **33** was not produced in the reactions of alcohols with **29**; but the related isomer **17** was isolated from the same reactions of allyl alcohol **12** (Table 1). Compounds **31b**−**e** could not be separated from **32b**−**e** by silica gel column chromatography, and their structures and ratios were determined by chemical shifts and integrations of the vinyl and methine protons.

Thiols gave a much shorter reaction time (2−4 h) than alcohols in the allylic rearrangement of **29** catalyzed by CSA (entries 9−12). Variations in the amount of CSA and EtSH at 0 °C had no visible influence on chemical yield and product distribution, as shown in entries 9 and 10. It is interesting to note that the sterically demanding *t*-BuSH gave essentially the same result as that of EtSH (entries 10 and 11); this is a different profile from the reactions of alcohols. However, more than two products were isolated from the thiol-associated allylic migration. In regard to the product distribution, there are two ratios that need to be mentioned, regioselectivity (**31**:**33**) and cis/trans diastereoselectivity (**31**:**32**). Reactions of EtSH, *t*-BuSH, and PhSH afforded 92:8, 90:10, and 87:13 ratios for **31**:**33**, respectively. These values are higher than the corresponding data obtained from the reactions of EtSH (67:33), *t*-BuSH (73:27), and PhSH (69:31) with allyl alcohol **12** at 20 °C (Table 1). Ratios of enediynes **31** to **32** are 84:16 (EtSH), 80:20 (*t*-BuSH), and 90:10 (PhSH), which are lower than the analogous reactions of EtOH (94:6) and *t*-BuOH (86:14) with **29**. A fourth compound **34h** was formed in the reaction of PhSH with **29**. Compounds **31**−**34** (Nu = EtS, *t*-BuS, PhS) are inseparable mixtures whose ratios were measured by the integrations of their characteristic signals in the ^{1}H NMR spectra.

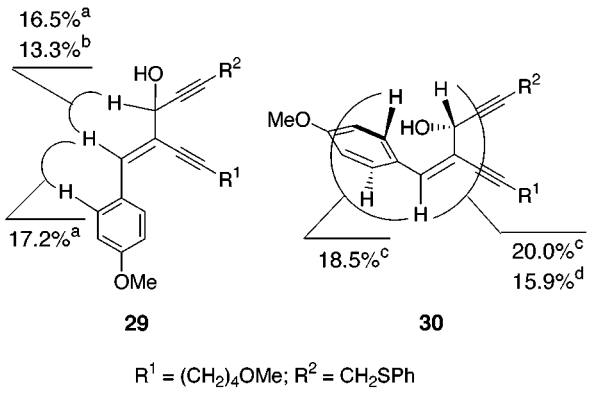
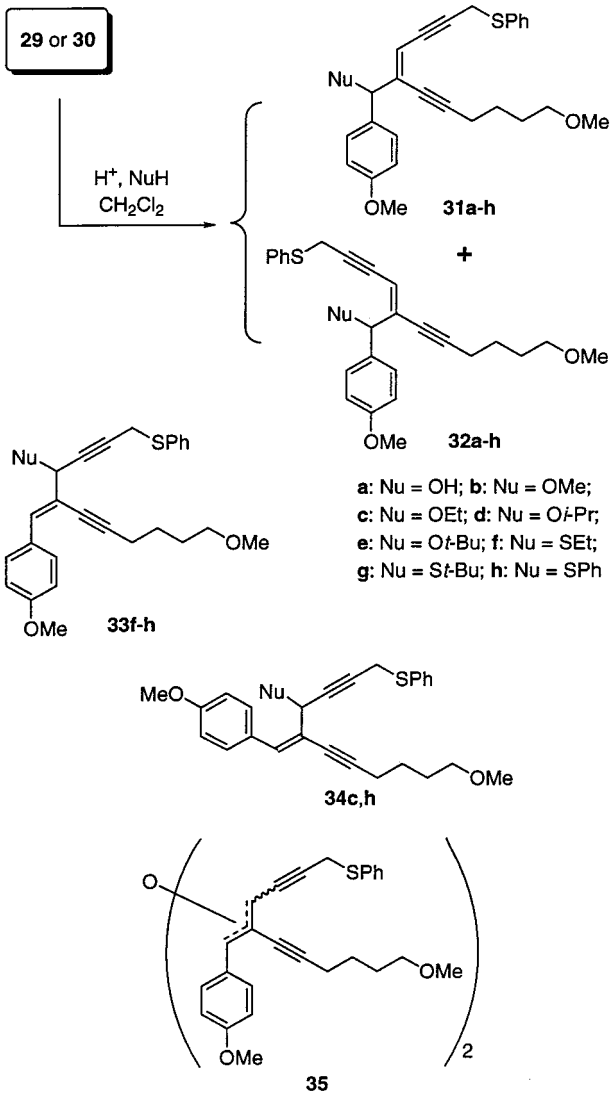


Figure 3. NOE experiments for compounds **29** and **30** measured on a 400 MHz instrument in $CDCl_3$ at room temperature: (a) irradiated at the vinyl proton at 6.73 ppm; (b) irradiated at the methine proton at 4.92 ppm; (c) irradiated at the vinyl proton at 6.80 ppm; (d) irradiated at the methine proton at 5.17 ppm.

Reaction of allyl alcohol **30** with EtOH was performed in the presence of 0.5 equiv of CSA and 4 equiv of EtOH in CH_2Cl_2 (Table 3, entry 13). Compound **30** did not show visible change at 0 °C under the same acidic conditions used for **29**. It suggests that formation of the allylic cation from **30** is much more difficult. At higher temperature (20 °C for 90 h), a mixture of **31c** and **32c** (74:26) was isolated in 32% yield together with the dimeric ethers **35** (31%). It is interesting to note that compound **34c** (Nu = EtO) was not formed in the reaction of **30**, which provides a piece of evidence for the discussion of isomerization of the allylic cations in the acid-catalyzed allylic rearrangement (vide infra).

Kinetic Studies. The acid-catalyzed isomerization of *cis*-1-methyl-3-phenylallyl alcohol (**36**) and *trans*-1-phenyl-3-methylallyl alcohol (**37**) were reported by Pocker and Hill (Scheme 8).[32] Pseudo-first-order rate constants were

Scheme 7



measured at different $HClO_4$ concentrations in 40% aqueous dioxane. On the basis of the kinetics, these authors concluded that formation of allylic cations **36′** and **37′** is the rate-determining step in the acid-catalyzed allylic rearrangement. Activation energies (E_a) of 23.6[32b] and 18.8[32a] kcal/mol were obtained for the loss of water from the protonated allyl alcohols. It is interesting to note that the rearranged product from both **36** and **37** is *trans*-1-methyl-3-phenylallyl alcohol (**38**), in which conjugation among the phenyl ring and the double bond is maintained. Moreover, a rapid isomerization of the sickle allylic cation **36′** into the W-type allylic cation **37′** was proposed, and the rotation barrier[33] (**36′** → **37′**) and energy difference between **36′** and **37′** were estimated to be 7.6 and 7.3 kcal/mol, respectively.[34]

We carried out kinetic studies on the acid-catalyzed conversion of 3-aryl-1,2-dialkynylallyl alcohols **12** and **29** in a mixed solvent system, i.e., $CD_3OD-CDCl_3$ (1:1). Because the reaction rate is dependent on acid concentration, by selecting a suitable concentration of CSA we can follow the reaction course on the NMR time scale. Use of CD_3OD as the cosolvent has two considerations: (a) methanol is known to slow the reaction (see entry 1, Table 1) and then allows the kinetic measurements using the NMR technique; and (b) methanol is a nucleophile that reacts with the allylic cation to form the allyl ethers. The disapperance of **12** or **29** was monitored on a 400 MHz NMR instrument by measuring the relative ratios of the substrate to an acid-stable internal reference compound, methyl 3,5-dinitrobenzoate, at different reaction times. Figure 4 shows the pseudo-first-order reaction of **12** in the given acid concentrations at 30, 40, and 55 °C. The slopes of the plots in Figure 4 give the pseudo-first-order rate constants (k_{obs}) from which the rate constants (k) were calculated by the equation $k = k_{obs}/[CSA]$. The rate constants (k) and half-lives ($t_{1/2}$) for the conversion of **12** at the given temperatures and acid concentrations are summarized in Table 4. On the basis of the rate constants (k) at 30, 40, and 55 °C, an activation energy (E_a) of 19.1 kcal/mol is estimated from the Arrhenius equation by the plot of ln k versus $1/T$.

Because the *p*-MeOPh-substituted allyl alcohol **29** is much more reactive than **12**, the kinetic measurements were performed at further diluted acid concentrations. Figure 5 shows the pseudo-first-order reactions of **29** at 30, 40, 50, and 60 °C. From these plots and the acid concentrations [CSA], the rate constants (k) were calculated and are listed in Table 5. An activation energy (E_a) of 17.2 kcal/mol is estimated using the Arrhenius equation. The reduced activation energy for **29** clearly indicates the involvement of a positively charged species in the rate-determining step.

Reactions of Chiral Allyl Alcohols. Regioselectivity of the CSA-catalyzed allylic rearrangement varies remarkably with different nucleophilic species. In general, excellent ratios (≥ 96:4) in favor of enediyne products are achieved for alcohols. In contrast, thiol nucleophiles give low regioselectivity (ca. 70:30 for **12** and ca. 90:10 for **29**). We consider that the two reactive intermediates **43** and **44** might be involved in the product-forming step (Scheme 9).[35] A nucleophile attacks at the protonated allyl alcohol in either an S_N2 or an S_N2' fashion to form two regioisomers. The same regioisomers can be produced through nucleophilic trapping at either the α or γ carbon of the allylic cation. If a chiral substrate is used, we are able to differentiate these reaction pathways by simply measuring the enantiomeric ratios of the products.

We prepared two chiral allyl alcohols (−)-**12** and (−)-**18c** by asymmetric reduction of ketones **45a**,**b** using (+)-DIP-chloride[36] (Scheme 10). Oxidation of racemic (±)-**12** to ketone **45a** failed with MnO_2. By the use of PCC in the presence of 4 Å MS (20 °C, 5 h), **45a** was obtained from (±)-**12** in 51% yield. Oxidation of racemic (±)-**18c** using MnO_2 (20 °C, 1 h) provided ketone **45b** in 83% yield. Reduction of **45a**,**b** by (+)-DIP-chloride in Et_2O at −25 °C for 7.5 h followed by the standard workup procedure[37] afforded (−)-**12** and (−)-**18c** in good yield and

(32) (a) Pocker, Y.; Hill, M. J. *J. Am. Chem. Soc.* **1969**, *91*, 3243. (b) Pocker, Y.; Hill, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 691.

(33) Isomerization barrier for allylic cations, see: Bollinger, J. M.; Brinich, J. M.; Olah, G. A. *J. Am. Chem. Soc.* **1970**, *92*, 4025.

(34) Izawa, K.; Okuyama, T.; Sakagami, T.; Fueno, T. *J. Am. Chem. Soc.* **1973**, *95*, 6752.

(35) An ion-neutral complex was proposed for intramolecular racemization and regioisomerization of chiral allyl alcohol in the gas phase, see: (a) Troiani, A.; Gasparrini, F.; Graninetti, F.; Speranza, M. *J. Am. Chem. Soc.* **1997**, *119*, 4525. (b) Troiani, A.; Speranza, M. *J. Org. Chem.* **1998**, *63*, 1012. (c) Speranza, M.; Troiani, A. *J. Org. Chem.* **1998**, *63*, 1020.

(36) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16. Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201. Brown, H. C.; Ramachandran, P. V. *Organomet. Chem.* **1995**, *500*, 1. Dhar, R. K. *Aldrichimica Acta* **1994**, *27*, 43.

Table 3. Synthesis of Enediynes 31 and 32 by Acid-Catalyzed Rearrangement of 29 and 30[a]

entry	substrate	acid (equiv)	NuH (equiv)	*T* (°C), *t* (h)	products (%)	ratio (**31**:**32**:**33**:**34**)[b]
1	**29**	CSA (1)	EtOH (2)	20, 0.25	**31c** + **32c** (78)	77:23:0:0
2	**29**	CF_3CO_2H (1)	EtOH (2)	20, 48	**31c** + **32c** (68)	82:18:0:0
3	**29**	CSA (0.2)	EtOH (2)	20, 2	**31c** + **32c** (84); **31a** (15)	86:14:0:0
4	**29**	CSA (0.2)	EtOH (2)	0, 28	**31c** + **32c** (74); **31a** (3)[c]	95:5:0:0
5	**29**	CSA (0.5)[d]	EtOH (4)	0, 7	**31c** + **32c** (89)	94:6:0:0
6	**29**	CSA (0.5)	MeOH (4)	0, 3.5	**31b** + **32b** (90)	94:6:0:0
7	**29**	CSA (0.5)	*i*-PrOH (4)	0, 9	**31d** + **32d** (77); **35** (11)	82:18:0:0
8	**29**	CSA (0.5)	*t*-BuOH (4)	0, 23	**31e** + **32e** (20); **35** (78)	86:14:0:0
9	**29**	CSA (0.2)	EtSH (2)	0, 12	**31f** + **32f** + **33f** (88)	75:17:8:0
10	**29**	CSA (0.5)	EtSH (4)	0, 3	**31f** + **32f** + **33f** (88)	78:15:7:0
11	**29**	CSA (0.5)	*t*-BuOH (2)	0, 4	**31g** + **32g** + **33g** (85)	74:18:8:0
12	**29**	CSA (0.5)	PhSH (2)	0, 2	**31h** + **32h** + **33h** + **34h** (76)	74:8:11:7
13	**30**	CSA (0.5)	EtOH (4)	20, 90	**31c** + **32c** (32); **35** (31)	74:26:0:0

[a] Reactions were performed in CH_2Cl_2. [b] Determined by ^{1}H NMR. [c] Also, 16% of **29** recovered. [d] Final concentration of CSA is 0.03 M.

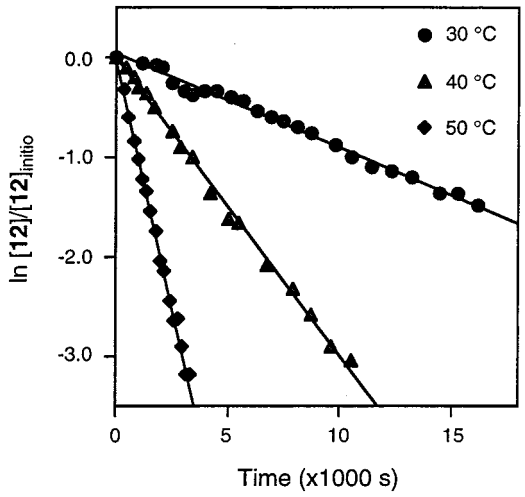
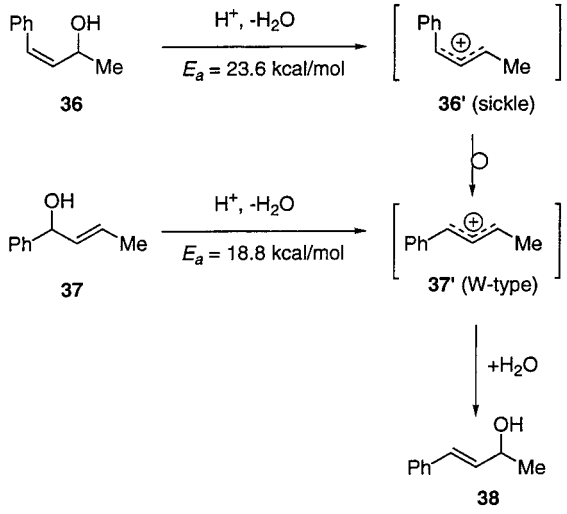


Figure 4. CSA-catalyzed conversion of **12** in $CDCl_3$−CD_3OD (1:1) at 30, 40, and 55 °C, as measured by ^{1}H NMR on a 400 MHz instrument.

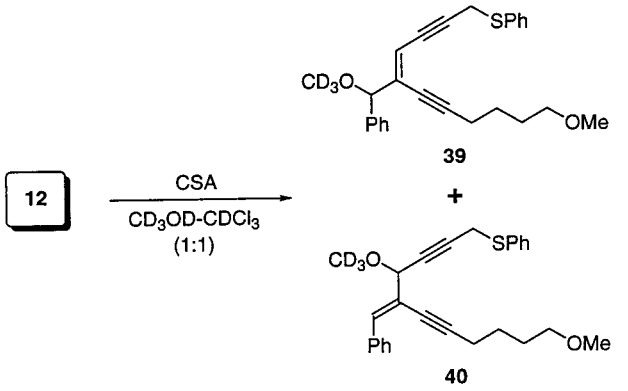
Scheme 8



in >94% ee, respectively. Enantiomeric excess of the chiral alcohols was determined by HPLC analysis in comparison with racemic authentic samples using a Chiralpak AD or AS column. The absolute stereochemistry of the chiral alcohols was not determined. Reactions of (−)-**12** and (−)-**18c** with EtOH and EtSH were then

(37) Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379.

Table 4. Rate Constants (*k*) and Half-Lives ($t_{1/2}$) of Allyl Migration of 12 Catalyzed by CSA in CD_3OD−$CDCl_3$ at Various Temperatures As Measured by ^{1}H NMR; $k = k_{obs}$/[CSA]



T (°C)	[CSA] (M)	*k* (s^{-1})	correlation coeff	$t_{1/2}$ (min)
30	4.38×10^{-2}	2.15×10^{-3}	0.995	128.2
40	4.47×10^{-2}	6.64×10^{-3}	0.998	37.0
55	4.08×10^{-2}	23.8×10^{-3}	0.998	11.1

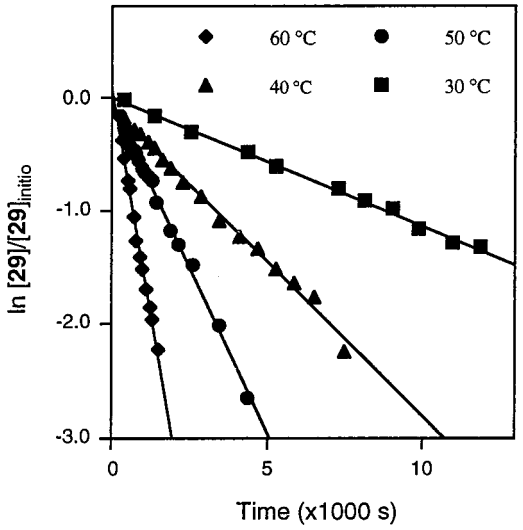
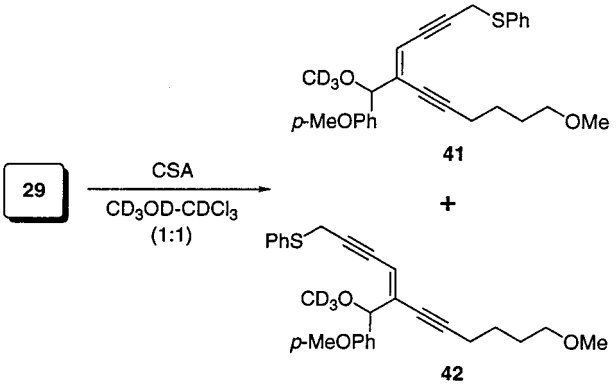


Figure 5. CSA-catalyzed conversion of **29** in $CDCl_3$−CD_3OD (1:1) at 30, 40, 50, and 60 °C, as measured by ^{1}H NMR on a 400 MHz instrument.

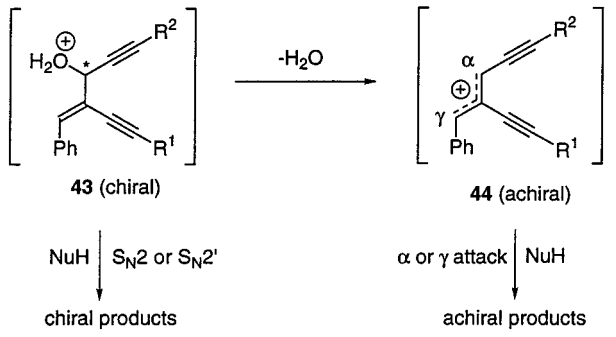
carried out under the same acidic conditions used for the racemic substrates. The results are summarized in Table 6. The enantiomeric ratios of products **16b**,**d**, **17b**,**d**, **19c**,

Table 5. Rate Constants (k) and Half-Lives ($t_{1/2}$) of Allyl Migration of 29 Catalyzed by CSA in $CD_3OD-CDCl_3$ at Various Temperatures As Measured by ^1H NMR; $k = k_{obs}/[CSA]$



T (°C)	[CSA] (M)	k (s^{-1})	correlation coeff	$t_{1/2}$ (min)
30	4.73×10^{-4}	0.24	0.998	102.2
40	4.88×10^{-4}	0.56	0.997	42.6
50	5.16×10^{-4}	1.13	0.998	19.7
60	4.73×10^{-4}	3.33	0.997	7.3

Scheme 9



46, and **47** were analyzed by HPLC over chiral columns and all were proved to be in racemic form. These findings confirm that the regioisomeric products are formed from the dissociated allylic cation **44**. The protonated intermediate **43** is not involved in the product-forming step.

Mechanistic Considerations. With regard to the structures of the allylic cations, we suggest the possibility of three species, the W-type allylic cations (**48** and **49**) and two kinds of sickle allylic cations (**50**−**53**), being formed from allyl alcohols **12**−**15**, **29**, and **30** via acid-catalyzed ionization (Scheme 11). The U-type allylic cation is not considered because of its extremely high instability. The two sickle allylic cations suffer from $A^{1,3}$ strain among the substituent and the proton at the α and γ positions and are less stable than the W-type allylic cation. Severe $A^{1,3}$ strain is expected for **52** and **53** between the aryl group and the allylic proton.[32b] This accounts for the relatively high ratio of **15** to **14** (66:34) in the equilibrium mixture obtained from the acid-catalyzed rearrangement given in Scheme 4 and Figure 1. Ionization of **15** to form **52** should be much more difficult compared to that of **14**, and allyl alcohol **15** is then accumulated in the reaction mixture. Moreover, the high instability facilitates a rapid isomerization[32b,34] of allylic cation **53** into **49**. This explains why compound **34c** (formed by attack of a nucleophile at the α position of **53**) is not formed from **30** and EtOH under the acidic conditions (Scheme 7 and Table 3, entry 13). Acid-catalyzed ionization of **12** and **13** should form predominantly the W-type allylic cation **48**, although enediyne alcohol **13** undergoes ionization slower than **12**. This is attributed to the great thermodynamical stability of **13** over **12** (see the ab inito calculations below). Thus, we assume that it is almost impossible for **13** to form the much more unstable cation **52** at room temperature, whereas **12** may give cation **50** as the minor ionization pathway. A rapid isomerization eventually converts **50** into the W-type allylic cation **48**. The above argument is supported by the fact that both **12** and **13** furnish the same product mixtures with EtOH and EtSH in the presence of CSA (Scheme 5 and Table 1). When the lifetime of allylic cation **51** increases as a result of extra stabilization (ca. 12 kcal/mol, see the ab inito calculations below) from the *p*-MeO group, nucleophilic trapping at the γ position of **51** is then able to provide *trans*-enediynes **32b**−**h** (Scheme 7 and Table 3). Because of the reduced activation energy for ionization of **29** (1.9 kcal/mol less than **12**), formation of cation **51** could be much more competitive than formation of **49**. However, we can manipulate the reaction temperature to enhance the selectivity among the two ionization pathways. Low temperature favors the route **29** → **49**, and higher ratios

Scheme 10

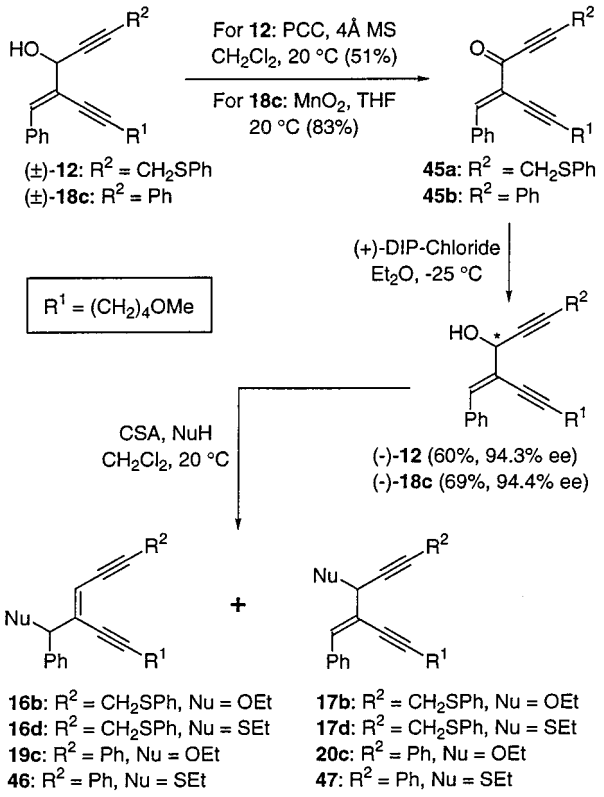


Table 6. Enediynes Formed from Chiral Alcohols (−)-12 and (−)-18c[a]

entry	substrate	NuH, t (h)	products (%)	ratio[c]
1	(−)-**12**	EtOH, 4	**16b** (64); **17b** (4)	96:4
2	(−)-**12**	EtSH, 4	**16d** + **17d** (55)	70:30
3	(−)-**18c**	EtOH, 2	**19c** (65); **20c** (0)	100:0
4	(−)-**18c**	EtSH, 0.5	**46** + **47** (60)	69:31

[a] Reactions were performed in CH_2Cl_2 in the presence of 1 mole equiv of CSA (0.055−0.067 M) and 2 mole equiv of nucleophile at 20 °C. [b] All products were obtained in racemic forms as checked by HPLC over a chiral column. See Experimental Section for details. [c] The regioisomeric ratio of **16b**:**17b**, **16d**:**17d**, **19c**:**20c**, and **46**:**47**, respectively.

Scheme 11

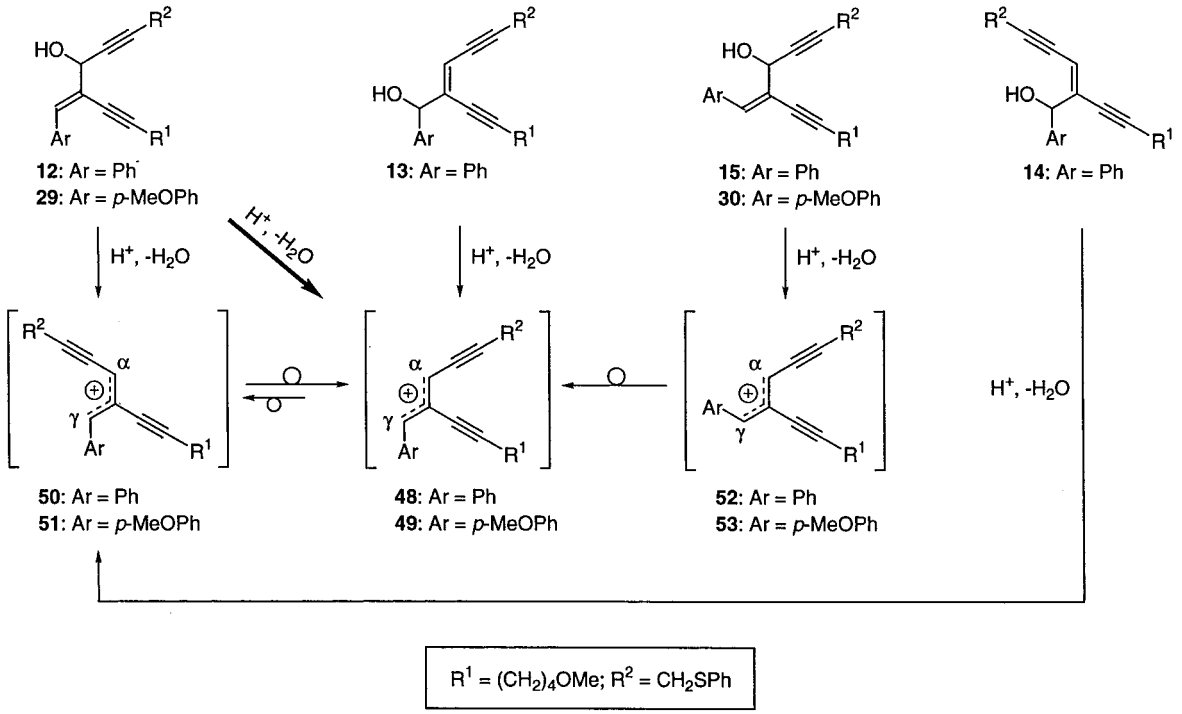


Table 7. Total Energies of the Most Stable Conformers of 54a−f and 55a−f Calculated at the RHF/3-21G Level

54a-f **55a-f**

a: X = H, Nu = OH; **b**: X = Me, Nu = OH;
c: X = Ph, Nu = OH; **d**: X = *p*-MeOPh, Nu = OH;
e: X = Ph, Nu = OMe; **f**: X = Ph, Nu = SMe

54 (hartrees)[a]	**55** (hartrees)	Δ*E* (kcal/mol)[b]
54a: −341.359 077 7	**55a**: −341.363 476 7	2.76
54b: −380.183 074 1	**55b**: −380.189 502 8	4.03
54c: −569.629 115 1	**55c**: −569.637 270 5	5.12
54d: −682.879 662 5	**55d**: −682.890 242 0	6.64
54e: −608.442 490 5	**55e**: −608.450 235 1	4.86
54f: −929.569 134 0	**55f**: −929.571 106 5	1.24

[a] One hartree = 627.5 kcal/mol. [b] Energy difference between **54** and **55**. In all cases, enediyne **55** is more stable than 1,5-diyne **54**.

of the nucleophilic trapping products **31** and **32** are obtained at 0 °C compared to the reactions at 20 °C. The different ionization profiles of allylic alcohols **12** and **29** provide a key to understanding the cis/trans diastereoselectivity associated with enediyne formation under the acid catalysis.

Computational Calculations. To understand the substituent effect on reactivity of allyl alcohols and the origin of regioselectivity observed in the allylic rearrangement, we performed ab initio molecular orbital calculations at the RHF/3-21G level using the Gaussian 94 sets of programs on the model compounds **54a−f** and **55a−f** and the allylic cations **56−59**. The total energies and geometries of the most stable conformers **54a−f** and **55a−f** are given in Table 7 and Figure 6. We first calculated the three conformations **54a**, **54a′**, and **54a″** (see Supporting Information). We found that **54a** is more stable than **54a′** and **54a″** by 3.03 and 3.96 kcal/mol, respectively, because of a favorable electrostatic interaction between the oxygen atom and the olefinic proton. In contrast, the sulfur analogue **54g** (structure not shown) is 0.26 kcal/mol less stable than **54g′** as a result of the larger van der Waal radius of sulfur (see Supporting Information). We noted a similar electrostatic interaction in other oxygen-containing systems. For examples, allyl alcohol **54c** is more stable than **54c′** by 1.20 kcal/mol, and allylic ether **54e** is more stable than **54e′** by 3.75 kcal/mol. The hydroxy or methoxy group in **54a−e** and **55a−e** is generally out of the allylic plane by ca. 10°, and the distance between the oxygen atom and the olefinic proton is within 2.175−2.296 Å. However, allylic thioether **54f** possesses a conformation different from that of **54e**, for example. The sulfur group in **54f** is almost in the perpendicular position relative to the allylic plane (94.9°). Conformer **54f** is 0.77 kcal/mol more stable than **54f′**, in which the allylic and olefinic protons are in close contact (2.208 Å, twisted from the allylic plane by only 4.2°). The most important structural feature of the C_3-aryl-substituted compounds **54c−f** is that the aromatic ring twists from coplanarity with the double bond by 28−33° (Figure 6). This conformation avoids the severe van der Waal interaction among one of the *ortho* protons in the aryl group and the C_2-alkynyl unit. However, the distances of 2.526−2.581 Å for **54c−f** are shorter than those of **55c−f** (3.085−3.322 Å). We found that enediynes **55a−f** are much more stable than the corresponding regioisomers **54a−f**, perhaps because of the conjugation of both alkynyl groups with the double bond (Table 7). When Nu = OH, the energy difference between **54** and **55** (Δ*E* in kcal/mol) increases in the order of X = H (2.76) < X = Me (4.03) < X = Ph (5.12) < X = *p*-MeOPh (6.64). We found that this order is parallel to the stability order of the corresponding allylic cations **56−59** (Figure 7). The bulkiness of the Nu group has a significant influence on Δ*E* for C_3-phenyl-substituted compounds: OH (5.12) >

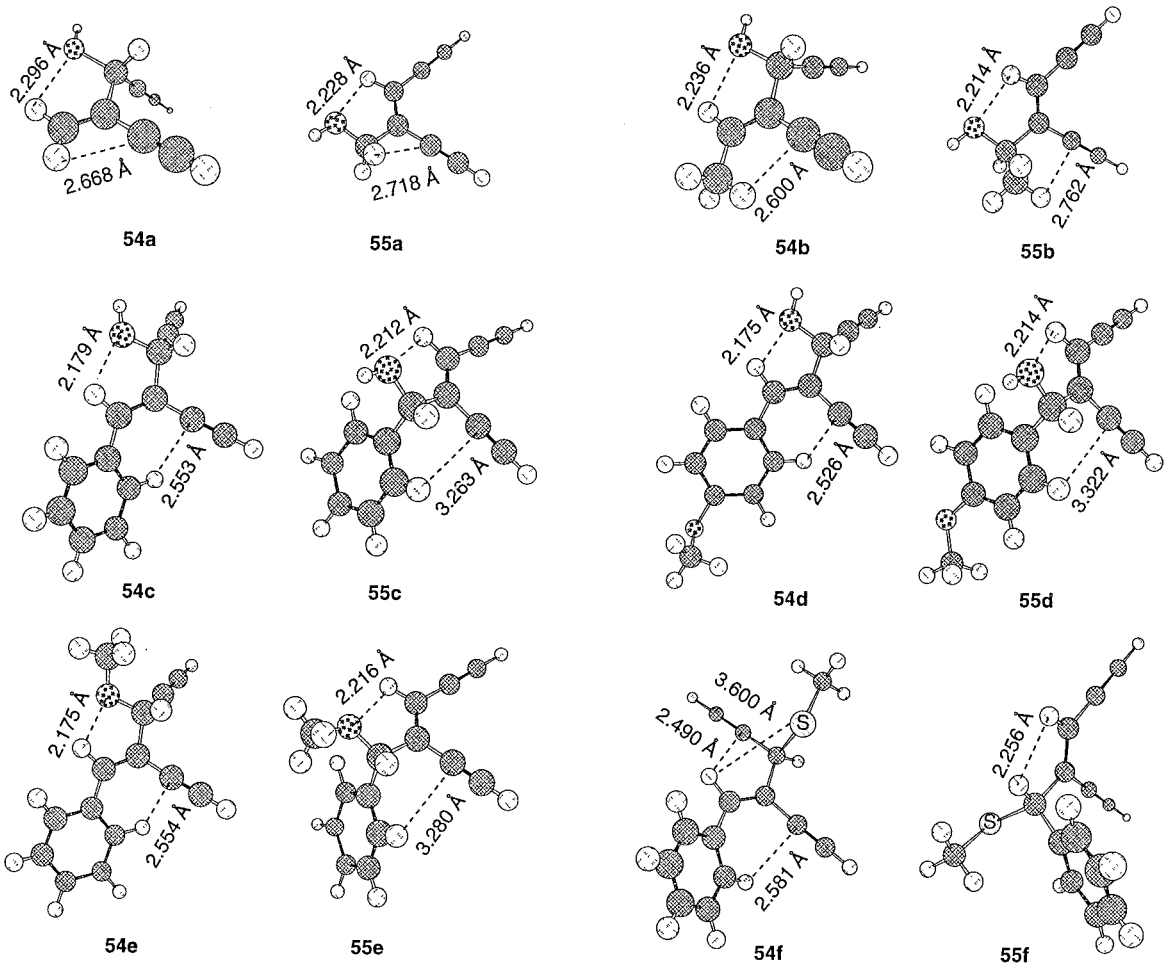


Figure 6. The most stable geometries of **54c**−**f** and **55c**−**f** optimized at the RHF/3-21G level.

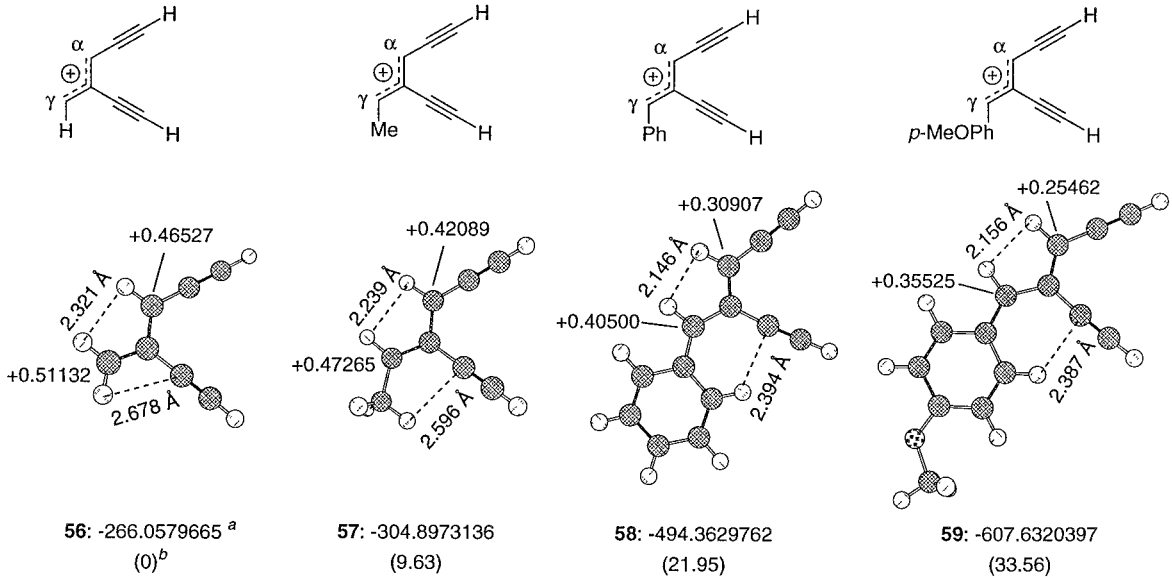


Figure 7. Total energies, geometries, and Mulliken charge distribution at the α and γ carbons of allylic cations **56**−**59** optimized at the RHF/3-21G level. [a]Total energies in hartrees. [b]Increased stability compared to **56** due to the substituent at the γ carbon in kcal/mol.

OMe (4.86) ≫ SMe (1.24) (in units of kcal/mol). This stability order is explained by considering the steric demand at the Nu-bearing carbon atom. For example, Ph(MeS)CH− in **55f** should suffer from much more repulsive interaction compared to HC≡C(MeS)CH− in **54f**. The larger the van der Waal radius of the heteroatom is, the more severe the destabilization suffered.

The ab initio calculations on the W-type allylic cations **56**−**59** show that all structures are planar with a separation of 2.146−2.321 Å between the allylic protons

(Figure 7). Notably, full conjugation with the aromatic ring is observed in **58** and **59** and is distinguished from the conformations **54c**−**f**. Much more positive charge is found at the γ carbon compared to the α carbon in all cations. Using **56** as the reference, a C_3 substituent greatly enhances the stability of the cation in the following order: Me (9.63) < Ph (21.95) < *p*-MeOPh (33.56) (in units of kcal/mol). Accordingly, the sum of charge at both α and γ carbons decreases with increasing cation stability: +0.97659 (**56**) > +0.89354 (**57**) > +0.71407 (**58**) > +0.60987 (**59**). The calculated stability and charge distribution of allylic cations **56**−**59** provide the key to understand the reactivity and regioselectivity observed in the acid-catalyzed allylic rearrangement.

Origin of Reactivity and Regioselectivity. As shown in Schemes 2 and 3, the C_3-unsubstituted and C_3-methyl allyl alcohols **5** and **9** did not undergo allylic rearrangement at room temperature in the presence of a strong acid, such as TfOH. Now, we understand that these alcohols are difficult to undergo acid-catalyzed ionization because the corresponding allylic cations cannot be better stabilized by the C_3 substituent. In contrast, the C_3-arylallyl alcohols **12** and **29** are readily converted into allylic cations **48** and **49** at room temperature or below. The calculated substituent effects on the cation stability given in Figure 7 provide the basis for design of suitable precursors that can be transformed into enediynes under mild conditions.

The last issue that needs to be addressed is the regioselectivity observed for nucleophilic trapping of the W-type allylic cations **48** and **49**. Reactions of alcohols give excellent selectivity (≥ 94:6) in favor of attack at the γ position to form enediynes. In contrast, thiols provide diminished selectivity of ca. 70:30 with cation **48** at 20 °C and ca. 90:10 with cation **49** at 0 °C. We confirmed that nucleophilic trapping of allylic cations **48** and **49** with thiols is not reversible under the mild acidic conditions. Change in the ratio was not noted in the control experiments using a 67:33 mixture of **16d**:**17d** (1 equiv of CSA, dry CH_2Cl_2, 20 °C, 5 h). Pure isomer **16b** was also recovered without change after treatment with CSA (1 equiv, dry CH_2Cl_2, 20 °C, 5 h). However, a slow isomerization of the less stable regioisomer **17b** into **16b** was observed; **17b** gave a 1:1 mixture of **16b**:**17b** in 80% recovery after treatment under the same acidic conditions (1 equiv of CSA, dry CH_2Cl_2, 20 °C, 5 h). Considering these facts, we believe that the product ratios given in Tables 1 and 3 for reactions of thiols are kinetically controlled and the ratios for reactions of alcohols are partially thermodynamically controlled. Because the transition state (TS) of the nucleophilic trapping reaction has partial double bond character, the path for formation of the more stable regioisomer should have a better stabilized TS and should take place preferentially. This argument agrees with the finding that enediynes **16a**−**f** and **31a**−**h** are the major products of allylic cations **48** and **49**. The diminished selectivity of thiols is consistent with the smaller energy difference among thioethers **54f** and **55f** compared to that of the oxygen analogues **54e** and **55e**.

Alternatively, regioselective formation of enediynes can be discussed according to the charge distribution in the allylic cations **58** and **59**. A hard nucleophile (alcohol) should favor attack at the γ carbon to form enediynes, and a soft nucleophile (thiol) should give less preference to γ attack. However, allylic cation **58** carries a sum of +0.71407 charge at the α and γ positions, and less charge (+0.60987) is found for **59**. The increased stability of **59** allows the nucleophilic trapping TS to have much more double bond character. Thus, allylic cation **59** demonstrates an enhanced selectivity for formation of the thermodynamically stable enediynes. The computational calculation results agree well with the experimental observations.

Conclusion

We have developed a novel synthetic method for the rearrangement of 3-aryl-1,2-dialkynylallyl alcohols into *cis*-enediynes under mild acidic conditions. High regio- and cis/trans diastereoseletivity is achieved for the reactions carried out in the presence of an alcoholic nucleophile. The allylic rearrangement is confirmed to take place in a stepwise mechanism. It involves an acid-catalyzed ionization step to convert the allyl alcohol into an allylic cation intermediate followed by a nucleophilic trapping step to form the products. Pocker and Hill[32] reported that formation of the allylic cation is the rate-determining step for the acid-catalyzed isomerization of allyl alcohols lacking a C_2 substituent. We observed loss of chirality in the rearrangement of chiral alcohols (−)-**12** and (−)-**18c**. This confirms that the allylic cation is the intermediate that produces the final products upon nucleophilic trapping. Enhanced stability of the allylic cation by a C_3 substituent facilitates the allylic rearrangement under mild acidic conditions. This explains the failure in reactions of C_3-unsubstituted and C_3-methyl allyl alcohols **5** and **9**.

The effect of a C_3-aryl group on the ionization of allyl alcohols has been examined. A diminished activation energy of ca. 2 kcal/mol is observed for CSA-catalyzed rearrangement of the *p*-MeOPh-substituted allyl alcohol **29** compared to the Ph analogue **12** in 50% CD_3OD in $CDCl_3$. Stability of the C_3-aryl-substituted allylic cations accounts for the different ionization profiles of **12** and **29**. Alcohols **12** and **29** preferentially form the most stable W-type allylic cations **48** and **49**. A minor ionization pathway to the sickle allylic cation **51** seems possible for **29**; however, it is difficult to form the sickle allylic cation **50** from alcohol **12**. This argument is supported by the fact that *trans*-enediynes **32** are obtained from **29**. The competitive pathways **29** → **49** and **29** → **51** can be modulated by temperature, and higher ratios are achieved at 0 °C in favor of *cis*-enediynes **31**. Nucleophilic attack at the allylic cations **48** and **49** possibly produces two regioisomers. We have carried out ab initio molecular orbital calculations at the RHF/3-21G level on the model compounds **54** and **55**. The results reveal that enediynes **55c**−**f** are much more stable than 1,5-diynes **54c**−**f**, perhaps as a result of the twisted orientation of the C_3 aryl group in **54c**−**f**. However, the energy difference between **55c**,**e**,**f** and **54c**,**e**,**f** decreases with increasing bulkiness of the Nu group: OH > MeO ≫ MeS. It provides the basis for understanding the diminished regioselectivity in reaction of allylic cations **48** and **49** with thiols. Calculations on the cations **58** and **59** show that the γ carbon is much more electron-deficient and is therefore much more reactive toward nucleophiles. Enhanced stability contributed from the *p*-MeO group for cation **49** makes it less reactive toward nucleophiles and much more regioselective compared to cation **48**.

In summary, an acid-catalyzed allylic rearrangement of 3-aryl-1,2-dialkynylallyl alcohols into *cis*-enediynes has

been established. We have demonstrated the feasibility of this methodology for the synthesis of cyclic enediynes.[24b,38] Our allylic rearrangement is conceptually related to the mechanism of action of maduropeptin chromophore artifacts[10] and opens a novel approach to enediyne prodrug design and synthesis.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (300 or 400 MHz for ^{1}H and 75 or 100 MHz for ^{13}C) with $CDCl_3$ as the internal reference. IR spectra were taken on a FT-IR spectrophotometer. Mass spectra (MS) were measured by CI or FAB method. High-resolution mass spectra (HRMS) were measured by the EI or FAB method at Kunming Institute of Botany, The Chinese Academy of Sciences. Elemental analysis was performed by the Microanalytic Laboratory of Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences. All reactions were carried out under a nitrogen atmosphere and monitored by thin-layer chromatography on 0.25-mm E. Merck silica gel plates (60 F-254) using UV light or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. E. Merck silica gel (60, particle size 0.040−0.063 mm) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Phenyl propargyl sulfide was synthesized according to the literature procedure.[28] Other reagents were obtained commercially and used as received. Room temperature is around 20 °C.

6-Methoxy-1-hexyne. To a suspension of 60% NaH (1.17 g, 29.3 mmol) in dry THF (40 mL) cooled in an ice−water bath (0 °C) was added hex-5-yn-1-ol (2.00 g, 19.6 mmol) followed by stirring at room temperature for 30 min. The resultant mixture was cooled back to 0 °C, and MeI (2.40 mL, 39.2 mmol) was added followed by stirring at 40 °C for 2 days. The reaction mixture was quenched by saturated aqueous NH_4Cl (10 mL) and extracted with ethyl ether (50 mL). The organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by distillation to give the product (1.43 g, 65%): colorless liquid; bp = 120−125 °C; IR (neat) 2118, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (t, J = 6.34 Hz, 2 H), 3.33 (s, 3 H), 2.21 (td, J = 6.44, 2.44 Hz, 2 H), 1.94 (t, J = 2.44 Hz, 1 H), 1.72−1.59 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.3, 72.2, 68.4, 58.5, 28.6, 25.1, 18.2; MS (+CI) m/z (relative intensity) 81 (M^+ − MeO, 100).

2-Bromo-6-(phenylthio)hex-4-yn-1-en-3-ol (4). To a solution of phenyl propargyl sulfide (0.779 g, 5.26 mmol) in dry THF (20 mL) cooled in a dry ice−acetone bath (−78 °C) was added *n*-BuLi (2.5 M in hexanes, 1.91 mL, 4.79 mmol) followed by stirring at the same temperature for 30 min to give the THF solution of $PhSCH_2C{\equiv}CLi$. To a solution of α-bromoacrolein (**3**)[27] (0.646 g, 4.79 mmol) in dry THF (20 mL) in a separate flask cooled at −78 °C was added the THF solution of $PhSCH_2C{\equiv}CLi$ prepared above. The resultant mixture was stirred at the same temperature for 1 h and quenched with a saturated aqueous solution of NH_4Cl (40 mL). The reaction mixture was extracted with EtOAc (30 × 3 mL) and washed with brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc−hexane) to give **4** (0.563 g, 51%): pale yellow oil; R_f = 0.31 (20% EtOAc−hexane); IR (neat) 3384, 2228, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.32 Hz, 2 H), 7.28 (t, J = 7.32 Hz, 2 H), 7.22 (d, J = 7.33 Hz, 1 H), 5.95 (dd, J = 2.45, 0.98 Hz, 1 H), 5.53 (d, J = 1.95 Hz, 1 H), 4.84 (d, J = 4.88 Hz, 1 H), 3.62 (d, J = 1.95 Hz, 2 H), 2.37 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 132.2, 130.6, 129.0, 127.1, 118.5, 83.2, 80.4, 66.9, 22.9; MS (+CI) m/z (relative intensity) 284 (M^+, ^{81}Br, 100), 282 (M^+, ^{79}Br, 90), 267 (M^+ − OH, ^{81}Br, 78), 265 (M^+ − OH, ^{79}Br, 54); HRMS (+FAB) calcd for $C_{12}H_{11}OS^{81}Br$ (M^+) 283.9694, found 283.9635.

11-Methoxy-5-methylidene-1-(phenylthio)undeca-2,6-diyn-4-ol (5). To a suspension of $Pd(PPh_3)_4$ (86.1 mg, 7.45 × 10^{-2} mmol) and CuI (56.8 mg, 0.298 mmol) in degassed THF (25 mL) maintained at 0 °C in an ice−water bath was added a solution of alcohol **4** (0.421 g, 1.49 mmol), 6-methoxy-1-hexyne (0.250 g, 2.24 mmol), and triethylamine (0.42 mL, 2.98 mmol) in degassed THF (70 mL) via a syringe. The reaction flask was covered against light with a sheet of aluminum foil, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (10 × 2 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20% EtOAc−hexane) to give **5** (0.447 g, 95%): pale yellow oil; R_f = 0.46 (40% EtOAc−hexane); IR (neat) 3374, 2224, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.32 Hz, 2 H), 7.33 (t, J = 7.32 Hz, 2 H), 7.27 (d, J = 7.80 Hz, 1 H), 5.53 (s, 1 H), 5.40 (s, 1 H), 4.82 (d, J = 5.37 Hz, 1 H), 3.69 (d, J = 1.95 Hz, 2 H), 3.42 (t, J = 5.86 Hz, 2 H), 3.34 (s, 3 H), 2.39 (s, 1 H), 2.38 (t, J = 6.84 Hz, 2 H), 1.74−1.61 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 131.5, 130.3, 128.9, 126.9, 120.6, 93.1, 82.5, 81.8, 76.8, 72.2, 65.2, 58.5, 28.7, 25.2, 23.0, 19.2; MS (+CI) m/z (relative intensity) 332 (M + NH_4^+, 100); HRMS (+FAB) calcd for $C_{19}H_{23}O_2S$ (M + H^+) 315.1419, found 315.1486.

(*Z*)-α-Bromocrotonaldehyde (7). To a solution of *trans*-crotonaldehyde (5.92 mL, 71.4 mmol) in dry CH_2Cl_2 (100 mL) cooled in an ice−water bath (0 °C) was added bromine (3.7 mL, 71.8 mmol) in CH_2Cl_2 (4 mL) followed by stirring at room temperature for 1 h. Triethylamine (12 mL, 86.1 mmol) was added, and the mixture was allowed to stir at room temperature for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL), and the organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by vacuum distillation to give the product **7** (7.76 g, 72%): bp = 134−135 °C/∼0.1 mmHg; pale yellow liquid; IR (neat) 1698, 1624 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1 H), 7.25 (q, J = 6.84 Hz, 1 H), 2.14 (d, J = 6.84 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 150.7, 130.2, 17.9; MS (+CI) m/z (relative intensity) 151 (M + H^+, ^{81}Br, 58), 149 (M + H^+, ^{79}Br, 91).

(*E*)-2-Ethylidene-8-methoxyoct-3-ynal (8). To a suspension of $Pd(PPh_3)_4$ (194.0 mg, 0.17 mmol) and CuI (0.13 g, 0.67 mmol) in degassed THF (30 mL) maintained at 0 °C in an ice−water bath was added a solution of (*Z*)-α-bromocrotonaldehyde (**7**, 0.50 g, 3.36 mmol), 6-methoxy-

(38) Dai, W.-M.; Fong, K. C.; Lau, C. W.; Zhou, L.; Hamahuchi, W.; Nishimoto, S. *J. Org. Chem*. **1999**, *64*, 682.

1-hexyne (0.56 g, 5.03 mmol), and triethylamine (0.70 mL, 5.03 mmol) in degassed THF (40 mL) via a syringe. The reaction flask was covered against light with a sheet of aluminum foil, and the mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (60 mL). The organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20% EtOAc−hexane) to give **8** (59.3 mg, 10%): pale yellow oil; $R_f = 0.58$ (20% EtOAc−hexane); IR (neat) 2230, 1700, 1616, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1 H), 6.96 (q, J = 6.98 Hz, 1 H), 3.43 (t, J = 6.05 Hz, 2 H), 3.35 (s, 3 H), 2.50 (t, J = 6.62 Hz, 2 H), 2.16 (d, J = 7.05 Hz, 3 H), 1.77−1.64 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 155.1, 129.7, 100.2, 72.1, 72.0, 58.5, 28.7, 25.2, 19.4, 16.9; MS (+CI) *m*/*z* (relative intensity) 149(M^+ − OMe, 100).

(*E*)-5-Ethylidene-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ol (9). To a solution of phenyl propargyl sulfide (74.8 mg, 0.51 mmol) in dry THF (3 mL) cooled in an acetone bath maintained at −80 °C by a chiller was added *n*-BuLi (1.6 M in hexanes, 0.35 mL, 0.51 mmol) followed by stirring at the same temperature for 30 min to give the THF solution of $PhSCH_2C{\equiv}CLi$. To a solution of aldehyde **8** (70 mg, 0.39 mmol) in dry THF (3 mL) in a separate flask cooled at −80 °C was added the THF solution of $PhSCH_2C{\equiv}CLi$ prepared above. The resultant mixture was stirred at the same temperature for 1 h and quenched with a methanolic solution of acetic acid (31 mg of acetic acid in 0.5 mL MeOH). The reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was washed with brine (2 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc−hexane) to give **9** (79.2 mg, 62%): pale yellow oil; R_f = 0.30 (20% EtOAc−hexane); IR (neat) 3380, 2220, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.44 (m, 2 H), 7.34−7.24 (m, 3 H), 6.02 (q, J = 6.75 Hz, 1 H), 4.77 (d, J = 6.54 Hz, 1 H), 3.68 (s, 2 H), 3.41 (t, J = 6.14 Hz, 2 H), 3.33 (s, 3 H), 2.56 (d, J = 7.08 Hz, 1 H), 2.42 (t, J = 6.69 Hz, 2 H), 1.83 (d, J = 6.78 Hz, 3 H), 1.73−1.61 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 132.7, 130.2, 128.8, 126.8, 124.6, 96.9, 82.2, 75.8, 72.1, 65.4, 58.3, 28.6, 25.3, 22.9, 19.3, 15.7; MS (+CI) *m*/*z* (relative intensity) 346 (M + NH_4^+, 100).

(*E*)-8-Methoxy-2-(phenylmethylidene)oct-3-ynal (11). To a suspension of $Pd(PPh_3)_4$ (0.27 g, 0.23 mmol) and CuI (0.18 g, 0.95 mmol) in degassed THF (20 mL) maintained at 0 °C in an ice−water bath was added a solution of α-bromocinnamaldehyde (**10**, 1.02 g, 4.83 mmol), 6-methoxy-1-hexyne (417 mg, 3.72 mmol), and triethylamine (1.30 mL, 9.30 mmol) in degassed THF (30 mL) via a syringe. The reaction flask was covered against light by a sheet of aluminum foil, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (60 mL). The organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20% EtOAc−hexane) to give **11** (811 mg, 90%): pale yellow oil; R_f = 0.55 (25% EtOAc−hexane); IR (neat) 2250, 1692, 1602, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1 H), 8.08−8.05 (m, 2 H), 7.44−7.42 (m, 3 H), 7.40 (s, 1 H), 3.41 (t, J = 5.86 Hz, 2 H), 3.32 (s, 3 H), 2.58 (t, J = 6.59 Hz, 2 H), 1.80−1.70 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 151.0, 134.1, 131.2, 130.3, 128.6, 123.3, 102.9, 74.5, 72.0, 58.4, 28.7, 25.0, 19.8; MS (+CI) *m*/*z* (relative intensity) 243 (M + H^+, 100).

(*E*)-11-Methoxy-5-phenylmethylidene-1-(phenylthio)undeca-2,6-diyn-4-ol (12). To a solution of aldehyde **11** (2.80 g, 11.6 mmol) in dry THF (70 mL) cooled at −80 °C was added a THF (30 mL) solution of $PhSCH_2C{\equiv}CLi$ prepared from phenyl propargyl sulfide (2.20 g, 15.0 mmol) and *n*-BuLi (1.44 M in hexanes, 10 mL, 15.0 mmol). The reaction was stirred at the same temperature for 1 h and quenched with a methanolic solution of acetic acid (0.9 g of acetic acid in 5 mL MeOH). The resultant mixture was extracted with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc−hexane) to give **12** (3.50 g, 79%): pale yellow oil; R_f = 0.17 (20% EtOAc−hexane); IR (neat) 3380, 2218, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 6.84 Hz, 2 H), 7.42 (d, J = 6.83 Hz, 2 H), 7.32−7.15 (m, 6 H), 6.75 (s, 1 H), 4.90 (d, J = 6.83 Hz, 1 H), 3.66 (s, 2 H), 3.38 (t, J = 6.11 Hz, 2 H), 3.29 (s, 3 H), 2.50 (d, J = 7.81 Hz, 1 H), 2.45 (t, J = 6.59 Hz, 2 H), 1.91−1.74 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.1, 133.7, 130.3, 128.9, 128.7, 128.4, 128.1, 126.9, 122.0, 99.5, 82.7, 82.2, 77.6, 72.1, 66.9, 58.5, 28.6, 25.1, 23.1, 19.7; MS (+CI) *m*/*z* (relative intensity) 390 (M^+, 100). Anal. Calcd for $C_{25}H_{26}O_2S$: C, 76.89; H, 6.71. Found: C, 76.78; H, 6.88.

Acid-Catalyzed Isomerization of 12. (*E*)-8-Methoxy-1-phenyl-2-[4′-phenylthio(but-2′-ynylidene)]oct-3-yn-1-ol (13), (*Z*)-8-Methoxy-1-phenyl-2-[4′-phenylthio(but-2′-ynylidene)]oct-3-yn-1-ol (14), and (*Z*)-11-Methoxy-5-phenylmethylidene-1-(phenylthio)undeca-2,6-diyn-4-ol (15). To a solution of **12** (198 mg, 0.50 mmol) in dry CH_2Cl_2 (3 mL) was added CSA (111 mg, 0.50 mmol) followed by stirring at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL) and brine (2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc−hexane) to give **13** (111 mg, 56%) and a mixture of **14** and **15** (**14**:**15** = 34:66, 52 mg, 26%). **13**: pale yellow oil; R_f = 0.32 (20% EtOAc−hexane); IR (neat) 3414, 2208, 1116, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 7.32 Hz, 2 H), 7.36−7.18 (m, 8 H), 5.95 (s, 1 H), 5.17 (d, J = 3.90 Hz, 1 H), 3.80 (d, J = 1.95 Hz, 2 H), 3.30 (t, J = 6.10 Hz, 2 H), 3.27 (s, 3 H), 2.33 (s, 1 H), 2.31 (t, J = 6.35 Hz, 2 H), 1.59−1.51 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 137.6, 135.5, 129.8, 128.9, 128.4, 128.0, 126.6, 113.3, 110.4, 91.8, 81.1, 76.2, 72.1, 58.5, 28.5, 25.0, 23.9, 19.5; MS (+CI) *m*/*z* (relative intensity) 408 (M + NH_4^+, 100). Anal. Calcd for $C_{25}H_{26}O_2S$: C, 76.89; H, 6.71. Found: C, 76.81; H, 6.67. **14**: colorless oil; R_f = 0.52 (20% EtOAc−hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.24 (m, 2 H), 7.32−7.19 (m, 8 H), 6.00 (s, 1 H), 4.80 (s, 1 H), 3.80 (d, J = 1.95 Hz, 2 H), 3.25 (s, 3 H), 3.24 (t, J = 6.35 Hz, 2 H), 2.24 (t, J = 6.60 Hz, 2 H), 1.57−1.42 (m, 4 H). **15**: colorless oil; R_f = 0.52 (20% EtOAc−hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.42 (m, 2 H), 7.32−7.19

(m, 8 H), 6.06 (s, 1 H), 4.80 (s, 1 H), 3.82 (d, $J = 2.44$ Hz, 2 H), 3.29 (t, $J = 6.84$ Hz, 2 H), 3.27 (s, 3 H), 2.28 (t, $J = 6.60$ Hz, 2 H), 1.57−1.42 (m, 4 H).

Acid-Catalyzed Isomerization of 12 or 13 in the Presence of Nucleophiles. Typical Procedure. (*E*)-5-(1′-Ethoxy-1′-phenyl)methyl-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ene (16b) and (*E*)-4-Ethoxy-11-methoxy-5-phenylmethylidene-1-(phenylthio)-undeca-2,6-diyne (17b). To a solution of **12** (0.15 g, 0.38 mmol) and EtOH (44 μL, 0.75 mmol) in dry CH_2Cl_2 (2.5 mL) was added CSA (87 mg, 0.39 mmol, 0.16 M). The mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue over silica gel provided **16b** (114 mg, 71%) and **17b** (3.0 mg, 3%). The reaction conditions, yield, and product distribution are summarized in Table 1. **16b**: pale yellow oil; $R_f = 0.56$ (20% EtOAc−hexane); IR ($CDCl_3$) 2246, 1114 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, $J = 7.33$ Hz, 2 H), 7.28−7.11 (m, 8 H), 5.94 (s, 1 H), 4.67 (s, 1 H), 3.74 (d, $J = 1.96$ Hz, 2 H), 3.49−3.43 (m, 1 H), 3.40−3.32 (m, 1 H), 3.24 (t, $J = 6.30$ Hz, 2 H), 3.22 (s, 3 H), 2.24 (t, $J = 6.59$ Hz, 2 H), 1.60−1.40 (m, 4 H), 1.15 (t, $J = 6.25$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 136.6, 135.6, 129.7, 128.8, 128.1, 127.7, 127.1, 126.5, 113.0, 99.5, 91.4, 83.3, 81.3, 77.9, 72.1, 64.6, 58.5, 28.5, 25.0, 23.8, 19.4, 15.2; MS (+CI) *m*/*z* (relative intensity) 436 (M + NH_4^+, 76); HRMS (+EI) calcd for $C_{27}H_{30}O_2S$ (M^+) 418.1966, found 418.1945. **17b**: pale yellow oil; $R_f = 0.48$ (20% EtOAc−hexane); IR ($CDCl_3$) 2248, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, $J = 7.20$ Hz, 2 H), 7.47−7.44 (m, 2 H), 7.37−7.18 (m, 6 H), 6.83 (s, 1 H), 4.70 (d, $J = 2.00$ Hz, 1 H), 3.71 (s, 2 H), 3.60−3.54 (m, 1 H), 3.54−3.48 (m, 1 H), 3.40 (t, $J = 6.00$ Hz, 2 H), 3.32 (s, 3 H), 2.48 (t, $J = 6.60$ Hz, 2 H), 1.76−1.60 (m, 4 H), 1.25 and 1.22 (t, $J = 6.84$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.2, 134.6, 130.3, 128.9, 128.8, 128.3, 128.1, 126.8, 120.1, 98.5, 83.2, 80.6, 78.4, 77.3, 73.6, 72.2, 63.7, 58.5, 28.8, 25.2, 23.1, 19.8, 15.1; MS (+CI) *m*/*z* (relative intensity) 436 (M + NH_4^+, 100).

(*E*)-11-Methoxy-5-(1′-methoxy-1′-phenyl)methyl-1-(phenylthio)undeca-2,6-diyn-4-ene (16a). Pale yellow oil; $R_f = 0.66$ (20% EtOAc−hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, $J = 7.32$ Hz, 2 H), 7.39−7.22 (m, 8 H), 6.02 (s, 1 H), 4.66 (s, 1 H), 3.85 (s, 2 H), 3.37 (s, 3 H), 3.35 (t, $J = 6.10$ Hz, 2 H), 3.32 (s, 3 H), 2.35 (t, $J = 6.59$ Hz, 2 H), 1.67−1.52 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 136.1, 135.6, 129.7, 128.9, 128.2, 127.9, 127.0, 126.6, 113.4, 99.6, 91.5, 85.3, 81.2, 77.7, 72.2, 58.5, 57.0, 28.5, 25.0, 23.8, 19.5.

(*E*)-5-(1′-Isopropyloxy-1′-phenyl)methyl-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ene (16c). Pale yellow oil; $R_f = 0.73$ (20% EtOAc−hexane); IR (neat) 2222, 2174, 1120, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, $J = 7.32$ Hz, 2 H), 7.71−7.34 (m, 8 H), 6.00 (s, 1 H), 4.85 (s, 1 H), 3.80 (d, $J = 2.45$ Hz, 2 H), 3.34 (sept, $J = 6.34$ Hz, 1 H), 3.31 (t, $J = 6.35$ Hz, 2 H), 3.28 (s, 3 H), 2.31 (t, $J = 6.84$ Hz, 2 H), 1.64−1.57 (m, 2 H), 1.54−1.48 (m, 2 H), 1.18 (d, $J = 5.86$ Hz, 3 H), 1.12 (d, $J = 6.34$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 137.1, 135.6, 129.6, 128.8, 128.1, 127.6, 127.1, 126.6, 113.0, 99.4, 91.3, 81.3, 80.5, 78.1, 72.1, 69.5, 58.4, 28.5, 25.0, 23.8, 22.2, 22.0, 19.4. Anal. Calcd for $C_{28}H_{32}O_2S$: C, 77.74; H, 7.46. Found: C, 77.87; H, 7.40.

(*E*)-5-(1′-Ethylthio-1′-phenyl)methyl-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ene (16d). Obtained as the major component in a 67:33 mixture with **17d**. Pale yellow oil; $R_f = 0.42$ (10% Et_2O−hexane); IR (neat) 2220, 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.12 (m, 10 H), 5.88 (s, 1 H), 4.47 (s, 1 H), 3.74 (d, $J = 1.96$ Hz, 2 H), 3.25 (t, $J = 6.20$ Hz, 2 H), 3.22 (s, 3 H), 2.40 (q, $J = 7.44$ Hz, 2 H), 2.29 (t, $J = 6.80$ Hz, 2 H), 1.68−1.46 (m, 4 H), 1.14 (t, $J = 7.60$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 135.7, 134.1, 129.7, 128.8, 128.6, 128.3, 128.2, 126.6, 114.5, 99.5, 91.4, 81.3, 78.4, 72.1, 58.4, 54.7, 28.5, 26.1, 25.0, 23.8, 19.5, 14.1; MS (+CI) *m*/*z* (relative intensity) 435 (M + H^+, 100); HRMS (+EI) calcd for $C_{27}H_{30}OS_2$ (M^+) 434.1738, found 434.1730.

(*E*)-5-(1′-*tert*-Butylthio-1′-phenyl)methyl-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ene (16e). Obtained as the major component in a 73:27 mixture with **17e**. Pale yellow oil; $R_f = 0.66$ (10% EtOAc−hexane); IR ($CDCl_3$) 2246, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.10 (m, 10 H), 5.92 (s, 1 H), 4.48 (s, 1 H), 3.73 (d, $J = 2.44$ Hz, 2 H), 3.25 (t, $J = 6.35$ Hz, 2 H), 3.22 (s, 3 H), 2.30 (t, $J = 6.84$ Hz, 2 H), 1.68−1.50 (m, 4 H), 1.23 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 137.5, 134.1, 129.7, 128.9, 128.5, 128.3, 128.2, 126.6, 114.4, 99.4, 91.5, 81.5, 79.1, 72.2, 58.5, 52.8, 44.6, 31.2, 28.6, 25.1, 23.9, 19.5; MS (+CI) *m*/*z* (relative intensity) 480 (M + NH_4^+, 100).

(*E*)-11-Methoxy-5-(1′-phenyl-1′-phenylthio)methyl-1-(phenylthio)undeca-2,6-diyn-4-ene (16f). Obtained as the major component in a 69:31 mixture with **17f**. Pale yellow oil; $R_f = 0.29$ (10% Et_2O−hexane); IR (neat) 2218, 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.16 (m, 15 H), 5.83 (s, 1 H), 4.84 (s, 1 H), 3.78 (d, $J = 2.44$ Hz, 2 H), 3.34 (t, $J = 6.35$ Hz, 2 H), 3.29 (s, 3 H), 2.37 (t, $J = 6.59$ Hz, 2 H), 1.70−1.53 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (aromatic carbons cannot be assigned) 115.1, 99.9, 91.7, 81.3, 78.5, 72.2, 58.5, 47.4, 28.8, 25.1, 23.9, 19.7; MS (+CI) *m*/*z* (relative intensity) 500 (M + NH_4^+, 100). Anal. Calcd for $C_{31}H_{30}OS_2$: C, 77.14; H, 6.26. Found: C, 76.94; H, 6.07.

(*E*)-4,11-Dimethoxy-5-phenylmethylidene-1-(phenylthio)undeca-2,6-diyne (17a). Pale yellow oil; $R_f = 0.63$ (20% EtOAc−hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, $J = 6.83$ Hz, 2 H), 7.39 (d, $J = 7.80$ Hz, 2 H), 7.28−7.11 (m, 6 H), 6.76 (s, 1 H), 4.56 (s, 1 H), 3.66 (s, 2 H), 3.33 (t, $J = 6.10$ Hz, 2 H), 3.28 (s, 3 H), 3.25 (s, 3 H), 2.41 (t, $J = 6.84$ Hz, 2 H), 1.68−1.61 (m, 4 H).

(*E*)-4-Isopropyloxy-11-methoxy-5-phenylmethylidene-1-(phenylthio)undeca-2,6-diyne (17c). Pale yellow oil; $R_f = 0.70$ (20% EtOAc−hexane); IR (neat) 2219, 1118, 1076 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, $J = 7.20$ Hz, 2 H), 7.45 (d, $J = 7.60$ Hz, 2 H), 7.34−7.17 (m, 6 H), 6.84 (s, 1 H), 4.73 (s, 1 H), 3.82 (sept, $J = 6.34$ Hz, 1 H), 3.70 (d, $J = 2.00$ Hz, 2 H), 3.40 (t, $J = 6.2$ Hz, 2 H), 3.32 (s, 3 H), 2.47 (t, $J = 6.80$ Hz, 2 H), 1.76−1.65 (m, 4 H), 1.19 (d, $J = 6.35$ Hz, 3 H), 1.17 (d, $J = 5.86$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.2, 134.2, 130.2, 128.9, 128.8, 128.2, 128.0, 126.8, 120.7, 98.3, 82.5, 81.3, 78.6, 72.2, 71.3, 69.9, 58.5, 28.8, 25.2, 23.2, 22.5, 22.0, 19.7.

(*E*)-4-Ethylthio-11-methoxy-5-phenylmethylidene-1-(phenylthio)undeca-2,6-diyne (17d). Obtained as the minor component in a 67:33 mixture with **16d**. Pale yellow oil; $R_f = 0.42$ (10% Et_2O−hexane); IR (neat) 2220,

1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, $J = 7.60$ Hz, 2 H), 7.40−7.12 (m, 8 H), 6.70 (s, 1 H), 4.23 (s, 1 H), 3.67 (d, $J = 2.40$ Hz, 2 H), 3.32 (t, $J = 6.20$ Hz, 2 H,), 3.23 (s, 3 H), 2.60−2.40 (m, 2 H), 2.29 (t, $J = 6.80$ Hz, 2 H), 1.68−1.46 (m, 4 H), 1.16 (t, 3 H, $J = 7.60$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 135.2, 134.1, 129.9, 128.9, 128.2, 128.0, 127.4, 126.7, 119.5, 98.0, 82.7, 80.1, 78.9, 72.1, 58.4, 42.4, 28.7, 25.0, 24.8, 23.1, 19.6, 14.1; MS (+CI) *m/z* (relative intensity) 435 ($M + H^+$, 100); HRMS (+EI) calcd for $C_{27}H_{30}OS_2$ (M^+) 434.1738, found 434.1730.

(*E*)-4-*tert*-Butylthio-11-methoxy-5-phenylmethylidene-1-(phenylthio)undeca-5,9-diyne (17e). Obtained as the minor component in a 73:27 mixture with **16e**. Pale yellow oil; $R_f = 0.66$ (10% EtOAc−hexane); IR ($CDCl_3$) 2246, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, $J = 7.32$ Hz, 2 H), 7.69−7.10 (m, 8 H), 6.78 (s, 1 H), 4.17 (s, 1 H), 3.66 (d, $J = 1.95$ Hz, 2 H), 3.26 (t, $J = 6.35$ Hz, 2 H), 3.24 (s, 3 H), 2.40 (t, $J = 6.84$ Hz, 2 H), 1.68−1.50 (m, 4 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.6, 135.3, 129.9, 128.8, 128.2, 128.0, 127.1, 126.6, 120.3, 97.8, 82.7, 81.7, 79.3, 72.2, 58.4, 44.7, 40.3, 31.0, 28.8, 23.2, 19.6; MS (+CI) *m/z* (relative intensity) 480 ($M + NH_4^+$, 100).

(*E*)-11-Methoxy-1,4-di(phenylthio)-5-(phenylmethylidene)undeca-2,6-diyne (17f). Obtained as the minor compounent in a 69:31 mixture with **16f**. Pale yellow oil; $R_f = 0.29$ (10% Et_2O−hexane); IR (neat) 2218, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, $J = 6.83$ Hz, 2 H), 7.49−7.16 (m, 13 H), 6.37 (s, 1 H), 4.49 (s, 1 H), 3.68 (d, $J = 2.44$ Hz, 2 H), 3.40 (t, $J = 6.10$ Hz, 2 H), 3.32 (s, 3 H), 2.47 (t, $J = 6.84$ Hz, 2 H), 1.76−1.50 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (aromatic carbons cannot be assigned) 119.0, 98.0, 83.4, 80.2, 78.9, 72.2, 58.9, 47.4, 28.6, 25.1, 23.0, 19.5; MS (+CI) *m/z* (relative intensity) 500 ($M + NH_4^+$, 100). Anal. Calcd for $C_{31}H_{30}OS_2$: C, 77.14; H, 6.26. Found: C, 76.94; H, 6.07.

(*E*)-10-Methoxy-4-phenylmethylidene-1-phenyldeca-1,5-diyn-3-ol (18c). To a solution of aldehyde **11** (0.380 g, 1.57 mmol) in dry THF (8 mL) cooled at −80 °C was added a THF (7 mL) solution of PhC≡CLi prepared from phenylacetylene (0.21 mL, 1.88 mmol) and *n*-BuLi (1.6 M in hexanes, 1.1 mL, 1.76 mmol). The reaction was stirred at the same temperature for 30 min and quenched with saturated aqueous NH_4Cl. The resultant mixture was extracted with EtOAc (50 mL) and washed with brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc−hexane) to give **18c** (0.415 g, 80%): pale yellow oil; $R_f = 0.18$ (20% EtOAc−hexane); IR (neat) 3368, 2198, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, $J = 7.32$ Hz, 2 H), 7.42−7.40 (m, 2 H), 7.30−7.19 (m, 6 H), 6.86 (s, 1 H), 5.12 (s, 1 H), 3.33 (t, $J = 5.85$ Hz, 2 H), 3.25 (s, 3 H), 2.77 (br s, 1 H), 2.47 (t, $J = 6.35$ Hz, 2 H), 1.73−1.61 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.7, 131.8, 128.7, 128.5, 128.4, 128.2, 128.1, 122.5, 122.2, 99.5, 87.8, 86.4, 77.7, 72.1, 67.4, 58.5, 28.7, 25.2, 19.7; MS (+FAB) *m/z* (relative intensity) 327 ($M^+ - OH$, 56); HRMS (+FAB) calcd for $C_{24}H_{24}O_2$ (M^+) 344.1776, found 344.1775.

Acid-Catalyzed Isomerization of 18a−c. (*E*)-4-(1′-Ethoxy-1′-phenyl)methyl-7-phenylthio-1-(trimethylsilyl)hept-1,5-diyn-3-ene (19a). To a solution of **18a**[24a] (71.7 mg, 0.19 mmol) and EtOH (44 μL, 0.75 mmol) in dry CH_2Cl_2 (2 mL) was added CSA (22.1 mg, 9.5×10^{-2} mmol, 48 mM). The mixture was stirred at room temperature for 93 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 10% Et_2O−hexane) provided an inseparable mixture of **19a** and **20a** (**19a**:**20a** = 94:6, 53.9 mg, 70%). **19a**: pale yellow oil; $R_f = 0.77$ (20% EtOAc in hexane); IR (neat) 2132, 1094, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, $J = 7.20$ Hz, 2 H), 7.29−7.19 (m, 8 H), 6.09 (s, 1 H), 4.71 (s, 1 H), 3.75 (s, 2 H), 3.53−3.39 (m, 2 H), 1.20 (t, $J = 6.80$ Hz, 3 H), 0.18 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 136.7, 135.4, 130.1, 128.9, 128.2, 127.8, 127.0, 126.7, 114.6, 102.3, 102.1, 94.8, 83.0, 80.3, 64.7, 23.8, 15.2, −0.1; MS (+CI) *m/z* (relative intensity) 405 ($M + H^+$, 10), 359 ($M^+ - EtO$, 100).

(*E*)-4-(1′-Ethoxy-1′-phenyl)methyl-7-phenylthio-1-phenylhept-1,5-diyn-3-ene (19b). To a solution of **18b**[24a] (64.4 mg, 0.17 mmol) and EtOH (40 μL, 0.68 mmol) in dry CH_2Cl_2 (2 mL) was added CSA (19.7 mg, 8.5×10^{-2} mmol, 43 mM). The mixture was stirred at room temperature for 45 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 10% Et_2O−hexane) provided **19b** (56.4 mg, 82%): pale yellow oil; $R_f = 0.80$ (20% EtOAc−hexane); IR (neat) 2194, 1098, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.23 (m, 15 H), 6.35 (s, 1 H), 4.84 (s, 1 H), 3.84 (s, 2 H), 3.64−3.47 (m, 2 H), 1.28 (t, $J = 6.96$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 135.4, 131.8, 130.0, 128.9, 128.4, 128.3, 128.2, 127.8, 127.0, 126.7, 123.2, 114.9, 96.4, 94.8, 87.2, 83.2, 80.6, 64.7, 23.9, 15.2; MS (+CI) *m/z* (relative intensity) 426 ($M + NH_4^+$, 24), 363 ($M^+ - EtO$, 100).

(*E*)-4-(1′-Ethoxy-1′-phenyl)methyl-10-methoxy-1-phenyldeca-1,5-diyn-3-ene (19c). To a solution of **18c** (128 mg, 0.37 mmol) and EtOH (44 μL, 0.74 mmol) in dry CH_2Cl_2 (6 mL) was added CSA (86 mg, 0.37 mmol, 62 mM). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$ (4 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 20% Et_2O−hexane) provided **19c** (90.3 mg, 65%): pale yellow oil; $R_f = 0.49$ (20% EtOAc−hexane); IR (neat) 2220, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.27 (m, 10 H), 6.25 (s, 1 H), 4.82 (s, 1 H), 3.61 (dq, $J = 9.03$, 6.84 Hz, 1 H), 3.49 (dq, $J = 9.28$, 6.84 Hz, 1 H), 3.30 (t, $J = 5.86$ Hz, 2 H), 3.28 (s, 3 H), 2.41 (t, $J = 6.84$ Hz, 2 H), 1.68−1.60 (m, 4 H), 1.26 (t, $J = 6.84$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 136.4, 131.6, 128.2, 127.8, 127.1, 123.5, 113.4, 100.1, 95.5, 87.5, 83.5, 78.2, 72.1, 64.7, 58.5, 28.5, 25.2, 19.6, 15.2; MS (+CI) *m/z* (relative intensity) 373 (M^++1, 10), 327 ($M^+ - EtO$, 100); HRMS (+FAB) calcd for $C_{26}H_{28}O_2$ (M^+) 372.2089, found 372.2034.

Methyl (*E*)-4-Methoxycinnamate (22). To a solution of trimethyl phosphonoacetate (3.93 g, 21.6 mmol) in dry THF (150 mL) cooled in a dry ice−acetone bath (−78 °C) was added *n*-BuLi (1.6 M in hexanes, 14.8 mL, 23.7 mmol) followed by stirring for 30 min. To the resultant mixture was added *p*-anisaldehyde (**21**, 2.89 mL, 23.7 mmol) in dry THF (50 mL) at −78 °C, and the reaction

was allowed to warm to room temperature. After 5 h of stirring at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (60 × 2 mL). The organic layer was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% EtOAc−hexane) to give **22** (4.15 g, 100%): white solid; $R_f = 0.41$ (10% EtOAc−hexane); IR (Nujol) 1716, 1638, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 16.01 Hz, 1 H), 7.51−7.45 (AA′BB′, 2 H), 6.93−6.87 (AA′BB′, 2 H), 6.31 (d, J = 16.01 Hz, 1 H), 3.84 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 161.4, 144.5, 129.7, 127.1, 115.2, 114.3, 55.3, 51.3; MS (+CI) m/z (relative intensity) 193 ($M + H^+$, 58).

Methyl (*Z*)-α-Bromo-4-methoxycinnamate (23) and Methyl (*E*)-α-Bromo-4-methoxycinnamate (24). To a solution of ester **22** (4.15 g, 21.6 mmol) in dry CH_2Cl_2 (150 mL) cooled in a dry ice−acetone bath (−78 °C) was added bromine (1.12 mL, 21.6 mmol) in CH_2Cl_2 (10 mL) followed by stirring at −78 °C for 1 h. Triethylamine (3.65 mL, 25.9 mmol) was added, and the mixture was allowed to stir at room temperature overnight (16 h). The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL) and the organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 5% EtOAc−hexane) to give the product **23** and **24** as an inseparable mixture (**23**:**24** = 77:23, 4.66 g, 80%): white solid; R_f = 0.46 (10% EtOAc−hexane). **23**: IR (Nujol) 1720, 1604, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1 H), 7.31−7.25 (AA′BB′, 2 H), 6.89−6.83 (AA′BB′, 2 H), 3.82 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 160.2, 140.2, 130.1, 127.1, 113.8, 108.5, 55.2, 52.8; MS (+CI) m/z (relative intensity) 290 ($M + NH_4^+$, ^{81}Br, 98), 288 ($M + NH_4^+$, ^{79}Br, 100). Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09. Found: C, 48.64; H, 4.05. **24**: IR (Nujol) 1720, 1604, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 7.94−7.88 (AA′BB′, 2 H), 6.99−6.93 (AA′BB′, 2 H), 3.89 (s, 3 H), 3.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 160.2, 140.2, 130.1, 127.1, 113.8, 108.5, 55.2, 52.8; MS (+CI) m/z (relative intensity) 290 ($M + NH_4^+$, ^{81}Br, 98), 288 ($M + NH_4^+$, ^{79}Br, 100). Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09. Found: C, 48.64; H, 4.05.

Methyl (*E*)-8-Methoxy-2-[(4′-methoxyphenyl)methylidene]oct-3-ynoate (25) and Methyl (*Z*)-8-Methoxy-2-[(4′-methoxyphenyl)methylidene]oct-3-ynoate (26). To a suspension of $Pd(PPh_3)_4$ (124.4 mg, 0.10 mmol) and CuI (61 mg, 0.32 mmol) in degassed THF (3 mL) maintained at 0 °C in an ice−water bath was added a solution of the mixture of **23** and **24** prepared above (541.8 mg, 2.00 mmol), 6-methoxy-1-hexyne (268.8 mg, 2.40 mmol), and triethylamine (0.42 mL, 3.00 mmol) in degassed THF (4 mL) via a syringe. The reaction flask was covered against light by a sheet of aluminum foil, and the mixture was stirred at room temperature for 22 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 5% Et_2O−hexane) to give an inseparable mixture of **25** and **26** (**25**:**26** = 76:24, 523.4 mg, 87%): pale yellow oil; R_f = 0.23 (10% EtOAc−hexane). **25**: IR (neat) 2218, 1726, 1606, 1178, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.31 (AA′BB′, 2 H), 7.05 (s, 1 H), 6.83−6.77 (AA′BB′, 2 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.41 (t, J = 6.32 Hz, 2 H), 3.34 (s, 3 H), 2.41 (t, J = 6.60 Hz, 2 H), 1.77−1.65 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 160.2, 142.9, 130.6, 127.2, 114.1, 113.7, 91.8, 78.8, 72.2, 58.5, 55.2, 52.2, 28.7, 25.2, 19.3; MS (+CI) m/z (relative intensity) 303 ($M + H^+$, 56), 271 ($M^+ - MeO$, 100). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33; Found: C, 71.58; H, 7.40. **26**: IR (neat) 2218, 1726, 1606, 1178, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04−7.98 (AA′BB′, 2 H), 7.80 (s, 1 H), 6.95−6.89 (AA′BB′, 2 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.43 (t, J = 6.32 Hz, 2 H), 3.34 (s, 3 H), 2.56 (t, J = 6.60 Hz, 2 H), 1.77−1.65 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 161.2, 144.3, 132.1, 127.4, 113.8, 110.5, 99.1, 76.8, 72.1, 58.5, 55.3, 52.5, 28.8, 25.1, 19.9; MS (+CI) m/z (relative intensity) 303 ($M + H^+$, 56), 271 ($M^+ - MeO$, 100). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.58; H, 7.40.

(*E*)-8-Methoxy-2-[(4′-methoxyphenyl)methylidene]-oct-3-ynal (27) and (*Z*)-8-Methoxy-2-[(4′-methoxyphenyl)methylidene]oct-3-ynal (28). To a solution of **25** and **26** prepared above (460.6 mg, 1.53 mmol) in dry toluene (20 mL) cooled in a dry ice−acetone bath (−78 °C) was added DIBAL-H (1 M in CH_2Cl_2, 3.81 mL, 3.81 mmol) followed by stirring at the same temperature for 1 h. The reaction was quenched by MeOH (3 mL) at −78 °C and stirred for 30 min. Aqueous 5% HCl (35 mL) was added, and the mixture was stirred at room temperature for another 40 min. The mixture was extracted with EtOAc (30 × 2 mL), washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20% EtOAc−hexane) to give an inseparable mixture of the alcohols (major:minor = 71:29, 365.0 mg, 87%) as a pale yellow oil; R_f = 0.18 (20% EtOAc−hexane). **Major isomer**: IR (neat) 3414, 1178, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21−7.15 (AA′BB′, 2 H), 6.90−6.84 (AA′BB′, 2 H), 6.83 (s, 1 H), 4.32 (s, 2 H), 3.80 (s, 3 H), 3.42 (t, J = 6.01 Hz, 2 H), 3.34 (s, 3 H), 2.42 (t, J = 6.61 Hz, 2 H), 1.75−1.62 (m, 4 H); MS (+CI) m/z (relative intensity) 275 ($M + H^+$, 50); 257 ($M^+ - OH$, 100); HRMS (+EI) calcd for $C_{17}H_{22}O_3$ (M^+) 274.1569, found 274.1579. **Minor isomer**: IR (neat) 3414, 1178, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82−7.76 (AA′BB′, 2 H), 6.90−6.84 (AA′BB′, 2 H), 6.62 (s, 1 H), 4.22 (s, 2 H), 3.81 (s, 3 H), 3.42 (t, J = 6.01 Hz, 2 H), 3.34 (s, 3 H), 2.49 (t, J = 6.61 Hz, 2 H), 1.75−1.62 (m, 4 H); MS (+CI) m/z (relative intensity) 275 ($M + H^+$, 50); 257 ($M^+ - OH$, 100); HRMS (+EI) calcd for $C_{17}H_{22}O_3$ (M^+) 274.1569, found 274.1579.

To a solution of the alcohols prepared above (239.3 mg, 0.87 mmol) in dry THF (20 mL) cooled in an ice−water bath (0 °C) was added PDC (320 mg, 1.14 mmol) and some powdered 4 Å molecular sieves followed by stirring at room temperature for 4.5 h. The reaction mixture was filtered through a short plug of silica gel with rinsing by EtOAc. The combined organic layer was concentrated in vacuo, and the residue was purified by flash column chromatography (silica gel, 10% EtOAc−hexane) to give 25.3 mg of the starting alcohols (10.6%) and a mixture of aldehydes (**27**:**28** = 72:28, 167.4 mg, 81%). Analytic samples of pure **27** and **28** were obtained by repeated flash column chromatography. **27**: pale yellow oil; R_f = 0.35 (20% EtOAc−hexane); IR (neat) 1686, 1594, 1176, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1 H), 8.10−8.04 (AA′BB′, 2 H), 7.35 (s, 1 H), 6.98−6.92 (AA′BB′,

2 H), 3.86 (s, 3 H), 3.43 (t, J = 6.03 Hz, 2 H), 3.33 (s, 3 H), 2.59 (t, J = 6.60 Hz, 2 H), 1.85−1.70 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 162.0, 151.0, 132.3, 127.1, 120.9, 114.1, 102.1, 74.6, 72.1, 58.5, 55.4, 28.9, 25.2, 19.9; MS (+CI) *m*/*z* (relative intensity) 273 (M + H^+, 100); HRMS (+EI) calcd for $C_{17}H_{20}O_3$ (M^+) 272.1412, found 272.1421. **28**: pale yellow oil; R_f = 0.43 (20% EtOAc−hexane); IR (neat) 1686, 1594, 1176, 1118 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1 H), 7.81 (s, 1 H), 7.32−7.26 (AA′BB′, 2 H), 6.95−6.89 (AA′BB′, 2 H), 3.84 (s, 3 H), 3.40 (t, J = 5.52 Hz, 2 H), 3.34 (s, 3 H), 2.46 (t, J = 6.70 Hz, 2 H), 1.85−1.70 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 162.0, 151.0, 132.3, 127.1, 120.9, 114.1, 102.1, 74.6, 72.1, 58.5, 55.4, 28.9, 25.2, 19.9; MS (+CI) *m*/*z* (relative intensity) 273 (M + H^+, 100); HRMS (+EI) calcd for $C_{17}H_{20}O_3$ (M^+) 272.1412, found 272.1421.

(*E*)-11-Methoxy-5-(4′-methoxyphenyl)methylidene-1-(phenylthio)undeca-2,6-diyn-4-ol (29) and (*Z*)-11-Methoxy-5-(4′-methoxyphenyl)methylidene-1-(phenylthio)undeca-2,6-diyn-4-ol (30). To a solution of the above prepared mixture of aldehydes **27** and **28** (164.0 mg, 0.60 mmol) in dry THF (4 mL) cooled at −78 °C was added a THF (3 mL) solution of $PhSCH_2C{\equiv}CLi$ prepared from phenyl propargyl sulfide (182.3 mg, 1.23 mmol) and *n*-BuLi (1.6 M in hexanes, 0.69 mL, 1.11 mmol). The reaction was stirred at the same temperature for 1 h and quenched with saturated aqueous NH_4Cl (5 mL). The resultant mixture was extracted with EtOAc (10 × 2 mL) and washed with brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 15% EtOAc−hexane) to give **29** (180.3 mg, 71%) and **30** (18.2 mg, 7%). **29**: pale yellow oil; R_f = 0.18 (20% EtOAc−hexane); IR (neat) 3378, 2216, 1178, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.73 (AA′BB′, 2 H), 7.49−7.43 (m, 2 H), 7.31−7.18 (m, 3 H), 6.89−6.83 (AA′BB′, 2 H), 6.73 (s, 1 H), 4.92 (d, J = 6.21 Hz, 1 H), 3.83 (s, 3 H), 3.70 (d, J = 1.92 Hz, 2 H), 3.42 (t, J = 5.94 Hz, 2 H), 3.33 (s, 3 H), 2.55 (d, J = 7.38 Hz, 1 H), 2.49 (t, J = 6.45 Hz, 2 H), 1.78−1.66 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 135.2, 133.3, 130.2, 130.1, 128.9, 128.4, 126.9, 119.6, 113.5, 98.9, 82.6, 82.3, 77.8, 72.1, 67.0, 58.5, 55.2, 28.8, 25.2, 23.1, 19.7; MS (+CI) *m*/*z* (relative intensity) 420 (M^+, 5), 403 (M^+ − OH, 100); HRMS (+EI) calcd for $C_{26}H_{28}O_3S$ (M^+) 420.1759, found 420.1763. **30**: pale yellow oil; R_f = 0.20 (20% EtOAc−hexane); IR (neat) 3400, 2220, 1178, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.44 (m, 2 H), 7.36−7.21 (m, 3 H), 7.20−7.14 (AA′BB′, 2 H), 6.87−6.81 (AA′BB′, 2 H), 6.80 (s, 1 H), 5.17 (d, J = 9.00 Hz, 1 H), 3.81 (s, 3 H), 3.71 (d, J = 1.59 Hz, 2 H), 3.42 (t, J = 5.82 Hz, 2 H), 3.34 (s, 3 H), 2.60 (d, J = 9.51 Hz, 1 H), 2.43 (t, J = 6.81 Hz, 2 H), 1.79−1.58 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 135.2, 130.4, 130.3, 128.9, 127.8, 126.8, 123.6, 113.9, 93.1, 83.0, 81.4, 78.4, 72.2, 60.0, 58.5, 55.3, 28.7, 25.4, 23.1, 19.4; MS (+CI) *m*/*z* (relative intensity) 420 (M^+, 54), 403 (M^+ − OH, 100).

Acid-Catalyzed Isomerization of 29 in the Presence of Nucleophiles. Typical Procedure. (*E*)-5-[1′-Ethoxy-1′-(4″-methoxyphenyl)]methyl-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ene (31c). To a solution of alcohol **29** (50.7 mg, 0.12 mmol) and EtOH (28 μL, 0.48 mmol) in dry CH_2Cl_2 (2 mL) cooled in an ice−water bath (0 °C) was added CSA (14.3 mg, 0.06 mmol, 0.03 M). The mixture was stirred for 7 h at the same temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue provided an inseparable mixture of **31c** and **32c** (**31c**:**32c** = 94:6, 48.4 mg, 89%; entry 5 in Table 3). The reaction conditions, yield, and product distribution are summarized in Table 3. **31c**: pale yellow oil; R_f = 0.57 (20% EtOAc−hexane); IR (neat) 2220, 2179, 1172, 1116 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.39 (m, 2 H), 7.28−7.13 (m, 5 H), 6.83−6.74 (AA′BB′, 2 H), 5.95 (dd, J = 3.27, 1.14 Hz, 1 H), 4.66 (s, 1 H), 3.78 (d, J = 2.22 Hz, 2 H), 3.74 (s, 3 H), 3.50−3.36 (m, 2 H), 3.28 (t, J = 6.15 Hz, 2 H), 3.25 (s, 3 H), 2.28 (t, J = 6.78 Hz, 2 H), 1.70−1.47 (m, 4 H), 1.16 (t, J = 7.05 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 136.8, 132.1, 129.7, 128.9, 128.3, 127.6, 126.6, 113.6, 112.8, 99.4, 91.3, 82.9, 81.3, 78.0, 72.2, 64.5, 58.5, 55.2, 28.5, 25.1, 23.8, 19.5, 15.2; MS (+CI) *m*/*z* (relative intensity) 403 (M^+ − EtO, 100); HRMS (+EI) calcd for $C_{28}H_{32}O_3S$ (M^+) 448.2027, found 448.2061.

(*E*)-8-Methoxy-1-(4′-methoxyphenyl)-2-[4′-phenylthio(but-2′-ynylidene)]oct-3-yn-1-ol (31a). Pale yellow oil; R_f = 0.19 (20% EtOAc−hexane); IR (neat) 3402, 2220, 1174, 1116 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.34 (m, 2 H), 7.24−7.10 (m, 5 H), 6.82−6.74 (AA′BB′, 2 H), 5.89 (d, J = 1.38 Hz, 1 H), 5.08 (d, J = 3.36 Hz, 1 H), 3.75 (d, J = 2.13 Hz, 2 H), 3.73 (s, 3 H), 3.25 (t, J = 5.88 Hz, 2 H), 3.22 (s, 3 H), 2.27 (t, J = 6.69 Hz, 2 H), 1.61−1.44 (m, 4 H); MS (+CI) *m*/*z* (relative intensity) 421 (M + H^+, 26), 403 (M^+ − OH, 100).

(*E*)-11-Methoxy-5-[1′-methoxy-1′-(4″-methoxyphenyl)]methyl-1-(phenylthio)undeca-2,6-diyn-4-ene (31b). Obtained as the major component in an inseparable mixture (**31b**:**32b** = 94:6). **31b**: pale yellow oil; R_f = 0.49 (20% EtOAc−hexane); IR (neat) 2229, 1172 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.36 (m, 2 H), 7.25−7.13 (m, 5 H), 6.80−6.74 (AA′BB′, 2 H), 5.89 (d, J = 0.99 Hz, 1 H), 4.51 (s, 1 H), 3.75 (d, J = 2.19 Hz, 2 H), 3.72 (s, 3 H), 3.27 (t, J = 7.20 Hz, 2 H), 3.26 (s, 3 H), 2.25 (t, J = 6.78 Hz, 2 H), 1.65−1.45 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 136.3, 131.6, 129.8, 128.9, 128.3, 127.5, 126.6, 113.6, 113.1, 99.5, 91.4, 84.9, 81.3, 77.8, 72.2, 58.5, 56.8, 55.2, 28.5, 25.1, 23.9, 19.5; MS (+CI) *m*/*z* (relative intensity) 403 (M^+ − MeO, 100); HRMS (+EI) calcd for $C_{27}H_{30}O_3S$ (M^+) 434.1916, found 434.1914.

(*E*)-5-[1′-Isopropyloxy-1′-(4″-methoxyphenyl)]-methyl-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ene (31d). Obtained as the major component in an inseparable mixture (**31d**:**32d** = 82:18). **31d**: pale yellow oil; R_f = 0.62 (20% EtOAc−hexane); IR (neat) 2220, 1172, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.46 (m, 2 H), 7.35−7.23 (m, 5 H), 6.89−6.81 (AA′BB′, 2 H), 6.02 (d, J = 1.35 Hz, 1 H), 4.85 (s, 1 H), 3.85 (d, J = 2.19 Hz, 2 H), 3.81 (s, 3 H), 3.35 (t, J = 6.12 Hz, 2 H), 3.32 (s, 3 H), 2.35 (t, J = 6.81 Hz, 2 H), 1.70−1.52 (m, 4 H), 1.21 (d, J = 6.12 Hz, 3 H), 1.16 (d, J = 6.09 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 137.4, 132.5, 129.7, 128.9, 128.4, 127.6, 126.5, 113.5, 112.7, 99.3, 91.2, 81.4, 80.1, 78.2, 72.2, 69.4, 59.5, 55.2, 28.5, 25.1, 23.8, 22.2, 22.1, 19.5; MS (+CI) *m*/*z* (relative intensity) 480 (M + NH_4^+, 5), 403 (M^+ − *i*-PrO, 100); HRMS (+EI) calcd for $C_{29}H_{34}O_3S$ (M^+) 462.2229, found 462.2226.

(*E*)-5-[1′-*tert*-Butyloxy-1′-(4″-methoxyphenyl)]-methyl-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ene (31e). Obtained as the major component in an inseparable mixture (**31e**:**32e** = 86:14). **31e**: pale yellow oil; R_f

= 0.69 (20% EtOAc−hexane); IR (neat) 2222, 2179, 1172, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.45 (m, 2 H), 7.34−7.24 (m, 5 H), 6.87−6.81 (AA′BB′, 2 H), 6.06 (d, J = 1.59 Hz, 1 H), 4.93 (s, 1 H), 3.84 (d, J = 2.19 Hz, 2 H), 3.81 (s, 3 H), 3.34 (t, J = 6.09 Hz, 2 H), 3.32 (s, 3 H), 2.34 (t, J = 6.81 Hz, 2 H), 1.68−1.52 (m, 4 H), 1.20 (s, 9 H); MS (+CI) m/z (relative intensity) 494 ($M + NH_4^+$, 4); HRMS (+EI) calcd for $C_{30}H_{36}O_3S$ (M^+) 476.2386, found 476.2381.

(*E*)-5-[1′-Ethylthio-1′-(4″-methoxyphenyl)]methyl-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ene (31f). Obtained as the major component in an inseparable mixture (**31f**:**32f**:**33f** = 78:15:7). **31f**: pale yellow oil; R_f = 0.46 (20% EtOAc−hexane); IR (neat) 2229, 1178, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.45 (m, 2 H), 7.36−7.30 (m, 5 H), 6.87−6.84 (AA′BB′, 2 H), 5.95 (br s, 1 H), 4.54 (s, 1 H), 3.85 (d, J = 2.13 Hz, 2 H), 3.81 (s, 3 H), 3.37 (t, J = 6.06 Hz, 2 H), 3.32 (s, 3 H), 2.51−2.37 (m, 4 H), 1.70−1.58 (m, 4 H), 1.24 (t, J = 7.35 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 136.0, 131.2, 129.8, 129.7, 129.3, 129.2, 128.9, 114.3, 113.7, 99.5, 91.4, 81.4, 78.5, 72.2, 58.5, 55.2, 54.1, 28.6, 26.1, 25.1, 23.8, 19.5, 14.2; MS (+CI) m/z (relative intensity) 465 ($M + H^+$, 19), 403 (M^+ − EtS, 100); HRMS (+EI) calcd for $C_{26}H_{27}O_2S$ (M^+ − EtS) 403.1732, found 403.1690.

(*E*)-5-[1′-*tert*-Butylthio-1′-(4″-methoxyphenyl)]methyl-11-methoxy-1-(phenylthio)undeca-2,6-diyn-4-ene (31g). Obtained as the major component in an inseparable mixture (**31g**:**32g**:**33g** = 74:18:8). **31g**: pale yellow oil; R_f = 0.53 (20% EtOAc−hexane); IR (neat) 2229, 1176, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.45 (m, 2 H), 7.39−7.28 (m, 5 H), 6.85−6.80 (AA′BB′, 2 H), 6.00 (s, 1 H), 4.57 (s, 1 H), 3.84 (d, J = 2.10 Hz, 2 H), 3.80 (s, 3 H), 3.38 (t, J = 6.18 Hz, 2 H), 3.33 (s, 3 H), 2.41 (t, J = 6.84 Hz, 2 H), 1.80−1.57 (m, 4 H), 1.33 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 137.8, 133.0, 130.0, 129.7, 129.0, 128.8, 126.6, 114.1, 113.7, 99.3, 91.4, 81.5, 79.1, 72.2, 58.4, 55.2, 52.2, 44.5, 31.2, 28.6, 25.1, 23.9, 19.5; MS (+CI) m/z (relative intensity) 510 ($M + NH_4^+$, 10), 403 (M^+ − t-BuS, 100); HRMS (+EI) calcd for $C_{30}H_{36}O_2S_2$ (M^+) 492.2157, found 492.2136.

(*E*)-11-Methoxy-5-[1′-phenylthio-1′-(4″-methoxyphenyl)]methyl-1-(phenylthio)undeca-2,6-diyn-4-ene (31h). Obtained as the major component in an inseparable mixture (**31h**:**32h**:**33h**:**34h** = 74:8:11:7). **31h**: pale yellow oil; R_f = 0.45 (20% EtOAc−hexane); IR (neat) 2220, 1176, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.43 (m, 2 H), 7.40−7.25 (m, 10 H), 6.90−6.82 (AA′BB′, 2 H), 5.86 (s, 1 H), 4.86 (s, 1 H), 3.83 (d, J = 2.16 Hz, 2 H), 3.82 (s, 3 H), 3.38 (t, J = 6.06 Hz, 2 H), 3.33 (s, 3 H), 2.41 (t, J = 6.78 Hz, 2 H), 1.72−1.61 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.4, 134.7, 131.9, 131.3, 130.2, 129.4, 128.9, 128.7, 128.5, 127.0, 126.6, 114.9, 113.8, 99.8, 91.6, 81.3, 78.6, 72.2, 58.5, 58.2, 55.2, 28.6, 25.1, 23.9, 19.6; MS (+CI) m/z (relative intensity) 513 ($M + H^+$, 32), 403 (M^+ − PhS, 100); HRMS (+EI) calcd for $C_{32}H_{32}O_2S_2$ (M^+) 512.1844, found 512.1855.

Acid-Catalyzed Isomerization of 30 in the Presence of Ethanol. To a solution of alcohol **30** (50.7 mg, 0.12 mmol) and EtOH (28 μL, 0.48 mmol) in dry CH_2Cl_2 (2 mL) was added CSA (14.3 mg, 0.06 mmol, 0.03 M). The mixture was stirred for 90 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue provided an inseparable mixture of **31c** and **32c** (**31c**:**32c** = 74:26, 17.2 mg, 32%) together with a mixture of the dimeric ethers **35** (16.5 mg, 31%). **35**: pale yellow oil; IR (neat) 2220, 1176, 1116 cm^{-1}; MS (+CI) m/z (relative intensity) 823 ($M + H^+$, 1), 403 (M^+ − 419, 100).

Acid-Catalyzed Isomerization of 12 and 29 in the Presence of Methyl-d_3 Alcohol-d. Typical Procedure. (*E*)-11-Methoxy-5-[1′-(trideuteriomethoxy)-1′-phenylmethy]-1-(phenylthio)undeca-2,6-diyn-4-ene (39) and (*E*)-11-Methoxy-5-(phenylmethylidene)-1-phenylthio-4-(trideuteriomethoxyl)undeca-2,6-diyne (40). To a solution of **12** (55.5 mg, 0.14 mmol) and CD_3OD (11 μL, 0.27 mmol) in dry CH_2Cl_2 (1.5 mL) was added CSA (16.5 mg, 0.07 mmol, 46 mM). The mixture was stirred for 10.5 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (3 mL) and washed with saturated aqueous $NaHCO_3$ (1 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 10% EtOAc−hexane) provided **39** (40.7 mg, 70%) and **40** (5.0 mg, 8.7%). **39**: colorless oil; R_f = 0.65 (20% EtOAc−hexane); ^1H NMR (300 MHz, $CDCl_3$) 7.50−7.24 (m, 10 H), 6.02 (s, 1 H), 4.66 (s, 1 H), 3.85 (s, 2 H), 3.35 (t, J = 6.03 Hz, 2 H), 3.32 (s, 3 H), 2.35 (t, J = 6.38 Hz, 2 H), 1.68−1.52 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 136.1, 135.6, 129.7, 128.9, 128.2, 127.9, 127.0, 126.6, 113.4, 99.6, 91.5, 85.3, 81.2, 77.7, 72.2, 58.5, 57.0, 28.5, 25.0, 23.8, 19.5; MS (+CI) m/z (relative intensity) 425 ($M + NH_4^+$, 100). **40**: colorless oil; ^1H NMR (300 MHz, $CDCl_3$), δ 7.84 (d, J = 6.69 Hz), 7.36 (m, 3 H), 6.87 (s, 1 H), 3.90 (s, 1 H), 3.74 (d, J = 1.89 Hz, 2 H), 3.43 (t, J = 6.00 Hz, 2 H), 3.32 (s, 3 H), 2.51 (t, J = 6.38 Hz, 2 H), 1.66−1.29 (m, 4 H).

(*E*)-11-Methoxy-5-[1′-(trideuteriomethoxy)-1′-(4″-methoxyphenyl)methyl]-1-(phenylthio)undeca-2,6-diyn-4-ene (41). Obtained as the major component in an inseparable mixture (**41**:**42** = 75:25). **41**: pale yellow oil; R_f = 0.43 (20% EtOAc−hexane); IR (neat) 2202, 1172, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.33 Hz, 2 H), 7.31−7.20 (m, 5 H), 6.88−6.83 (AA′BB′, 2 H), 5.97 (S, 1 H), 4.59 (s, 1 H), 3.83 (d, J = 1.95 Hz, 2 H), 3.80 (s, 3 H), 3.32 (t, J = 5.86 Hz, 2 H), 2.33 (t, J = 6.83 Hz, 2 H), 1.68−1.49 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 136.3, 131.6, 129.7, 128.9, 128.3, 127.5, 126.6, 113.8, 113.1, 99.5, 91.4, 84.8, 81.2, 77.8, 72.2, 58.5, 55.2, 28.6, 25.1, 23.8, 19.5; MS (+CI) m/z (relative intensity) 437 (M^+, 7), 403 (M^+ − OMe-d_3, 100).

(*Z*)-11-Methoxy-5-[1′-(trideuteriomethoxy)-1′-(4″-methoxyphenyl)methyl]-1-(phenylthio)undeca-2,6-diyn-4-ene (42). Obtained as the minor component in an inseparable mixture (**41**:**42** = 75:25). **42**: pale yellow oil; R_f = 0.43 (20% EtOAc−hexane); IR (neat) 2202, 1172, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.33 Hz, 2 H), 7.31−7.20 (m, 5 H), 6.82−6.79 (AA′BB′, 2 H), 5.82 (S, 1 H), 5.18 (s, 1 H), 3.88 (d, J = 1.95 Hz, 2 H), 3.79 (s, 3 H), 3.35 (t, J = 5.86 Hz, 2 H), 2.34 (t, J = 6.83 Hz, 2 H), 1.68−1.49 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 137.8, 1315.6, 134.9, 129.8, 129.0, 128.5, 126.9, 115.3, 113.5, 96.9, 95.0, 80.6, 79.8, 78.1, 72.1, 58.5, 55.2, 28.5, 25.0, 23.7, 19.4; MS (+CI) m/z (relative intensity) 437 (M^+, 7), 403 (M^+ − OMe-d_3, 100).

Oxidation of Allyl Alcohol 12. (*E*)-11-Methoxy-5-phenylmethylidene-1-(phenylthio)undeca-2,6-diyn-4-one (45a). To a solution of alcohol **12** (0.597 g, 1.53 mmol) and powdered 4 Å molecular sieves in dry CH_2Cl_2

(50 mL) cooled at 0 °C in an ice−water bath was added PCC (495 mg, 2.30 mmol) followed by stirring at room temperature for 5 h. The reaction mixture was diluted with Et_2O (50 mL) and filtered through a short plug of silica gel with rinsing by Et_2O. The combined organic layer was concentrated in vacuo, and the residue was purified by flash column chromatography (silica gel, 20% EtOAc−hexane) to give **45a** (300 mg, 51%): yellow oil; R_f = 0.26 (20% EtOAc−hexane); IR (neat) 2224, 1638, 1594, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97−7.93 (m, 2 H), 7.83 (s, 1 H), 7.54−7.22 (m, 8 H), 3.84 (s, 2 H), 3.41 (t, J = 5.82 Hz, 2 H), 3.32 (s, 3 H), 2.56 (t, J = 6.57 Hz, 2 H), 1.78−1.69 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 147.9, 134.2, 134.1, 131.1, 130.7, 130.6, 129.2, 128.5, 127.5, 122.6, 102.7, 91.2, 80.7, 75.3, 72.1. 58.5, 28.8, 25.0, 23.2, 19.9; MS (+CI) *m/z* (relative intensity) 389 ($M + H^+$, 100); HRMS (+FAB) calcd for $C_{25}H_{25}O_2S$ ($M + H^+$) 389.1575, found 389.1506.

Oxidation of Allyl Alcohol 18c. (*E*)-10-Methoxy-4-phenylmethylidene-1-phenyldeca-1,5-diyn-3-one (45b). To a solution of alcohol **18c** (130 mg, 0.38 mmol) in dry THF (5 mL) was added MnO_2 (657 mg, 5.67 mmol) followed by stirring at room temperature for 1 h. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a short plug of silica gel with rinsing by EtOAc. The combined organic layer was concentrated in vacuo, and the residue was purified by flash column chromatography (silica gel, 20% EtOAc−hexane) to give **45b** (107 mg, 83%): yellow oil; R_f = 0.32 (20% EtOAc−hexane); IR (neat) 2200, 1634, 1490, 1174, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12−8.10 (m, 2 H), 8.07 (s, 1 H), 7.65−7.63 (m, 2 H), 7.48−7.39 (m, 6 H), 3.41 (t, J = 6.34 Hz, 2 H), 3.32 (s, 3 H), 2.62 (t, J = 6.83 Hz, 2 H), 1.78−1.75 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 146.9, 134.4, 132.9, 131.1, 130.7, 130.4, 128.6, 128.5, 122.7, 120.3, 102.5, 93.7, 86.7, 75.9, 72.1. 58.5, 28.9, 25.1, 19.9; MS (+CI) *m/z* (relative intensity) 343 ($M + H^+$, 100).

Reduction of Ketones 45a,b. Typical Procedure. (−)-(*E*)-11-Methoxy-5-phenylmethylidene-1-(phenylthio)undeca-2,6-diyn-4-ol (12). To a solution of (+)-DIP-chloride (331 mg, 1.03 mmol) in dry Et_2O (2 mL) cooled at −20 °C was added a solution of **45a** (334 mg, 0.86 mmol) in dry Et_2O (8 mL). The resultant mixture was stirred at the same temperature for 7.5 h. Excess acetaldehyde (∼1.5 mL) was then added to the reaction mixture, and stirring was continued for another 4 h at room temperature. The reaction was quenched with 2 N NaOH (20 mL) and stirred for 3 h at room temperature. The reaction mixture was extracted with Et_2O (20 × 3 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 30% EtOAc−hexane) provided (−)-**12** (200 mg, 60%): $[\alpha]^{20}_D$ −27.6° (c = 1.02, $CHCl_3$); 94.3% ee determined by HPLC over Chiralpak AD column eluted with hexane−2-propanol (95:5) at 1 mL/min using UV detector at 254 nm; t_R = 32.5 min for (−)-**12** and t_R = 26.3 min for the other enantiomer. The absolute stereochemistry of (−)-**12** is not determined.

(−)-(*E*)-10-Methoxy-4-phenylmethylidene-1-phenyldeca-1,5-diyn-3-ol (18c). Obtained in 69% yield from the (+)-DIP-chloride reduction of ketone **45b** as described for **45a**. **18c**: $[\alpha]^{20}_D$ −16.4° (c = 1.03, $CHCl_3$); 94.4% ee determined by HPLC over Chiralpak AS column eluted with hexane−2-propanol (95:5) at 1 mL/min using UV detector at 254 nm; t_R = 20.1 min for (−)-**18c** and t_R = 17.8 min for the other enantiomer. The absolute stereochemistry of (−)-**18c** is not determined.

Acid-Catalyzed Isomerization of (−)-12 and (−)-18c in the Presence of Ethanol or Ethanethiol. Typical Procedure. (*E*)-4-(1′-Ethylthio-1′-phenyl)-methyl-10-methoxy-1-phenyldeca-1,5-diyn-3-ene (46) and (*E*)-3-Ethylthio-10-methoxy-4-phenylmethylidene-1-phenyldeca-1,5-diyne (47). To a solution of (−)-**18c** (46 mg, 0.134 mmol) and EtSH (20 μL, 0.27 mmol) in dry CH_2Cl_2 (2 mL) was added CSA (31 mg, 13.4 × 10^{-2} mmol, 67 mM). The mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 20% EtOAc−hexane) provided an inseparable mixture of **46** and **47** (**46**:**47** = 69:31, 60 mg, 60%). **46**: pale yellow oil; R_f = 0.49 (20% EtOAc−hexane); IR (neat) 2200, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.27 (m, 10 H), 6.21 (s, 1 H), 4.65 (s, 1 H), 3.33 (t, J = 5.86 Hz, 2 H), 3.29 (s, 3 H), 2.54 (q, J = 7.35 Hz, 2 H), 2.47 (t, J = 7.47 Hz, 2 H), 1.77−1.61 (m, 4 H), 1.27 (t, J = 7.32 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 135.5, 131.7, 128.4, 128.2, 127.5, 123.4, 114.8, 100.1, 95.6, 87.6, 78.7, 77.2, 72.1, 58.5, 54.9, 28.6, 26.2, 25.2, 19.6, 14.2; MS (+CI) *m/z* (relative intensity) 327 (M^+ − EtS, 100); HRMS (+FAB) calcd for $C_{26}H_{28}OS$ (M^+) 388.1861, found 388.1806. **47**: pale yellow oil; R_f = 0.49 (20% EtOAc−hexane); IR (neat) 2200, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.14 Hz, 2 H), 7.50−7.27 (m, 8 H), 6.96 (s, 1 H), 4.58 (s, 1 H), 3.40 (t, J = 5.85 Hz, 2 H), 3.33 (s, 3 H), 2.88−2.65 (m, 2 H), 2.54 (t, J = 6.60 Hz, 2 H), 1.77−1.61 (m, 4 H), 1.35 (t, J = 7.35 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 134.5, 131.6, 128.4, 128.3, 127.7, 123.0, 116.0, 101.0, 97.0, 86.9, 79.0, 74.0, 72.0, 64.3, 47.0, 41.8, 28.5, 25.1, 19.5, 14.4; MS (+CI) *m/z* (relative intensity) 327 (M^+ − EtS, 100).

Table 6 summaries the results of reactions of chiral alcohols (−)-**12** and (−)-**18c** with EtOH and EtSH. The products **16b**,**d**, **17b**,**d**, **19c**, **46**, and **47** given in Table 6 were proved to be racemic mixtures as analyzed by HPLC using chiral columns as specified below.

For compound **16b**: two Chiralpak AD columns eluted with hexane−2-propanol (99:1) at 0.6 mL/min using UV detector at 254 nm; t_R = 24.1 and 29.5 min for the two enantiomers.

For compound **17b**: two Chiralcel OD columns eluted with hexane−2-propanol (99:1) at 1 mL/min using UV detector at 254 nm; t_R = 24.1 and 25.1 min for the two enantiomers.

For compounds **16d** and **17d**: two Chiralpak AD columns eluted with hexane−2-propanol (99:1) at 0.8 mL/min using UV detector at 254 nm; t_R = 39.2 and 42.5 min for the two enantiomers of **17d**. Chiralcel OD column eluted with hexane−2-propanol (99:1) at 1 mL/min using UV detector at 254 nm; t_R = 12.7 and 17.1 min for the two enantiomers of **16d**.

For compound **19c**: Chiralpak AD column eluted with hexane−2-propanol (95:5) at 1 mL/min using UV detector at 254 nm; t_R = 4.5 and 6.4 min for the two enantiomers.

For compounds **46** and **47**: two Chiralpak AD columns eluted with hexane−2-propanol (99:1) at 0.6 mL/min using UV detector at 254 nm; t_R = 23.8 and 24.6 min for

the two enantiomers of **47**; t_R = 27.4 and 35.3 min for the two enantiomers of **46**.

Kinetic Measurement. Conversion of **12** in CD_2Cl_2 in the presence of 1.0 equiv of CSA at 20 °C was monitored by ^{1}H NMR on a 400 MHz instrument. The relative integration values for compounds **12** (at 5.0 ppm), **13** (at 5.2 ppm), and the mixture of **14** and **15** (at 4.8 ppm) in the ^{1}H NMR spectrum were recorded at the specified reaction time and were plotted against the time shown in Figure 1.

Conversion of alcohols **12** and **29** in $CDCl_3-CD_3OD$ (1:1 v/v) in the presence of CSA at the indicated temperature was monitored by ^{1}H NMR on a 400 MHz instrument. Methyl 3,5-dinitrobenzoate was used as the internal reference compound. At the given temperature and CSA concentration, the relative integration values of the substrate (at ca. 6.80 ppm for both **12** and **29**) to methyl 3,5-dinitrobenzoate (at 9.10 ppm) in the ^{1}H NMR spectrum were recorded at the specified reaction time. These data were used to construct the plots shown in Figures 4 and 5. The rate constants and half-lives were calculated from the slopes of the plots in Figures 4 and 5 and listed in Tables 4 and 5. Activation energies were estimated from the Arrhenius equation by the plot of ln k versus $1/T$ for both **12** and **29**.

Computational Calculations. The ab initio molecular orbit calculations were performed using the Gaussian 94[39] sets of programs. The geometries of the examined structures were optimized at the RHF/3-21G level of theory. Table 7 and Figures 6 and 7 list the total energies and geometries of the most stable conformations of **54a**−**f**, **55a**−**f**, and **56**−**59**. Calculation results for **54g** and other less stable conformations are found in the Supporting Information. Substituent effect ($\Delta\Delta E = \Delta E_{ref} - \Delta E_{subst}$) on the stability of allylic cations **57**−**59** are obtained by the difference in the energy gap (ΔE_{subst}) between the cations **57**−**59** and the most stable conformation of the allylic alcohols **54b**−**d**, respectively, compared to that (ΔE_{ref}) of **56** and **54a**. The data are given in Figure 7.

Acknowledgment. This work was supported by the UGC Competitive Earmarked Research Grants [HKUST212/93E and HKUST590/95P] from the Research Grants Council of the Hong Kong Special Administrative Region, China. Financial support from the Department of Chemistry, HKUST is also acknowledged.

Supporting Information Available: *Z*-Matrixes and total energies for **54a**−**g**, **55a**−**f**, **56**−**59**, and related species and copies of ^{1}H and ^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO982476V

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